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An in-vitro investigation of drug availability from lipophilic solutions

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An in-vitro model, previously described, has been modified and used to investigate the effects of volume and concentration on the release of 4-hydroxybenzoic acid from 1-octanol and isopropyl myristate. Solutions encapsulated in soft gelatin shells have also been examined. The quantity of solute released can be increased by reducing the volume of solvent used to prepare the solution, or by increasing the concentration of the solution. The release profile from an encapsulated solution is different from that obtained with the same, unencapsulated solution. The difference is attributed to absorption of the solute by the capsule shell.

Whilst considerable interest has been directed towards the bioavailability of solids from tablets and hard gelatin capsules, little attention has been paid to the effects of oil-based drug delivery systems, of which the soft gelatin capsule is the best known example. The availability of drugs from orally administered lipid solutions has been reviewed by Armstrong & James (1980), who were unable to find any general pattern which explained how availability was influenced by lipid environment. Kakemi et al (1966, 1972) considered that the major mechanism of drug absorption in-vivo from a lipid solution involves the liberation of the drug from the vehicle into the aqueous luminal fluid, followed by absorption through the gastrointestinal wall. They considered that direct absorption from the oil phase could be neglected. Armstrong et al (1979) designed an apparatus for simulating the first of these stages. Weak aromatic acids were used as substrates. A non-aqueous solution was spread on to the surface of the acidic solution, and the aqueous phase monitored for the concentration of the solute. A large volume (150 ml) of non-aqueous solution was used, which gave a general idea of solute release, but the process was slow, and the volume unrealistic compared with that used in soft gelatin capsules. The effect of volume and concentration of lipid solution was therefore investigated, and is described below. The method was also adapted for the examination of intact soft gelatin capsules containing lipid solutions.

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MATERIALS AND METHODS

1-Octanol and 4-hydroxybenzoic acid were of 99% purity, and isopropyl myristate of Pharmaceutical Codex quality. All were obtained from BDH Ltd.

Partition-permeation apparatus

This has been described previously (Armstrong et al 1979). It consisted of two half cells separated by a simulated lipid membrane, one containing buffer at pH 1·2 and the other containing buffer at pH 7·4. The non-aqueous solution was spread on the surface of the acidic solution, and both aqueous phases monitored for the concentration of solute. For capsules and small volumes of solution, an inverted cylinder was attached to the shaft of the stirrer. The cylinder dipped into the surface of the pH 1·2 solution, so that when the non-aqueous solution was introduced into the cylinder, an effective area of contact of 15·9 cm^2 was provided between the two solutions. This adaptation is shown in Fig. 1. As the cylinder was a closed system it was necessary to remove some air by means of a bent pipette. Air was removed until the levels inside and outside the cylinder were the same. The required volume of solution was then passed into the inverted cylinder, using another bent pipette. A similar procedure was used for capsules. Not more than 1 min elapsed during addition of the sample. Each experiment was repeated a minimum of 5 times, and carried out at 37 °C. 80 minim round soft gelatin capsules containing 4·3 ml of a 0·02% w/v solution of 4-hydroxybenzoic acid in isopropyl myristate were prepared by the rotary die process at R. P. Scherer Ltd., Treforest, Mid Glamorgan. The shells consisted of gelatin, glycerol and water only, with no preserva-

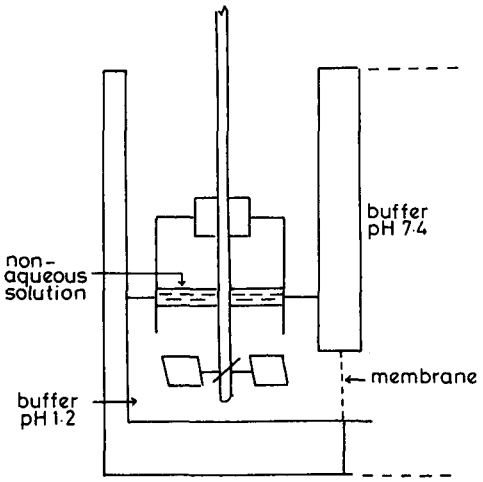

FIG. 1. Modified partition-permeation apparatus.

tive. At the same time, an identical batch of capsules was made containing isopropyl myristate only. Background determinations had to be made with each run, using a capsule identical in every respect, except for the absence of solute, because the shell contents absorbed in the uv region used for analysis.

RESULTS AND DISCUSSION

The three phases in the partition permeation apparatus represented the contents of a soft gelatin capsule, the stomach and the vascular system, and are designated compartments 1, 2 and 3 respectively. In practice the apparatus was adaptable only to weak organic acids, which are soluble in the organic solvent and the pH 7·4 solution, so that the pH 7·4 buffer withdraws solute from the pH 1·2 solution, and maintains the concentration at sub-saturation level. The kinetics of the model are described by equation 1. F_1, F_2 and F_3 are the fractions of the total weight of solute residing in compartments 1, 2 and 3 respectively. The constants k_{ij} are therefore

$$F_1 \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} F_2 \xrightarrow{k_{23}} F_3 \qquad (1)$$

expressed in terms of weight fractions rather than concentrations, and are called transfer rate constants to distinguish them from first order rate constants.

A possible criticism of our previous work (Armstrong et al 1979) is that the volume of non-aqueous solution was the same as that of the simulated gastric contents, so that the conditions did not match the relative volumes of soft gelatin capsule and human stomach. An additional criticism is that the proportion of solute transferred from the lipid was small. Thus for example, only 1% of 4-hydroxybenzoic acid was transferred from 150 ml of 1-octanol solution in 4 h. The object of the present work was to use volumes of oil which were small and realistic and which, it was hoped, would increase the proportion of solute transferred. It was also intended to adapt the apparatus for use with entire soft gelatin capsules, rather than only their contents.

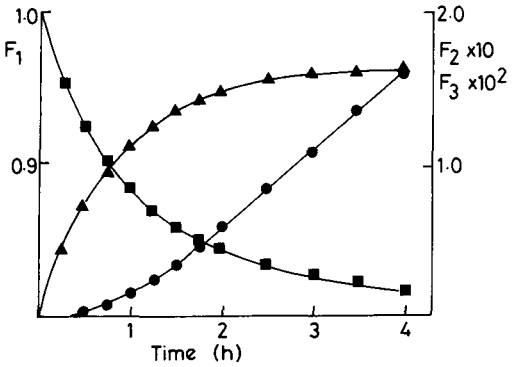

FIG. 2. Migration of 4-hydroxybenzoic acid from 25 ml of $2{\cdot}18 \times 10^{-3}$ M solution in 1-octanol. V_2 = 150 ml, V_3 = 75 ml. ■, F_1; ▲, F_2; ●, F_3.

Reduction of the volume of non-aqueous solution had a marked effect on the rate of migration. Fig. 2 is an example, and is a composite plot of solute levels in the three compartments against time. It represents the migration of 4-hydroxybenzoic acid from 25 ml of a $2{\cdot}17 \times 10^{-3}$ M solution in 1-octanol in equilibrium with 150 ml of pH 1·2 buffer solution. For hydrostatic reasons, the volume of compartment 3 had to be reduced to 175 ml. Nearly 20% of the solute left the non-aqueous phase in 4 h, in contrast to only 4% released from 150 ml of 1-octanol. The effect of a sixfold change in the volume of 1-octanol solution is given in Table 1, which shows a steady decrease in the fraction transferred with increasing volume of 1-octanol phase.

Table 1. Transfer rate constants for release of 4-hydroxybenzoic acid from various volumes of $2{\cdot}18 \times 10^{-3}$ M solution in 1-octanol.

Transfer rate constant (h^{-1})	Volume of 1-octanol solution (ml) 25	50	100	150
k_{12}	0·188	0·161	0·072	0·034
k_{21}	0·900	1·600	1·410	1·000
k_{23}	0·042	0·042	0·042	0·042
Initial transfer rate ($mg \times 10^2 h^{-1}$)	1·02	1·75	1·57	1·11
$(k_{21}V_2/k_{12}V_1)$	28·7	29·8	29·4	29·4

The rate of transfer of solute from compartment 1 is given by equation 2. c_0 represents the concentration in compartment 1 at zero time, and c_i that at any time corresponding to weight fractions F_1 and F_2. k'_{12} and k'_{21} are first order transfer constants, and V_1 and V_2 volumes of compartments 1 and 2 respectively.

$$\frac{-dc_i}{dt} = k'_{12}c_0F_1 - k'_{21}\frac{c_0V_1}{V_2} = k_{12}F_1 - k_{21}F_2 \quad (2)$$

Comparison of coefficients gives equations 3 and 4,

$$k'_{12} = k_{12}/c_0 \quad (3)$$

$$k'_{21} = \frac{k_{21}V_2}{c_0V_1} \quad (4)$$

which leads to the calculation of partition coefficient (K_d) from equation 5.

$$K_d = \frac{k'_{21}}{k'_{12}} = \frac{k_{21}V_2}{k_{12}V_1} \quad (5)$$

Partition coefficients were calculated from the results in Table 1, using equation 5, and gave results which were constant, and in reasonable agreement with the value of 25·6 obtained by classical procedures (Armstrong et al 1979). Similar results were obtained with isopropyl myristate.

Reducing the volume of solution, while keeping its initial concentration constant, does not provide a therapeutic advantage, because although the fraction transferred decreases with increasing volume of lipid solution, the actual amount of solute which is available for transfer decreases proportionately with decreasing volume of solution. Thus the initial rate of transfer from compartment 1 to compartment 2, expressed as weight of solute transferred in unit time, is equal to $k_{12}c_1V_1$, where c_1 is concentration in compartment 1, in mol litre^{-1}, and V_1 is the volume in compartment 1 expressed as a fraction of a litre. These rates are reproduced in Table 1, and were almost constant in comparison with a nearly six-fold change in transfer rate constant. It therefore follows that to increase the actual weight of drug transferred, the volume of solution must be decreased without decreasing the total weight of drug in solution, or the total weight of solute increased without increasing the volume. Both procedures have the net result of increasing the concentration.

The first suggestion was tested by observing the migration of 3.23×10^{-2} mmol of 4-hydroxybenzoic acid from a range of volumes of solution in isopropyl myristate. Both k_{12} and k_{21} increased with decreasing volume, while k_{23} remained constant. The overall result was as shown in Fig. 3, which gives the weight

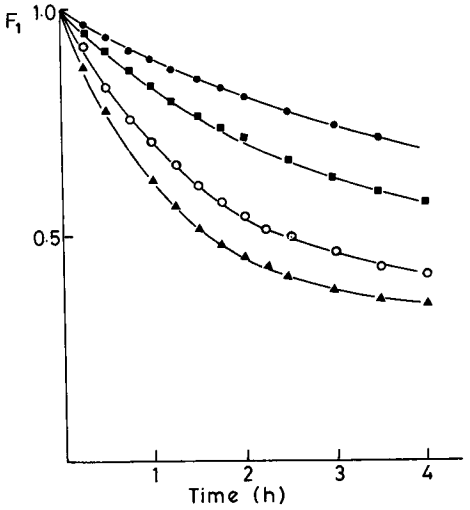

FIG. 3. Weight fractions of 4-hydroxybenzoic acid remaining in compartment 1 during release from $3·23 \times 10^{-2}$ mmol dissolved in ▲, 25 ml; ○, 50 ml; ■, 100 ml; ●, 150 ml of isopropyl myristate. V_2 = 150 ml, $V_3 = V_1 + V_2$.

fractions released over 4 h. The quantity released clearly increases as the volume is decreased, with double the quantity discharged from 25 ml of solution than from 150 ml.

The effects of changing the concentration of the non-aqueous solution are shown in Fig. 4, which gives the release of 4-hydroxybenzoic acid from 25 ml quantities of solution containing multiples of $2·15 \times 10^{-2}$ mmol litre^{-1}. The figure gives the misleading impression that release of solute from

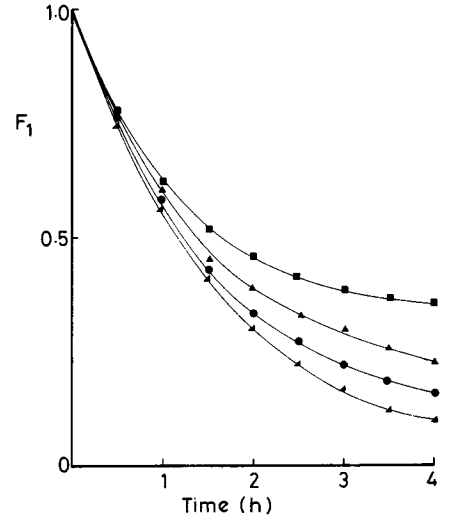

FIG. 4. Weight fractions of 4-hydroxybenzoic acid remaining in 25 ml of isopropyl myristate solution in compartment 1. Concentrations (mmol litre^{-1}), ◢, 0·108; ●, 0·215; ▲, 0·645; ■, 1·290.

compartment 1 is improved by dilution of the solution in the capsule. However, in terms of the actual amount of solute transferred, a given weight fraction for the most concentrated solution is equivalent to 12 times the weight of drug released when the same weight fraction is applied to the most dilute solution.

This experimental procedure failed to give reproducible results with volumes of non-aqueous solution smaller than 25 ml, because there was not sufficient liquid to provide a uniform interface between compartments 1 and 2. The problem was overcome by attaching an inverted cylinder to the shaft of the stirrer, thereby confining the non-aqueous layer to a limited area of interface. With this modification, the method could be extended not only to smaller volumes, but also to entire capsules.

The release of 4-hydroxybenzoic acid from a capsule and from a non-encapsulated isopropyl myristate solution of the same concentration and volume, into the pH 1·2 solution, is shown in Fig. 5.

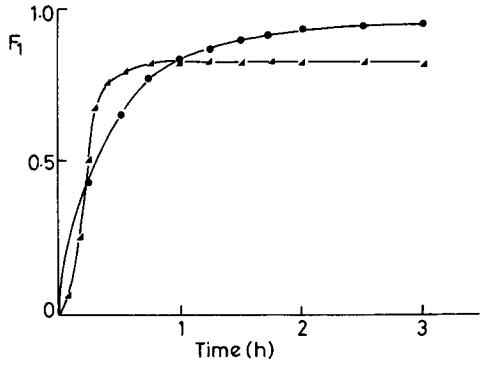

FIG. 5. Weight fractions of 4-hydroxybenzoic acid appearing in compartment 2 from isopropyl myristate solution; ◢, encapsulated; ●, unencapsulated.

The release profile of the non-encapsulated solution is typical of those obtained before, but with the encapsulated solution it was observed that before the rupturing of the shell, some of the solute appeared in the acidic buffer. When the capsule ruptured, the amount of solute released rapidly exceeded that from the non-encapsulated solution before reaching a plateau at about 85% of the total content after 45 min. The difference in release profiles is attributed to the presence of solute in the shell, and to the shell dissolving faster than the solute is released from the oily solution. This concept will be considered in more detail in a later publication.

It may be argued that after ingestion of the capsule, subdivision of the oily mass will ensue, and the resultant increase in interfacial area will negate the factors investigated here. Preliminary in-vivo data indicate that unless the capsule contents include a surface active agent, such subdivision is not great, and so the validity of this study is maintained.

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