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Measurement of diffusion rates across fragile polymeric films

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In recent years there has been an increase in the interest in the administration of drugs via the transdermal route. Transdermal devices have been developed to control accurately the release of the active ingredient to the skin surface. These devices typically contain the drug dispersed within a thin polymeric film. Consequently, it is useful to know the diffusional characteristics of a drug across such films.

Polymeric films that are used as adhesives in transdermal drug delivery are thin (of the order of 50 μm) and have no inherent strength. If they are mounted in conventional diffusion cells they distort under the stirring conditions required to minimise the formation of stagnant diffusion layers. Novel techniques are therefore required to determine the diffusion of drugs through such membranes. The diffusional characteristics are required in order to optimise the formulation and deliver the drug to the skin surface at the correct rate. In this paper we have investigated the transport of glyceryl trinitrate (GTN) across an adhesive polyisobutylene film containing different concentrations of miglyol.

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The rotating diffusion cell (Albery et al., 1976) can be used to study diffusion processes under well controlled hydrodynamic conditions. However, in previous experiments with this system the membranes used have been sufficiently strong to withstand small hydrostatic pressure differences. The adhesive films described above are not strong enough to support any hydrostatic pressure difference. In order to circumvent this problem an inert backing membrane was investigated.

Transfer of drug from the donor to the receptor compartment in the rotating diffusion cell can be described by a simple flux equation,

$$J = kAc_d \quad (1)$$

where J is the flux across the membrane of surface area A, c_d is the concentration of the drug in the donor compartment, and k is a first order rate constant which can be split into a number of diffusional resistances. Since diffusion in polymeric systems is slower than in simple solutions it is assumed that interfacial kinetics will not be significant. In the subsequent analysis it is also assumed that the rate of transfer across the aqueous–polymer interface is rapid compared to any of the other steps. If an inert backing membrane is fixed to the adhesive film the following diffusional steps are possible: [a] stagnant diffusion layer in

donor compartment (Z_D); [b] adhesive film, thickness l_p; [c] backing membrane, thickness l_m; [d] stagnant diffusion layer in receptor compartment (Z_D).

In the experiments the backing membrane was a 1.0 μm cellulose nitrate membrane, porosity α, filled with water. The resistances can be described mathematically where D_a and D_p are the diffusion

$$\frac{l}{k} = \frac{Z_D}{D_a} + \frac{l_p}{KD_p} + \frac{l_m}{\alpha D_a} + \frac{Z_D}{D_a} \quad (2)$$

coefficients of the drug in water and polymer respectively. K is the partition coefficient of the drug between the adhesive film and water.

Glyceryl trinitrate (GTN) was used as the permeant. A 10% w/w lactose absorbate was dissolved in water at 50°C overnight and stirred until clear. The GTN content, determined by HPLC was found to be 5 mM.

The aqueous diffusion coefficient of GTN was determined in the following way. A 1.0 μm pore size cellulose nitrate filter (Whatman) was placed in the rotating diffusion cell (available area 3.14 cm^2) and washed with water to remove any surfactants present. It was then dried and treated with dimethyldichlorosilane to render it hydrophobic. Isopropyl myristate (Croda Chemicals) was then added dropwise until the membrane was fully saturated. Any excess was carefully removed with a tissue.

40 cm^3 of 1 mM GTN were placed in the donor compartment and 60 cm^3 of water in the receptor compartment. The water in the receptor phase was pumped continuously (1 ml/min^{-1}) through a flow through cell in an LKB spectrophotometer. The change in absorbance with time was monitored at 220 nm. The apparatus was thermostatted at 32°C and experiments were given a preequilibration time of 30 min prior to data collection. The values for k were determined at 4 rotation speeds in duplicate for each of 3 impregnated membranes.

When transfer across the adhesive film was measured, the following approach was adopted. The adhesive film was supplied sandwiched between two supports; the backing membrane and release liner of a transdermal system. The release liner was carefully removed and the adhesive membrane attached to the face of the rotating diffusion cell. A thin sheet of polyvinyl acetate (PVA) was applied to the inward facing side of the adhesive membrane and left in contact overnight. The metallic backing membrane was then removed carefully and 1.0 μm cellulose nitrate membrane filter placed on the outer surface of the adhesive film and held in place by the outer casing of the rotating diffusion cell. The PVA is then dissolved away using warm water.

GTN (5 mM) prethermostatted to 32°C was added to the donor compartment and the flux of GTN determined at the highest rotation speed (4.7 Hz) as described previously. The experiments were conducted in triplicate.

The first experiments with the IPM impregnated membrane were conducted at 4 rotation speeds (W). k^{-1} should be a linear function of $W^{-\frac{1}{2}}$ as predicted by the Levich equation. The gradients (G) in the experimental design used are related to the diffusion coefficient

$$G = 2 \times 0.643\ v^{1/6} D_a^{-2/3} \quad (3)$$

where v is the kinematic viscosity of water.

From the experiments conducted, G was found to be 3.2 $(\pm 0.5) \times 10^5 s^{\frac{1}{2}} m^{-1}$ which corresponds to D_a of $8.9 \times 10^{-10} m^2 s^{-1}$.

The physical characteristics of the cellulose nitrate membranes used are well defined: $\alpha = 0.8$, $l_m = 150$ μm. Thus in Eqn. 2 it is possible to calculate the first, third and fourth terms since the only diffusional steps are those of the GTN through water.

The second series of experiments provide values of k for the adhesive films used. It is possible to subtract from these the contributions from $l_m/\alpha D_a$ and $2Z_D/D_a$. This leaves l_p/KD_p.

The partition coefficient of GTN between the adhesive and water has been determined as 10.85 and its thickness, lp, is 50 μm. Consequently it is possible to calculate the values of the diffusion coefficient of GTN in the adhesive. These are provided in Table 1. The presence of miglyol in the adhesive increases the rate of diffusion by approximately a factor of two. It is interesting to note that the values of D are comparable to those

TABLE 1

Rate constants and diffusion coefficients through the different adhesive films

Miglyol content (% w/w)	k (nm/s)	D_p (m^2/s)
0	11.4 (±3.6)	5.2×10^{-14}
2	22.4 (±5.7)	1.0×10^{-13}
2.2	19.8 (±3.9)	9.1×10^{-14}
3.8	24.8 (±7.8)	1.1×10^{-13}
4.0	25.5 (±5.9)	1.5×10^{-13}

of a similarly sized molecule diffusing through the stratum corneum. Experiments of this type can be used to optimise the adhesives used in transdermal delivery systems. They can also be employed to measure diffusion coefficients through fragile membranes which cannot be supported in conventional diffusion apparatus.

Reference

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