J. Pharm. Pharmacol. 1979, 31: 65–68 Received May 30, 1978

# Percutaneous absorption: interfacial transfer kinetics

W. JOHN ALBERY* AND JONATHAN HADGRAFT†

*Physical Chemistry Laboratory, South Parks Road, Oxford, OX1 3QZ, U.K.*

A new rotating diffusion cell is described in which a solute diffuses through a rotating filter. The transport of the solute to both sides of the filter is controlled by the rotation. The filter is filled with an organic phase. The rate of transfer of the solute through the filter is determined by the transport and by the kinetics of the interfacial transfer reactions. Since the transport is controlled the rate constant for the transfer reaction can be measured. Results for eleven different systems are reported and it is found that the rate constants are all smaller than $10^{-4}$ ms$^{-1}$.

The understanding of the mechanism and rate limiting steps in the absorption of drugs through the skin is important both for its own sake and for the formulation of dermatological preparations. The drug applied in an external phase diffuses through the epidermal barrier. The rate of penetration can depend on one or more of the following: diffusion in the external phase, the rate of transfer across the interfaces on either side of the epidermal barrier, and diffusion through the barrier itself. It has been customary to assume (Katz & Poulsen 1971; Michaels et al 1975) that at any interface there is local equilibrium where the concentrations of the transferring species are given by the partition coefficient. In this paper we describe a new technique and results for the barriers to the interfacial transfer of solutes between two liquid phases. From a knowledge of such barriers one can estimate whether they limit the rate of the overall process or not.

Previously we have shown how a stable interface may be established between two liquids on the sinter of a Stokes cell (Stokes 1950) and we reported results for two systems (Albery et al 1974). This work has been extended using a new rotating diffusion cell (Albery et al 1976). This cell uses the hydrodynamics of the rotating disc system (Riddiford 1966), to impose a known pattern of convective diffusion on both sides of a Millipore filter. A Millipore filter is used rather than a sinter because its smaller thickness (0·1 mm compared with 3 mm) means that first the response time is much reduced and second faster interfacial transfer rates can be measured. The rotation of the filter establishes two stagnant diffusion layers of known thickness ($Z_D$) on either side of the filter. In most of the experiments reported here two interfaces are established with the aqueous phase above and below the filter while the filter is filled with the organic phase; this is shown in Fig. 1. We report results for eleven different systems we have studied in which small organic solutes are transferred between an organic and an aqueous phase. In every case there is a substantial free energy of activation for the transfer process.

* Correspondence and present address: Department of Chemistry, Imperial College of Science & Technology, Prince Consort Road, London.

† Department of Pharmaceutical Chemistry, University of Strathclyde, 204 George Street, Glasgow.

## METHOD

The rotating diffusion cell is shown in Fig. 2; a detailed description has been given elsewhere by Albery et al (1976). The Millipore filter FF is mounted on the cylinder CC which is rotated by the pulley PP. The stationary baffle B ensures that there

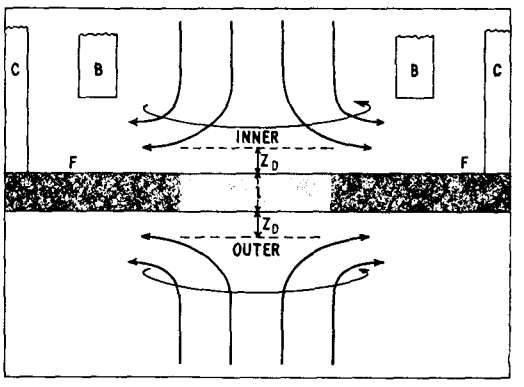


FIG. 1. Diagram of diffusion cell showing the rotating Millipore filter (FF) and a stationary cylindrical baffle (BB). The filter is treated so that the central dotted portion is permeable whereas the hatched portion is impermeable. The imposed convection is indicated by the stream lines. The purpose of the baffle is to prevent the hydrodynamics at the centre of the inner compartment being destroyed by the rotation of the cylinder (CC) that carries the filter.

is correct hydrodynamics on the inside of the filter. The diffusion of solutes from the inside to the outside was followed for systems 1 to 5 in Table 1 using a pH stat (Albery et al 1967), for systems 6 to 10 by removing samples every hour or so and measuring the concentration spectrophotometrically, and for system 11 by using a tritiated sample and measuring the radioactivity of the solution in the outer compartment.

All chemicals were supplied commercially except for butyl nicotinate which was made by esterifying nicotinic acid (Vogel 1951).

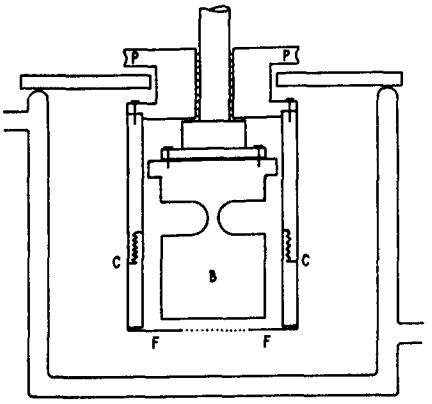


FIG. 2. Diagram of the rotating diffusion cell.

## THEORY

The rate (J mol $s^{-1}$) at which species are transferred from the inner phase (I) to the outer phase (O) is given by

$$J = k A c_I \quad .. \quad .. \quad ..(1)$$

where A is the area of the filter, $c_I$ is the bulk concentration in the inner phase and k (for a sandwich experiment) is given by

$$\frac{1}{k} = \frac{2Z_D}{D} + \frac{2}{\alpha k_{-I}} + \frac{\ell K}{\alpha D_*} \quad .. \quad (2)$$

In equation 2 the first term on the right-hand side describes the diffusion through the aqueous stagnant diffusion layers and $Z_D$ is given by the Levich equation (Levich, 1962)

$$Z_D = 0.64\, W^{-\frac{1}{2}} \nu^{\frac{1}{6}} D^{\frac{1}{3}} \quad .. \quad (3)$$

where $\nu$ is the kinematic viscosity and W(Hz) is the rotation speed. The next term on the right-hand side describes the interfacial transfer reaction; in it a ($\sim 0{\cdot}82$) is the area of the pores of the filter divided by A. For a species C we define $k_I$, $k_{-I}$ as follows

$$C_{org} \underset{k_{-I}}{\overset{k_I}{\rightleftharpoons}} C_{H_2O} \qquad K$$

The third term on the right-hand side of equation 2 describes diffusion through the filter of thickness $l$; $D_*$ is the diffusion coefficient of C in the organic phase. The largest of the three terms in equation 2 will be the most important in determining the rate of the transfer process.

## RESULTS AND DISCUSSION

From equations 2 and 3, $k^{-1}$ should vary linearly with $W^{-\frac{1}{2}}$. Fig. 3 shows a typical plot. The gradient is that calculated from equation 3. Similar results from nine different systems confirm that the hydrodynamics are properly established (Albery et al 1976). The intercept in Fig. 3 corresponds to an infinite rotation speed when the $Z_D$ term in equation 2 is zero. Of the remaining two terms the one describing diffusion through the filter can be calculated from the known characteristics of the filter and $D_*$ which was measured using the conventional Stokes cell (Albery et al 1974). Hence $k_{-I}$ can be found. Results are shown in Table 1. In calculating the free

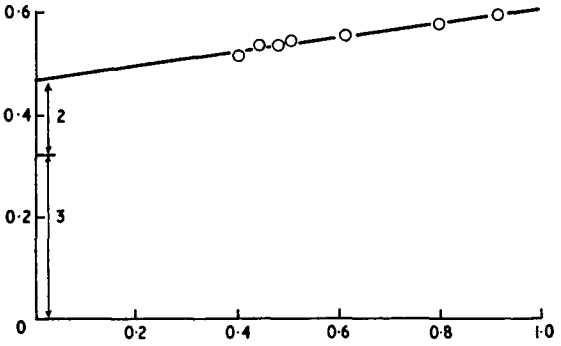


FIG. 3. Typical plot of $k^{-1}$ against rotation speed for acetic acid system. The labels '2' and '3' refer to the second and third terms in equation 2 which respectively describe the transfer reaction and diffusion through the filter. Ordinate: $(k/m\ Ms^{-1})^{-1}$. Abscissa: $(W/Hz)^{-\frac{1}{2}}$.

Table 1. Results for interfacial transfer kinetics.

| Number | Substrate C | Organic phase | K | $k_I$ | $k_{-I}$ | $\Delta G_K^\theta$ | $\Delta G_I^{\theta,\ddagger k}$ | $\Delta G_{-I}^{\theta,\ddagger}$ |
|---|---|---|---|---|---|---|---|---|
| | | | | $mMs^{-1}$ | $mMs^{-1}$ | $kJmol^{-1}$ | $kJmol^{-1}$ | $kJmol^{-1}$ |
| 1 | $CH_3CO_2H$ | IPM[a] | 25·3 | 7·18 | 0·28 | −8 | 41 | 49 |
| 2[j] | $C_5H_{11}CO_2H$ | $C_6H_{14}$ | $9·7 \times 10^{-2}$ | 2·9 | 30 | 6 | 43 | 37 |
| 3 | MBC[b] | IPM | $6 \times 10^{-4}$ | 0·017 | 26 | 18 | 56 | 38 |
| 4 | MBC[c] | IPM | $1 \times 10^{-3}$ | 0·25 | 24 | 17 | 55 | 38 |
| 5 | MBC[c] | $CCl_4$ | $5 \times 10^{-4}$ | 0·016 | 32 | 19 | 56 | 37 |
| 6 | MeNic[d] | IPM | 0·39 | 18 | 46 | 2 | 40 | 38 |
| 7 | MeNic[e] | IPM | 0·52 | 34 | 66 | 1 | 38 | 37 |
| 8 | MeNic[f] | IPM | 0·6 | 3·5 | 5·9 | 1 | 44 | 43 |
| 9 | BuNic[g] | IPM | 0·026 | 5·8 | 223 | 10 | 43 | 33 |
| 10 | HeNic[h] | IPM | 0·014 | 0·24 | 17 | 11 | 51 | 40 |
| 11 | B.17.v[i] | IPM | $7·5 \times 10^{-3}$ | 2·6 | 344 | 13 | 45 | 32 |

Notes
a IPM is isopropyl myristate.
b MBC is *p*-methyl-benzyl chloride.
c Determined in Stokes cell (Stokes, 1950) rather than rotating diffusion cell.
d MeNic is methyl nicotinate.
e Aqueous phase was 60% glycerol, 40% $H_2O$ rather than 100% $H_2O$.
f Aqueous phase was 80% glycerol, 20% $H_2O$.
g BuNic is n-butyl nicotinate.
h HeNic is n-hexyl nicotinate.
i B.17.v is betamethasone-17-valerate.
j System 2 to 5 were studied at 25° and systems 6 to 11 were studied at 37°.
k The free energies of activation $\Delta G_I^{\theta,\ddagger}$ and $\Delta G_{-I}^{\theta,\ddagger}$ were calculated from the corresponding rate constants using eqn (4).

energies of activation a frequency factor of $10^2$ m $s^{-1}$ (Marcus 1963) was used:

$$\Delta G^{\ominus}_{\ddagger} = -RT \ln(k_{\pm I}/10^2) \quad ..(4)$$

Good agreement is found for *p*-methylbenzyl chloride between the results from the Stokes cell (Albery et al 1974) and from the new rotating diffusion cell. Substantial free energy barriers are found even when the reaction is 'downhill' thermodynamically. In fact for these seven different substrates, three different organic phases and three different aqueous phases the barriers in the downhill direction ($G_{\downarrow,\ddagger}$) are all similar:

$$\text{with} \quad \Delta G_{\downarrow,\ddagger}/kJ\ mol^{-1} = 38 \quad .. \quad ..(5)$$
$$\sigma/\ J\ mol^{-1} = 3,$$

where $\sigma$ is the standard deviation. These figures correspond to

$$5 \times 10^{-6} < k_{\downarrow,\ddagger}/m\ s^{-1} < 10^{-4} \quad .. \quad (6)$$

The rate of the interfacial transfer reaction in the 'uphill' direction is slower; it can be calculated from the partition coefficient and equations 5 or 6.

It is unlikely that as more results become available all of them will be found to fit the simple pattern presented here, however for the meantime it may be better to use equations 4 and 5 rather than assume that there are no barriers to interfacial transfer.

In these studies isopropyl myristate was used as a non-aqueous phase because it has been suggested that it is a good model compound for skin lipids by Poulsen et al (1968). Similarly the esters of nicotinic acid were studied because their diffusion through the skin can be followed *in vivo* (Hadgraft et al 1972). The size of the interfacial rate constants found in this work means that if similar values are found in percutaneous absorption, then the interfacial transfer is unlikely to be the rate determining process. In general, however, the size of the free energy barriers found suggests that transport in biological systems may be partly controlled by the kinetics of interfacial transfer reactions.

*Acknowledgements*
We thank Professor Stanley Bruckenstein for a helpful and stimulating conversation, the S.R.C. for a CASE studentship for J.H., Glaxo for financial support and for a sample of [$^3$H]betamethasone-17-valerate, and Mr James Burke for his results on the MBC/IPM system.

REFERENCES

Albery, W. J., Burke, J. F., Leffler, E. B., Hadgraft, J. (1976) J. Chem. Soc., Faraday Trans.: I, 72: 1618–1626

Albery, W. J., Couper, A. M., Hadgraft, J., Ryan, C. (1974) Ibid. I, 70: 1124–1131

Albery, W. J., Greenwood, A. R., Kibble, R. F. (1967) Trans. Faraday Soc. 63: 360–368

Hadgraft, J., Hadgraft, J. W., Sarkany, I. (1972) Br. J. Dermatol. 87: 30–36

Katz, M., Poulsen, B. J. (1971) in: Brodie, B. B. and Gillette, J. (eds) Handbook of Experimental Pharmacology, Vol. 28, Springer Berlin

Levich, V. G. (1962) Physicochemical Hydrodynamics, Englewood Cliffs, New Jersey: Prentice Hall, p. 69

Marcus, R. A. (1963) J. Phys. Chem. 67: 853–857

Michaels, A. S., Chandrasekaran, S. K., Shaw, J. E. (1975) A.I.Ch.E. 21: 985–996

Poulsen, B. J., Young, E., Coquilla, V., Katz, M. (1968) J. Pharm. Sci. 57: 928–933

Riddiford, A. C. (1966) Adv. Electrochemistry and Electrochemical Engng 4: 47–116

Stokes, R. H. (1950) J. Am. Chem. Soc. 72: 763–767

Vogel, A. I. (1951) A Textbook of Practical Organic Chemistry Longmans, Green & Co. London