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An in vitro model to simulate drug release from oily media

N. Anthony Armstrong, Hazel-Anne Griffiths * and Kenneth C. James

Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cardiff (U.K).

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Summary

An in vitro method of measuring the release of drugs from non-polar media is described. The technique is based on the Sartorius Absorption Simulator. The base is spread as a thin film on a base plate, and the drug must diffuse across an aqueous layer before transfer through a simulated biomembrane. Salicylic acid was used as a model drug. The reproducibility of the technique is assessed, and 3 methods are given for manipulation of the release data; that for opposing first-order reactions was found to be the most appropriate. The fraction of drug released is shown to be dependent on the amount of base applied. It is suggested that the technique may be applicable to topical and rectal dosage forms and eye ointments.

Introduction

A number of in vitro techniques have been devised to simulate drug release from topical preparations and subsequent absorption through the skin. In the case of mucosa or damaged skin, the biological barrier is partially or completely absent, and therefore release from the dosage form becomes rate determining. According to Lippold (1982), this also occurs in the majority of cases after application of suppositories and eye ointments to the rectal mucosa and corneum, respectively.

Under these conditions, simulation of the absorption of a drug in vivo, i.e. bioavailability, means investigation of release. When the administered drug is required to produce a local effect, release from the dosage form is again the rate-determining step. However, even if the rate-limiting step is penetration of the barrier phase, maximising the release rate contributes to conditions for optimal penetration.

Many of the previously described models ignore the occlusive effects which non-polar bases may have on intact skin. The application to the skin of an occlusive film in the form of a hydrophobic semi-solid results in the accumulation of moisture beneath the film. Thus for a drug molecule to be absorbed, it must diffuse out of the vehicle, across an aqueous layer and then through the skin. A similar situation applies to eye ointments, where partition into the film of lachrymal secretion precedes absorption by the corneum, and to suppositories, where dissolution in aqueous rectal fluid is a preliminary to absorption (Kakemi et al., 1972).

Thus this investigation was initiated in order to develop an in vitro model, primarily for the determination of drug release from occlusive dermal

* *Present address*: Beecham Research Laboratories, Worthing, U.K.

Correspondence: N.A. Armstrong, Welsh School of Pharmacy, University of Wales Institute of Science and Technology, P.O. Box 13, Cardiff CF1 3XF, U.K.

preparations, but which also would be applicable to other lipophilic systems such as suppository bases and eye ointments. The model would then be used to investigate factors which affect the release of the incorporated drug substance from the base.

Experimental

Materials

Liquid paraffin, soft paraffin (Macarthy, Romford, U.K.) and salicylic acid (Hopkin and Williams, Chadwell Heath, U.K.) were of B.P. quality. Isopropyl myristate (95% pure) was obtained from Fluka, Switzerland. All were used without further purification.

Procedure

The Sartorius Absorption Simulator was originally designed for the estimation of the absorption rate coefficients of drugs from the gastrointestinal tract, using an artificial lipid barrier (Stricker, 1971). The main feature of this apparatus was the diffusion chamber, consisting of two perspex blocks separated by a thin inert membrane of cellulose nitrate, the pores of which were filled with a lipid phase to simulate the biomembrane. A solution of the drug (the donor phase) and a buffer solution (the recipient phase) were circulated on opposite sides of the membrane. The rate of diffusion of drug across the membrane into the buffer solution was taken to represent the rate of absorption.

The original Sartorius apparatus is shown diagramatically in Fig. 1A. For the current work, the front plate was replaced by a perspex plate to which a circular gasket, 1.5 mm thick, was glued and located so that when the plate was clamped in position, a sealed compartment was formed above the membrane. Two holes were bored in the perspex sheet near the inner perimeter of the gasket, so that the compartment could be filled with water. McIlvaine's citric acid phosphate buffer solution at pH 6.4, in a sealed reservoir, was maintained at 41°C by immersion in a constant temperature water bath. It was circulated successively through the compartment below the membrane, through a flow cell located in a Cecil spectrophotometer and then back to the reservoir, using a Watson-Marlow peristaltic pump and PTFE tubing. Salicylic acid, the chosen model drug, was determined at 298 nm.

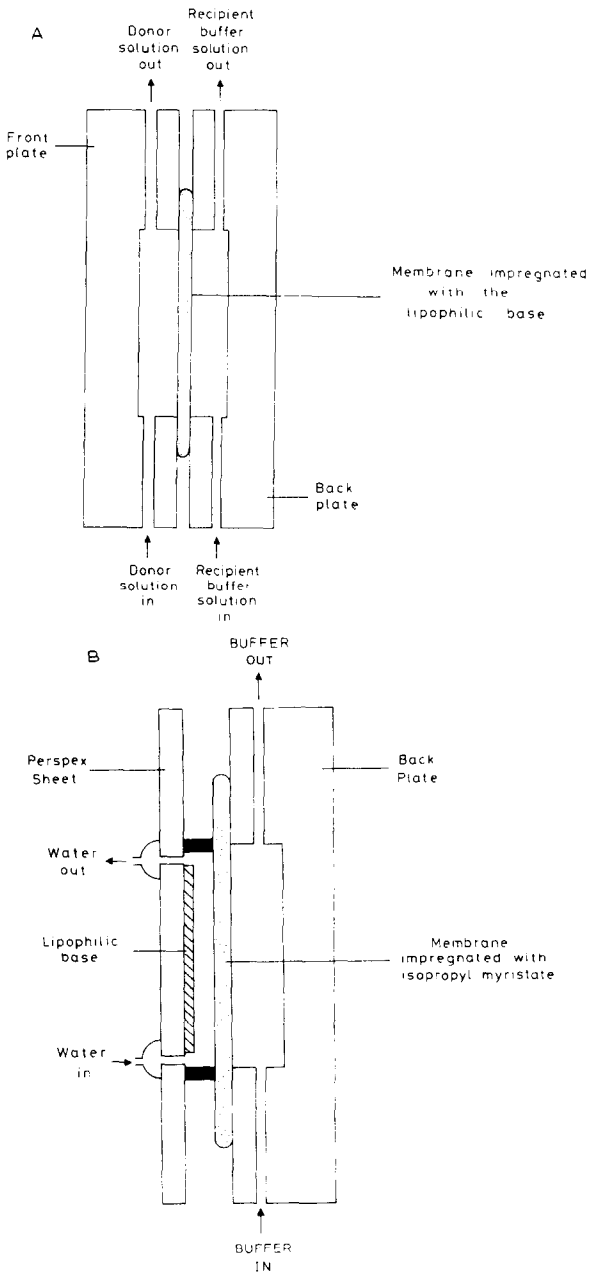

Fig. 1. The Sartorius Absorption Simulator. A: as originally designed. B: as modified for the present study.

A temperature of 41°C was chosen because preliminary experiments indicated that the temperature of the liquid would drop to 37°C by the time it reached the cell.

Zsigmondy cellulose nitrate membrane filters (9 cm diameter, 0.1 μm pore size) were immersed individually in isopropyl myristate. After removal, excess liquid was allowed to drip off, and the membrane pressed between sheets of blotting paper until excess liquid on the surface was removed. Preliminary experiments with 7 membranes gave a mean weight increase of 336 ± 8 mg ($P = 0.01$).

Salicylic acid was dissolved in bases consisting of white soft paraffin and isopropyl myristate. The mixture was applied to the pre-weighed perspex front plate, using a fine paint brush, until the required weight was reached. Preliminary experiments established that this was the most efficient way of adding the base. The modified apparatus is shown in Fig. 1B.

Results and Discussion

The experimental procedure followed was initially the same as that used by Armstrong et al. (1980) in a preliminary study involving drug release from an impregnated membrane. The suggestion made in that paper was that the membrane can be used as a support for various lipophilic dosage forms, e.g. ointments and suppository bases in which the drug is dissolved. The buffer, circulating over both sides of the membrane would then act as a reservoir for the drug. The rate of appearance of the drug in the buffer solution would be taken as its rate of release from the lipophilic base. Further work suggested that this technique did not give acceptable reproducibility, but the procedure described in the experimental section of this paper was found to give consistent results.

Two separately prepared samples (A and B) containing salicylic acid dispersed in a base consisting of white soft paraffin (80%) and isopropyl myristate (20%) were examined in preliminary experiments. Release was measured to beyond equilibrium time and carried out in quadruplicate for each sample. Results are shown in Table 1. There was no significant difference between the two samples, and the scatter within each set of 4 results was negligible. Similar reproducibility was obtained in all subsequent experiments.

TABLE 1

Reproducibility of release data

Time (min)	Fraction released			
	Sample A		Sample B	
	mean $\times 10^2$ ($n = 4$)	S.D. $\times 10^2$	mean $\times 10^2$ ($n = 4$)	S.D. $\times 10^2$
0	0	0	0	0
5	1.59	0.56	0.83	0.38
10	4.32	0.78	3.66	0.36
15	9.32	0.74	9.02	0.61
20	15.78	0.68	14.85	0.49
25	22.18	1.11	20.68	1.53
30	28.19	1.47	27.82	1.85
35	34.59	1.85	34.20	2.70
40	39.85	1.51	39.10	2.38
45	45.49	2.46	43.98	1.88
50	50.00	1.41	50.00	1.69
55	54.51	0.71	55.26	0.67
60	59.02	0.94	59.26	0.97
65	62.41	0.99	63.53	1.47
70	65.79	1.08	66.17	1.45
75	68.42	0.78	68.80	1.24
80	70.30	0.77	71.05	1.45
85	72.18	1.03	72.93	1.63
90	74.06	0.83	75.19	1.52
95	75.94	0.47	76.32	1.59
100	77.43	0.48	78.57	1.61
105	78.94	0.92	78.94	1.80
110	80.08	0.83	80.08	1.78
115	81.58	1.28	81.58	3.47
120	81.95	0.97	82.33	3.47
125	83.08	0.88	83.08	3.47
130	83.83	0.93	83.83	3.47
135	84.21	0.83	84.59	2.18
140	84.97	0.83	85.34	2.18
190	88.35	0.64	88.35	1.45
300	92.48	1.13	90.97	1.98

The data were treated in 3 ways:

(a) The fraction released (R) was plotted against root of time (t), a treatment introduced by Higuchi (1962) and the release rate constant (k_a) calculated from the equation

$$R = k_a t^{1/2} \qquad (1)$$

where

$$k_a = 2\left(\frac{D}{\pi h^2}\right)^{1/2} \quad (2)$$

and D = diffusion coefficient; h = thickness of applied layer.

(b) Release was treated as a first-order reaction (Washitake et al., 1975), the natural logarithm of the fraction remaining in the base being plotted against time. Thus:

$$\ln(1 - R) = k_b t \quad (3)$$

(c) Release data was manipulated according to the method of Frost and Pearson (1961) for opposing first-order reactions using Eqn. (4).

$$\ln\left(\frac{Q_0 - Q_e}{Q_t - Q_e}\right) = k_c t \quad (4)$$

where Q_0, Q_t and Q_e are the quantities of drug present in the base at zero time, time t and at equilibrium, respectively. The use of the 3 treatments is shown in Fig. 2, which shows the release data presented in Table 1.

All 3 treatments show an initial lag phase. A similar phenomenon has been reported by a number of other workers (see, for example, Spang-Brunner and Speiser, 1976), and is an indication

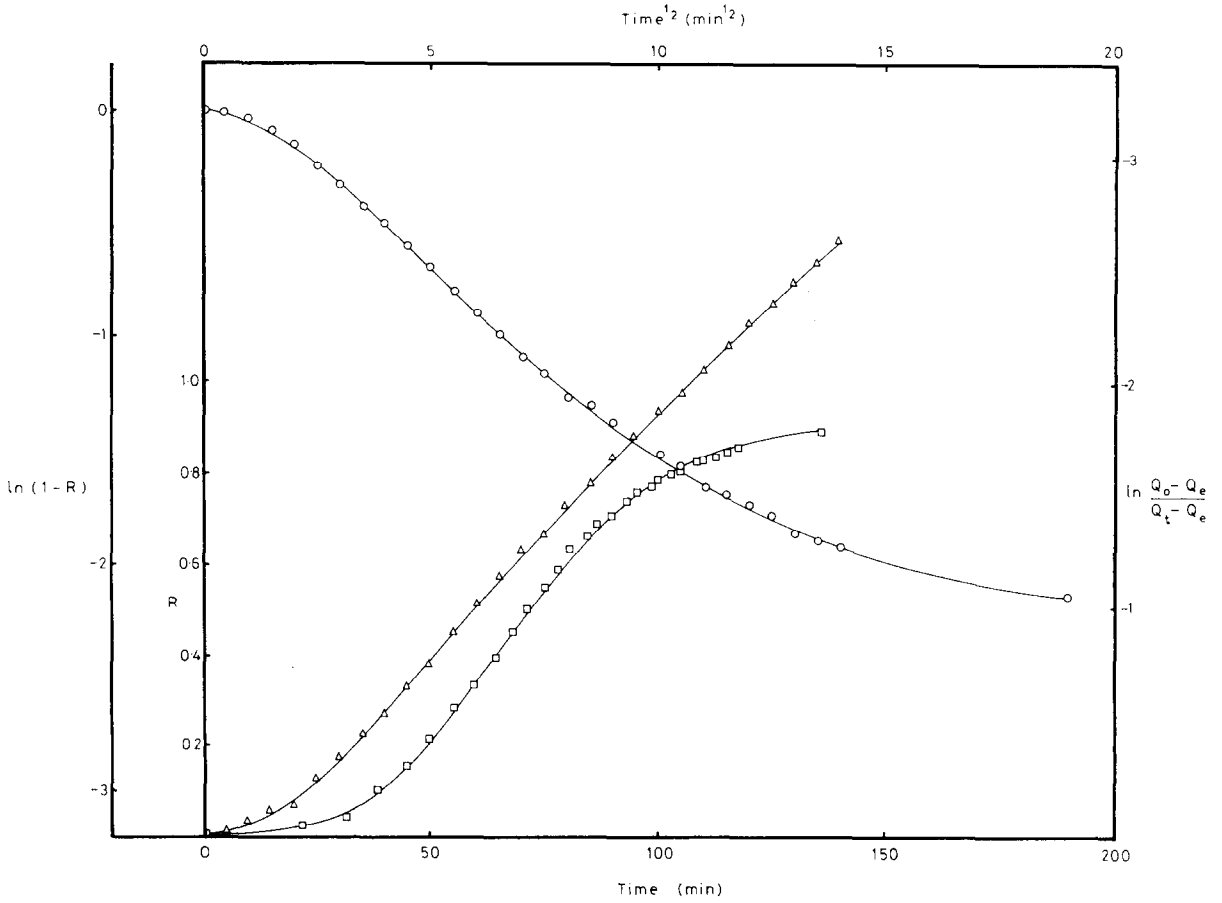

Fig. 2. Release of salicylic acid from a mixture of white soft paraffin and isopropyl myristate. □, data manipulated according to the root-time method of Higuchi (1962); ○, data manipulated according to first order kinetics (Washitake et al., 1975); △, data manipulated according to the opposing reaction method of Frost and Pearson (1961).

TABLE 2

Release rate constants (and correlation coefficients) for the release of salicylic acid from a 0.5% w/w solution in a mixture of white soft paraffin (80%) and isopropyl myristate (20%)

	Time range (min):	
	0–200 ($n = 29$)	25–90 ($n = 14$)
k_a ($min^{-0.5}$)	0.0770 (0.938)	0.109 (0.986)
k_b (min^{-1})	0.0108 (0.931)	0.0167 (0.996)
k_c (min^{-1})	0.0222 (0.996)	0.0217 (0.999)

of the time required for the membrane and the water film to reach a steady-state.

The first-order treatment shows linearity only over a limited time-span and pronounced curvature is apparent after about 60 min, indicative of the establishment of an equilibrium state. Similarly, the plot of fraction released against square root of time departs from linearity at about the same time. Both Higuchi (1962) and Spang-Brunner and Speiser (1976) found that this relationship was only linear up to a fraction released of 0.5–0.6, and this applies to the presently reported work.

The treatment according to the opposing first-order reaction method gives linearity over a much greater range. This method was originally devised to deal with the kinetics of reactions where both forward and backward reactions occurred to a significant extent, the net result being the establishment of an equilibrium. The method has been applied to drug release from oily solutions by Armstrong et al. (1981) and appears to be appropriate here.

The release rate constants both over the complete time range and between 25 and 110 min are shown in Table 2. These two times represent fractions released of 0.2 and 0.8, respectively. Correlation coefficients are also given.

The linear relationship obtained from treatment (c) suggests that the 4 phases present in the chamber represent a pseudo-two-phase system. Hence it can be assumed that the drug concentrations in the thin film of water and the impregnated membrane are constant for the duration of the experiment.

Different release rates were obtained when the weight of the sample was changed, even though the concentration of salicylic acid remained constant. This is not surprising, since Eqn. 2 predicts that k_a is inversely proportional to the thickness of the applied layer. The relationship is linear over much of its length, but decreases sharply when the layer thickness exceeds approximately 0.1 mm.

The transfer of dissolved molecules between two immiscible media is governed by the partition coefficient. However, this represents an equilibrium situation. The lack of linearity is presumably due to the fact that transfer across the interfacial barrier is diffusion rather than partition controlled. It is evident that for comparative work, the weight of material applied and hence the thickness of the resulting layer must be kept constant.

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