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Release of non-electrolytes from liposomes

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Equations have been derived to describe the release of non-electrolytes from liposomal suspensions. The effects of simple physicochemical parameters are shown and the way in which slow interfacial kinetics may dominate release is predicted.

In recent years there have been many reports in the literature concerning the potential of liposomes as model biological membrane systems and as possible drug delivery devices (e.g. Tien 1974; Juliano 1981). However, little attention appears to have focussed on the location of the rate-limiting step in non-electrolyte permeation from phospholipid vesicles. Diamond & Katz (1974) have correctly identified that the resistance to permeation is the sum of both the diffusional resistance offered by the membrane interior and the barriers present at the interfacial regions. The structure of the bilayer is such that different physicochemical parameters relate to the transport of solute molecules across the interfacial and interior components.

The rate of transport through the central hydrophobic core of the bilayer is a function of the thickness (h) of this region of the membrane and the solute diffusion coefficient (D_m). Movement across the interface between the membrane and its local aqueous environment may be described by a heterogenerous rate constant (k_I/ms^{-1}) (Albery et al 1976). The resistances to these two transport processes are directly related to their reciprocal permeabilities, viz

$$\frac{h}{KD_m} : \frac{1}{k_I}$$

where K is the membrane-water partition coefficient of the transferring solute.

The objective of this paper is to draw attention to the relative magnitude of these two terms and to show how the relative contributions to membrane permeation relate to and control the overall efflux of solute molecules from liposomes.

THEORY

Before considering the release from a complex structure like a liposome, it is instructive to examine the mathematics of release from a simple sphere containing no phase boundaries. The differential equation describing diffusion out of a sphere is given by Fick's second law of diffusion expressed in spherical co-ordinates (Carslaw & Jaeger 1959).

$$\frac{\partial c}{\partial t} = D\,\frac{\partial^2 c}{\partial r^2} + \frac{2\partial c}{r\partial r} \qquad (1)$$

where c is the solute concentration, t is the time, r is the radial distance from the centre of the sphere and D is the solute diffusion coefficient within the sphere.

The solution of this differential equation is dependent on the appropriate boundary conditions. For simplicity sink conditions are considered in which the surface concentration of the solute is zero. The following conditions therefore apply.

1. At $t = 0$, the solute concentration in the sphere is uniform and equal to c_0:

$$t = 0,\ c = c_0 \qquad (2)$$

2. Due to the imposed sink conditions, at the surface of the sphere the concentration of solute is zero:

$$r = r_0,\ c = 0 \qquad (3)$$

3. There is no reservoir of solute at the centre of the sphere:

$$r = 0,\ \left(\frac{\partial c}{\partial r}\right)_{r=0} = 0 \qquad (4)$$

Solving equation 1 with these boundary conditions gives the following expression for the amount of solute (M_t) released from the sphere at time t (Crank 1956; Guy et al 1982)

$$M_t = M_\infty\left(1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp(-n^2\pi^2 Dt/r_o^2)\right) \qquad (5)$$

where M_∞ is the total amount of solute contained in the sphere at time $t = 0$ (ie $M_\infty = \frac{1}{3}Ac_o r_o$ where A is the surface area of the sphere).

Simplifications to this complex expression are possible by considering release at short and long time

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periods (Baker & Lonsdale 1974; Guy et al 1982). At short times

$$M_t = 3M_\infty \frac{2D^{1/2}t}{\pi^{1/2}r_o} - \frac{Dt}{r_o^2} \quad (6)$$

which reduces further at even shorter times to

$$M_t = 6M_\infty D^{1/2}t^{1/2}\pi^{-1/2}r_o^{-1} \quad (7)$$

The conditions for which these two expressions are accurate representations of solute release have been discussed elsewhere (Guy et al 1982). The square root of time dependence is the same as that for release from a plane sheet (Hadgraft 1979); at very small times solutes are released from a sphere which behaves as though its surface is not curved.

At long periods of time, equation 5 may be simplified to give a characteristic exponential expression. For large values of t, the series in equation 5 converges so rapidly that only the first term need be considered.

$$M_t = M_\infty \left[1 - \frac{6}{\pi^2} \exp\left(-\frac{\pi^2 Dt}{r_o^2}\right)\right] \quad (8)$$

Application to multilamellar liposomes

For multilamellar liposomes, which may be idealized as spheres, it is not realistic to consider the sphere to be homogeneous. A better representation would be for the solute molecules to diffuse *and* transport across a series of interfacial kinetic barriers. In a previous publication (Albery & Hadgraft 1979) it was shown how transfer across a series of kinetic barriers could be modelled mathematically for percutaneous absorption. Instead of a simple translational diffusion coefficient, D_m, an overall transport coefficient $\bar{P}$ can be defined.

$$\frac{1}{\bar{P}} = \frac{1}{D_m} + \frac{n}{k_I l} \quad (9)$$

where n, in this case, is the number of constituent lamellae of the liposome of radius l. The interfacial transfer process is characterized by the rate constant k_I which is related to the kinetic term for the corresponding reverse process (k_{-I}) by the membrane-aqueous phase partition coefficient K.

$$C_{bilayer} \underset{k_{-I}}{\overset{k_I}{\rightleftharpoons}} C_{aqueous} \quad K = \frac{k_{-I}}{k_I}$$

The magnitude of k_I has been determined in a number of recent studies. For example, the rate of transfer of the simple non-electrolyte methyl nicotinate has been measured across different water-lipid interfaces and the relevant interfacial rate constants are given in Table 1.

Table 1. Interfacial transfer rate constants for a simple non-electrolyte (methyl nicotinate) crossing various water-lipid boundaries.

Lipid	T/°C	k_I/mMs^{-1}	k_{-I}/mMs^{-1}	Ref.
Nonane	25	42	30	Guy et al (1982)
Dodecane	20	22	15	,,
Dodecane	32	30	22	,,
Dodecane	37	73	54	,,
Pentadecane	25	40	29	,,
Isopropyl myristate	25	10	22	Fleming et al (1982)
Isopropyl myristate	30	16	38	,,
Isopropyl myristate	37	34	86	,,
DPPC*	37	0·03–0·18	2·5–1·8	Guy & Fleming (1981)

* Dipalmitoylphosphatidylcholine.

DISCUSSION

The permeability of a multilamellar liposome is described by equation 9; the relative importance of the two terms on the right hand side of this equation can be assessed by selecting values for n and l to cover a range of liposome sizes. For the purposes of illustration, multilamellar liposomes of between 0·1 and 1·0 μm radius are assumed having between 5 and 25 lamellae. From Table 1 it can be seen that k_I values are in the range 10^{-5} to 10^{-8} m s^{-1}. It is thus possible to calculate that for a simple non-electrolyte molecule the $n/k_I l$ term in equation 9 lies in the range 5×10^{11} to $2{\cdot}5 \times 10^{16}$ s m^{-2}. Under these circumstances, for simple translational diffusion to be a comparable transport limiting step, D_m has to lie in the range 2×10^{-12} to 4×10^{-17} m^2 s^{-1}. For methyl nicotinate the diffusion coefficient in isopropyl myristate is $5{\cdot}1 \times 10^{-10}$ m^2 s^{-1} at 37 °C

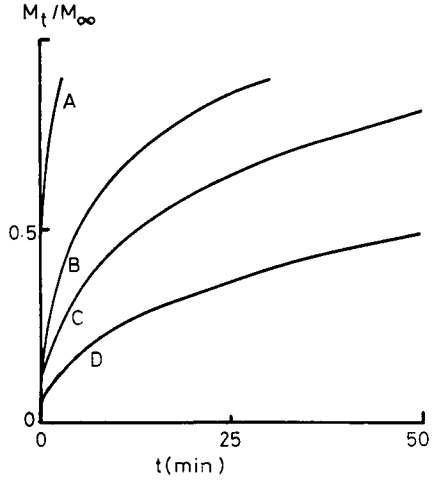

FIG. 1. Release profiles for different $\bar{P}$ and l values calculated using eqn 6 (short times) A, $\bar{P} = 10^{-15}$ m^2 s^{-1}, l = 1 μm; B, $\bar{P} = 10^{-16}$ m^2 s^{-1}, l = 1 μm; C, $\bar{P} = 10^{-17}$, m^2 s^{-1}, l = 0·5 μm; D, $\bar{P} = 10^{-17}$ m^2 s^{-1}, l = 1·0 μm.

(Albery et al 1976) and between 2–17 × 10^{-12} m^2 s^{-1} in dipalmitoylphosphatidylcholine (Guy & Fleming 1981). In both instances the values are greater than the limits for which interfacial kinetics become at least partially rate-limiting. Transport from liposomes may therefore be more realistically described by consideration of a series of interfacial kinetic barriers rather than a purely passive diffusion process.

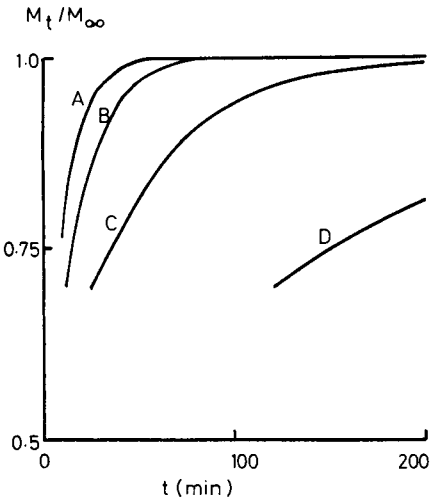

FIG. 2. Release profiles for different $\bar{P}$ and l values calculated using eqn 8 (long times) A, $\bar{P} = 10^{-17}$ m^2 s^{-1}, l = 0·25 μm; B, $\bar{P} = 10^{-16}$ m^2 s^{-1}, l = 1 μm; C, $\bar{P} = 10^{1-17}$ m^2 s^{-1}, l = 0·5 μm; D, $\bar{P} = 10^{-17}$ m^2 s^{-1}, l = 1 μm.

Figs 1 and 2 show theoretical release profiles from multilamellar liposomes at short and long times respectively for various $\bar{P}$ values. These are obtained by using equations 6 and 8 where the diffusion coefficient D has been replaced by the overall transport coefficient $\bar{P}$ (defined in eqn 9) and the radius of the sphere r_0 by the liposome radius l. The values of the liposome radii chosen for each $\bar{P}$ are indicated on the Figs. For $\bar{P}$ greater than 10^{-16} m^2 s^{-1} the solute is released rapidly. It is apparent from the different profiles that the liposome radius is an important factor in determining the rate of release.

Comparison of these theoretical profiles with experimental release studies by earlier workers (e.g. Bangham et al 1967) shows that the diffusional time periods are of a very similar order of magnitude. This suggests that the approach given in this paper is a plausible representation of the transport of solutes from liposomes and that further investigation of the independent determination of interfacial transfer kinetics is warranted.

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