This gives too low values for apparent affinity.

The present data on "receptor" affinities support the main conclusion reached by Kutter & others (1970) that lipophilic analgesics more easily cross the blood-brain barrier and get access to the biophase. Thus the extreme potency of etorphine (1000–10 000 × morphine) can to a large extent be explained by this factor.

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Department of Medical Pharmacology,
Box 573, 751 23, Uppsala, Sweden.

L. TERENIUS

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Permeability of films of ethyl cellulose and PEG to caffeine

Film coating by polymers is a method for producing sustained-release preparations (Munden, DeKay & Banker, 1964; Nessel, DeKay & Banker, 1964; Kleber, Nash & Lee, 1964; Lappas & McKeehan, 1965). A factor determining the suitability of a film for development of a sustained-release preparation of a drug is the permeability of the film to the drug. Other considerations are the physical properties, stability and toxicity of the film material. Providing drug dissolution is not the rate controlling factor, the release rate of medicinal substances from polymers which are soluble in the digestive system is determined both by the permeability of the film and the rate of dissolution of the polymer (Stempel, 1966), while permeability is the only factor governing the rate of release through a polymer which is insoluble in the digestive system. An added advantage of the insoluble type of film is that it is not absorbed by the body.

Ethyl cellulose is an example of a non-toxic polymer which is insoluble in the digestive system. Experiments in which the permeability of an ethyl cellulose film was increased by the addition of cellulosic polymers were carried out by Fites, Banker & Smolen (1970), Coletta & Rubin (1964) and Shah & Sheth (1972). We have examined the effect of using a water-soluble polyethylene glycol of high molecular weight (4000) as additive.

Membranes were prepared by the techniques of Munden, DeKay & Banker (1964)

and Kanig & Goodman (1962). 10% solutions (solvent chloroform) of the mixed solids were used. Films were made containing 0, 1, 2, 4 and 5% PEG (% w/v) with respectively 10, 9, 8, 6 and 5% ethylcellulose (% w/v). All the films except that containing ethyl cellulose alone were prepared by mercury substrate; for the latter, glass substrate was used. The thickness of each film was measured in ten different places by a Tesamaster Micrometer (Tesa, Switzerland). The figures given are the averages of the ten measurements.

Experiments on the determination of the rate of diffusion of the caffeine through films were carried out as follows. The film was placed between the two halves of a diffusion cell each of which holds a volume of 50 ml of liquid. The effective area of the film was constant in all this work and was 12·55 cm^2. One compartment of the cell contained distilled water and the other the drug solution, both previously warmed to 37°. Stirring of the solutions in the cells was performed by means of a polystaltic pump (Buchler, Model 2–6100) operated at a flow rate of 20 ml min^{-1}. Temperature was controlled at 37°. At suitable intervals, the concentration of caffeine which had diffused into the water through the film was measured spectrophotometrically at 273 nm, using a 10 mm flow cell. Measurements were continued for 6 to 7 h and experiments were quadruplicated.

Aqueous extracts of the membranes containing 50% PEG (area 12·55 cm^2 and thickness 80×10^{-4} cm) yielded after 15 min 109 mg of solid (theoretical PEG content 106 mg) with infrared spectra identical to that of the original PEG.

The effects of film thickness, caffeine concentration and film composition on the rate of penetration of caffeine were studied. In all cases, the concentration of caffeine passing through the film increased linearly in the water compartment as a function of time over the whole measurement period. This was in accordance with zero-order transfer, characteristic of steady-state diffusion through the membranes.

For the effect of membrane thickness, ethyl cellulose films containing 40% PEG were prepared measuring $26{\cdot}8 \times 10^{-4}$ (s.d. 1·27, c.v. 4·74%)*, $32{\cdot}7 \times 10^{-4}$ (s.d. 1·15, c.v. 2·39%) and $48{\cdot}0 \times 10^{-4}$ cm (s.d. 1·47, c.v. 2·59%) in thickness. The transfer rate

Table 1. *Transfer rate of caffeine as a function of film thickness, caffeine concentration and PEG concentration in film.*

Film thickness cm × 10^4	Rate of transfer mol s^{-1} × 10^9	Rate of transfer/ reciprocal thickness of film mol cm s^{-1} × 10^7
26·8	4·00	1·07
32·7	3·32	1·08
48·0	2·20	1·06
Concentration of of caffeine mol × 10^2 $litre^{-1}$		**Rate of transfer/ concentration of caffeine litre s^{-1} × 10^7**
1·03	0·52	0·505
2·06	1·06	0·509
4·12	2·10	0·509
Concentration of PEG in the film % w/w		**Rate of transfer/ concentration of PEG mol s^{-1}% × 10^9**
0	0·123	—
10	1·15	0·115
20	2·06	0·103
40	4·45	0·111
50	5·40	0·108

* s.d. = standard deviation; c.v. = coefficient of variation.

increased linearly with reciprocal of thickness (Table 1) at an initial caffeine concentration of $1{\cdot}44 \times 10^{-2}$M in accordance with the equation

$$\frac{DSc}{xV}$$

where D is the diffusion coefficient of the penetrant ($cm^2\ s^{-1}$), S is the surface area (cm^2), x the thickness of the membrane (cm), c the concentration of the solution in contact with the membrane surface and V the volume of solution in the half-cell.

The effect of caffeine concentration from 10^{-2} to 4×10^{-2}M on the diffusion rate is shown in Table 1. Films of the same composition as in the previous experiment were used, the average thickness being $26{\cdot}8.10^{-4}$ cm. There is again a linear relation, in accordance with the equation.

Film composition effects were studied using ethyl cellulose films containing 0, 10, 20, 40 and 50% PEG. The average thickness of the membranes used in each of the experiments was $41x10^{-4}$ cm (s.d. 1·49, c.v. 3·85%) and the caffeine concentration was $1{\cdot}44 \times 10^{-2}$M. The diffusion rate increased linearly with PEG concentration in the membrane (Table 1).

These experiments demonstrate that it is possible to increase the permeability of an ethyl cellulose film to caffeine by the addition of a hydrophilic polymer such as PEG. The permeability change is readily effected by a simple change in the proportion of the PEG and is reproducible. The rate of transfer of caffeine is directly proportional to the PEG concentration. The enhanced permeability could be due to increased hydrophilicity of the membrane, if the water-soluble polymer were bound within the membrane, or to increased porosity, if it were to be dissolved out by the water. No experimental evidence has been offered by previous workers (Shah & Sheth, 1972) to distinguish between these mechanisms in the case of hydrophilic cellulose additives.

In the present work, the operating mechanism is in fact increase in porosity. This was shown experimentally by analysis of the water in blank runs. On evaporation, a dry extract was obtained, the weight of which corresponded to the PEG content of the film. The infrared spectra of the extracts were identical to that of pure PEG. It is thought that solution of the PEG was rapid, since the diffusion rate remained constant in each experiment. It is also noteworthy that caffeine transfer through the membranes observed Fick's Law under steady-state conditions for the experimental systems and conditions studied, behaving as a model system for membrane-controlled drug release.

Department of Pharmacy,
School of Pharmacy,
Hebrew University of Jerusalem,
Jerusalem,
Israel.

M. DONBROW
M. FRIEDMAN

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