J. Pharm. Pharmac., 1975, 27, 633–646 *Received December 5, 1974*

Enhancement of permeability of ethyl cellulose films for drug penetration

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Permeability constants of salicylic acid, caffeine and benzoic acid have been measured at 37° for heterogeneous films of ethyl cellulose containing up to 50% PEG 4000, the latter component undergoing leaching out. For the first two compounds, steady state constants were independent of film thickness and solute concentration but increased linearly and sharply with PEG content and were reproducible. The films were impermeable to NaOH and permeation rates were independent of receiver compartment pH. Solubility coefficients and diffusion coefficients of the substances in the films were measured using sorption and/or time lag methods and were low as compared with polyethylene films. High solubility seemed to be associated with the presence of a free activated hydrogen, shown by sorption studies on other substances. From the evidence, it appeared that mass transfer was controlled by the solubility diffusion process in the ethyl cellulose of the membranes with all three substances. Enhancement of permeability by PEG thus seemed due to increased porosity, equivalent to reduction in the effective thickness of the matrix, which nevertheless retained its barrier properties. Enhancement coefficients calculated from the slopes of PEG concentration plots may be useful for predicting the increased mass transfer of drugs through such membranes and could enable the porosity and thickness factors to be balanced against each other for formulation of coated products.

The use of soluble and insoluble polymer films as coatings for obtaining controlled release of drugs was considered briefly in an introductory report in which it was demonstrated that the permeability of an ethyl cellulose membrane to caffeine could be altered fivefold by addition of a leachable polar substance to the membrane (Donbrow & Friedman, 1974).

Knowledge of the mechanism of penetration operative in these membranes could enable prediction of the types of drug for which such polymer films might be used as coatings and of their specific permeation properties towards each drug. If the permeation occurred essentially by transfer through a capillary network, the films should be suitable for a wide variety of drugs having molecular dimensions measuring less than the diameter of the channels. This would not be the case if the rate were controlled by diffusion through the matrix, since permeability would then be a function mainly of the solubility of the drug in the film. Permeation might also be influenced by interaction of the polar additive with the drug to form a complex or by plasticizing effects of the additive.

In the present work, the permeation studies have been extended to two aromatic acids and other substances, with the object of elucidating the permeation mechanism of this new type of membrane. For this purpose, the partition coefficients of these substances towards the film material were required, and have been measured directly and also from the permeation rates.

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MATERIALS AND METHODS

Materials

Ethyl cellulose, N-Type, had an ethoxyl content of 47·5 to 49·0% and the viscosity of a 5% w/w solution in toluene–ethanol 80:20 (w/w) was 100 c.p.s. (Hercules Incorporated, Delaware, U.S.A.). Polyethylene glycol (PEG) 4000, benzoic acid, phenol, sodium benzoate and *p*-hydroxybenzoic acid were from BDH Ltd., Poole, U.K., caffeine, salicylic acid and sodium salicylate were from Merck, Darmstadt, Germany, and all were of B.P., B.P.C., U.S.P. or reagent grade.

Preparation of films

Polymeric films containing different proportions of ethyl cellulose and PEG were cast using the techniques of Kanig & Goodman (1962) and Munden, De Kay & Banker (1964). Chloroformic solutions containing the requisite weights of the two solids were poured at a concentration of 10% w/v of total solids. Glass substrate was used for the ethyl cellulose films and mercury substrate for films containing 10, 20, 30, 40 and 50% w/w PEG, the composite films being difficult to remove from glass without other treatment. Slight differences in permeability using different substrates or different faces of the films were noted, but they fell within the range of variation of the permeation rates observed in the film thickness and drug concentration experiments.

Determination of film thickness

The thickness of each dry film was measured in ten different places by means of a Tesa master micrometer (Tesa, Switzerland). The figures given are the averages of the ten measurements.

Permeation studies

The permeation rates through the films were determined using dissembling diffusion cells in which the film was clamped centrally between the compartments, forming a hermetic seal between them. Two sizes of chamber were found convenient, holding respectively volumes of 50 or 25 ml of liquid in each compartment, the effective area of the film, however, being 12·55 cm^2 in all this work. The exact volumes of distilled water and drug solution, both previously warmed to 37°, were added to the respective compartments and both were stirred from the moment addition was completed, by utilizing two channels of a multi-channel peristaltic pump (Buchler, Model 2–6100) at flow rates of 20 ml min^{-1}. The sink solution flow was monitored spectrophotometrically (Unicam Model SP 1805) by use of a 10 mm flow cell in the channel, and the diffusion cell was maintained thermostatically at 37°. Experiments were quadruplicated and measurements continued for 24 h in the case of ethyl cellulose films and 6 to 7 h for the films containing PEG. The drugs were measured at the following wavelengths (nm): salicylic acid, 296, benzoic acid, 228, sodium salicylate, 296, sodium benzoate, 224 and caffeine, 273. The permeation of sodium hydroxide was studied conductimetrically (Radiometer Model CDM3 Conductivity Meter). Under the conditions used, the final concentrations of the sink solutions were very low and those of the permeating drug solutions essentially unchanged, so that the concentration gradient was virtually constant.

Drug concentration

The effect of drug concentration on the permeation rate was studied on caffeine and salicylic acid. In the case of caffeine, ethyl cellulose films containing 50% of PEG were used, their thickness being $20{\cdot}5 \times 10^{-4}$ cm (s.d. 1·38, c.v. 5·74%) and the concentration of caffeine ranging from 10^{-2} to 4×10^{-2}M. The study with salicylic acid was carried out on ethyl cellulose films of 40% PEG content and thickness 47×10^{-4} cm (s.d. 1·41, c.v. 3·51%), the concentration of salicylic acid ranging from 10^{-3} to 9×10^{-3}M.

Film thickness

The effect of film thickness on permeability was studied on caffeine and salicylic acid. Experiments with caffeine were carried out using ethyl cellulose films containing 50% PEG, whose thicknesses were $59{\cdot}2 \times 10^{-4}$ cm (s.d. 1·28, c.v. 2·4%), $20{\cdot}6 \times 10^{-4}$ cm (s.d. 1·56, c.v. 6·3%) and $15{\cdot}9 \times 10^{-4}$ cm (s.d. 0·82, c.v. 5·4%). The initial caffeine concentration was $1{\cdot}44 \times 10^{-2}$ M.

For salicylic acid, films containing 40% PEG were of thicknesses $50{\cdot}4 \times 10^{-4}$ cm (s.d. 1·00, c.v. 4·4%), $25{\cdot}5 \times 10^{-4}$ cm (s.d. 1·12, c.v. 3·0%) and $15{\cdot}8 \times 10^{-4}$ cm (s.d. 1·61, c.v. 8·4%). The initial concentration of salicylic acid was $7{\cdot}24 \times 10^{-3}$ M. Films containing 50% PEG were of thicknesses $53{\cdot}8 \times 10^{-4}$ cm (s.d. 1·32, c.v. 2·4%), $29{\cdot}0 \times 10^{-4}$ cm (s.d. 1·61, c.v. 4·4%) and $18{\cdot}7 \times 10^{-4}$ cm (s.d. 1·24, c.v. 2·9%), and were used with an initial salicylic acid concentration of $1{\cdot}44 \times 10^{-2}$ M.

pH variation

The effect of pH on the permeation properties of films containing 50% PEG and of thickness $27{\cdot}4 \times 10^{-4}$ cm (s.d. 1·76, c.v. 5·4%) was measured using concentrations of $4{\cdot}12 \times 10^{-2}$ M caffeine and $1{\cdot}44 \times 10^{-2}$ M salicylic acid at pH values between 2 and 14, obtained by addition of HCl or NaOH to the sink solution only.

Sorption studies

Solutions of benzoic acid, salicylic acid, caffeine, phenol, *p*-hydroxybenzoic acid, sodium salicylate, sodium benzoate and sodium *p*-hydroxybenzoate were used at three concentrations, 0·5, 1·0 and $1{\cdot}5 \times 10^{-2}$ M. Samples of ethyl cellulose films weighing 1·0, 1·5 and 2·0 g were added to 100 ml of the test solution and shaken in a water bath at 37°; with benzoic acid and salicylic acid, the experiments were continued to final equilibrium, i.e. until sorption by the film was complete, as shown by the absence of any further decrease in the drug concentration in solution. There were no changes in drug concentration in the absence of the polymer films. The sorption of caffeine and sodium salicylate on ethyl cellulose film was negligible over 24 h and therefore the results of the kinetic experiments on the permeability of caffeine through an ethyl cellulose film were used for the calculation of the solubility constant of caffeine.

RESULTS AND DISCUSSION

The permeation process for linear flow under steady state conditions may be characterized by means of Fick's first law (Jost, 1960). This may be expressed in the form

$$\frac{dQ}{dt} = PA\frac{c_2 - c_1}{x} \quad .. \quad .. \quad .. \quad .. \quad (1)$$

Q is the number of moles of drug penetrating in time t (s) through a surface of area A (cm^2), c_2 and c_1 are the concentration of the drug in the permeating and sink solutions respectively, x is the thickness of the membrane (cm) and P is the permeability constant. P is a measure of the transfer rate of a specific drug from bulk solution on one side of the membrane to bulk solution on the other side, through unit thickness and area of the specific membrane. Where the membrane acts as a barrier, penetration involves solution of the drug within the membrane and, provided that drug diffusion in the aqueous layers on either side of the membrane is not rate limiting, P may be related to D, the diffusion coefficient of the drug within the membrane, and S, the membrane-solution partition coefficient or solubility coefficient by the equation:

$$P = DS \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (2)$$

Though applied originally by Barrer (1939) to gas permeation of polymer membranes, this relation was considered to be generally applicable to barrier diffusion by Higuchi & Higuchi (1960) who developed equations for diffusion through certain types of heterogeneous barriers. Their equations involve a number of simplifying assumptions and are difficult to apply in practice to complex systems. In the present work, the initial approach adopted was to calculate P and D values for each membrane as if homogenous, using the S value for the ethyl cellulose matrix. This enables the dependence of the coefficients upon the membrane composition to be studied. It implies that the PEG component has no influence on the solubility coefficient, a point which will be taken up later.

Under the experimental conditions used, $c_2 \gg c_1$, when integration of equation (1) gives:

$$Q = \frac{PAc_2t}{x} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (3)$$

For a plot of concentration of drug transferred against time, the permeation rate is given by the slope dc/dt in accordance with the equation:

$$\frac{dc}{dt} = \frac{PAc_2}{xV} \quad .. \quad .. \quad .... \quad .. \quad (4)$$

where V is the volume of the sink solution. It follows that

$$P = \frac{\text{slope } xV}{A\,c_2} \quad .. \quad .. \quad .. \quad .. \quad (5)$$

Slopes were calculated by the least squares method from the results of the permeability experiments and as the other parameters of the equation were known, the permeability constants could be calculated. The very low final sink concentrations and the constancy of the P values for salicylic acid at high and low pH values of the sink solution accord with the use of the simplified steady state treatment.

The effect of concentration on drug transfer is summarized in Table 1. The rate of permeation increases linearly with drug concentration in accordance with equation 4 for both caffeine and salicylic acid with membranes containing 40 and 50% PEG over a range of initial concentrations up to $4{\cdot}12 \times 10^{-2}$ M for caffeine and $8{\cdot}4 \times 10^{-3}$ M for salicylic acid.

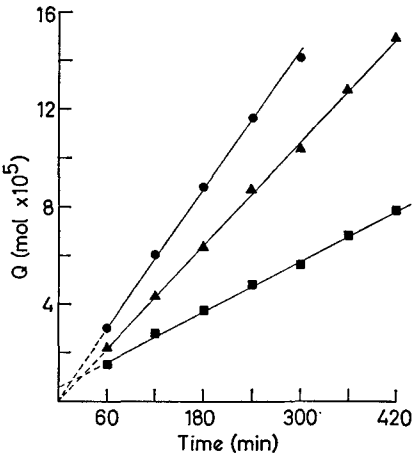

FIG. 1. Effect of film thickness on transfer on caffeine and on time lag. Film thicknesses (cm × 10^4): ● 15·9, ▲ 20·6, ■ 59·2. (Film: ethyl cellulose containing 50% PEG).

Increase of film thickness causes a reduction in the rate of permeation (Fig. 1). There is a linear relation between the permeation rate of both of the above drugs and the reciprocal thickness of the film (Table 1) in accordance with equation (4) for films containing 40 and 50% PEG.

Table 1. *Permeation rates at 37° of salicylic acid and caffeine as a function of film thickness and concentration.*

Effect of film thickness

	% PEG in film	Film thickness cm × 10^4	Rate of permeation mol s^{-1} × 10^7	Rate of permeation/ reciprocal thickness of film mol cm s^{-1} × 10^{10}
		15·8	1·87	2·96
	40	25·4	1·14	2·91
Salicylic acid		50·4	0·62	3·13
		18·7	2·68	5·06
	50	29·0	1·71	5·10
		53·8	0·92	5·03
			mol s^{-1} × 10^9	mol cm s^{-1} × 10^{11}
		15·9	8·54	1·36
Caffeine	50	20·6	6·51	1·34
		59·2	2·36	1·39

Effect of drug concentration

	% PEG in film	Drug concentration mol × 10^3 $litre^{-1}$	Rate of permeation mol s^{-1} × 10^7	Rate of permeation/ concentration of drug litre s^{-1} × 10^5
	50	2·1	0·18	0·86
		4·2	0·34	0·81
Salicylic acid		8·4	0·72	0·86
		2·1	0·13	0·62
	50	4·2	0·27	0·64
		8·4	0·50	0·59
		mol × 10^2 $litre^{-1}$	mol s^{-1} × 10^9	litre s^{-1} × 10^7
		1·03	2·41	2·34
Caffeine	50	2·06	4·69	2·28
		4·12	9·40	2·28

The invariance of the proportionality constants within the limits of experimental error for concentration and thickness is important in establishing that the porous membranes studied in this work show the typical characteristics expected of regular homogenous membranes, as demonstrated by Garrett & Chemburkar (1968) for silastic membranes and Serota, Meyer & Autian (1972) for polyethylene films. This also validates comparisons made of permeability constants determined using a variety of concentrations and thicknesses within the above range later in this work.

It is of interest that many of the permeation graphs show a positive intercept on extrapolation of the linear portion to the time axis. The time lag in achieving a steady state, implied by this behaviour, decreases towards zero as thinner films are used. The effect probably has a twofold cause: (1) the occurrence of two diffusion flows, that of the drug and that of the PEG, during the early stages (2) the "normal" lag period required for building up the concentration gradient of the drug in the membrane to its steady-state value. This conclusion is drawn because the time lag was also related to the PEG content, tending to rise both at high and low PEG concentrations, with a minimum in between.

In a few cases, a negative time lag, such as observed by Serota & others (1972) for polyethylene films permeated by aniline derivatives of low hexane–water partition coefficients, occurred. They were given exclusively by caffeine (q.v. Fig. 1), which also has a low partition coefficient, but there is insufficient evidence to suggest the cause of this unusual phenomenon.

Effect of PEG concentration

The addition of a hydrophilic substance to a hydrophobic polymer film is one of the methods by which the permeability properties of the film can be increased (Colletta & Rubin, 1964; Fites, Banker & Smolen, 1970; Shah & Sheth, 1972). This was demonstrated for caffeine previously with the present type of membrane (Donbrow & Friedman, 1974). In this work it was found that the permeability of an ethyl cellulose film was increased by addition of PEG also for benzoic acid and salicylic acid. The permeability constants were calculated from the permeation rates for caffeine and salicylic acid using equation (5) and are directly proportional to the PEG concentration (Table 2).

Table 2. *Permeability constants of salicylic acid and caffeine as functions of PEG content of ethyl cellulose films.*

	Concentration of PEG in the film % w/w	Permeability constant $cm^2\ s^{-1} \times 10^8$	% M.D.*	Permeability constant/ concn of PEG $cm^2\ s^{-1}\ \% \times 10^8$
Salicylic acid	0	0·27	6·3	—
	10	5·10	5·0	0·51
	20	8·89	1·5	0·44
	30	12·30	4·2	0·41
	40	16·50	4·6	0·41
	50	18·60	5·4	0·37
		$cm^2\ s^{-1} \times 10^{10}$		$cm^2\ s^{-1}\ \% \times 10^{10}$
Caffeine	0	0·44	4·5	—
	10	3·79	7·9	0·38
	20	6·69	3·4	0·33
	30	11·90	6·2	0·40
	40	14·30	1·8	0·36
	50	18·60	4·8	0·37

* M.D. = Maximum deviation (% difference of the most deviant result of four experiments from the mean).

Permeability constants for an ethyl cellulose film containing 50% PEG were measured with the sink solution adjusted to pH values of 2, 9 and 14 and compared with the values for permeation into water of pH 6·5 (see Table 2). The constants, in order of increasing pH, are: For caffeine, 1·90, 1·86, 1·82 and 1·87 $\times 10^{-9}$ cm^2 s^{-1} and for salicylic acid, 1·92, 1·86, 1·84 and 1·83 $\times 10^{-7}$ cm^2 s^{-1}. In neither case are the differences in permeability constant significant.

Several important conclusions may be drawn from these results. Firstly, drug transfer rates through this type of membrane should not be influenced by the pH of the biological fluid bathing a dosage form coated with it, i.e. its permeability should be constant throughout the gastrointestinal tract, provided that the absorption rate is sufficient to maintain the sink at zero concentration.* Moreover, *in vitro* analysis of transfer rates may be performed under zero-order conditions using water in place of simulated gastric or intestinal fluids, the ethyl cellulose polymer being insoluble in the digestive system (see Donbrow & Friedman, 1974).

Secondly, although swelling of the membranes in water or the drug solutions used could not be detected, differential swelling might have been a factor affecting the permeation rate. Most types of cellulosic membrane, with the exception of cellulose acetate, swell in water and even more so in alkalis, in which their permeability to inorganic ions increases greatly (Lane & Riggle, 1959). The failure of wide pH variation to change the permeability constants, together with the linear relation to film thickness and drug concentration shown earlier demonstrate that the film largely maintains its overall permeability characteristics over the range of conditions investigated for the two drugs. Furthermore, the passage of sodium hydroxide and other inorganic electrolytes through these films, could not be detected conductimetrically, nor did the pH change in the second compartment. It seems that channels through which ion diffusion might occur do not approach the diameter of these ions even in alkaline solution. This does not preclude the possiblity of transfer of electrolytes which are soluble in ethyl cellulose.

It may be inferred that these conclusions, drawn from work on the most hydrophilic of the ethyl cellulose—PEG films, hold for films containing lower proportions of PEG.

Solubility coefficients and binding of drugs by the film

For evaluation of diffusion coefficients of the drugs in ethyl cellulose membranes, the solubilities of the drugs in the film material were required. They were measured by sorption, from which the solubility coefficients of salicylic acid and benzoic acid for ethyl cellulose–water were calculated according to the equation:

$$S' = C_s / C_1 \quad .. \quad .. \quad .. \quad .. \quad .. \quad (6)$$

where S' = solubility coefficient, C_s = equilibrium concentration of the drug in the ethyl cellulose phase (moles kg^{-1}), and C_1 = equilibrium concentration of the drug in the aqueous phase (moles litre^{-1}). It is convenient to work with a dimensionless solubility coefficient, S, by converting weights of ethyl cellulose into volumes by means of the density, d, hence obtaining $S = S'/d$. The results of the sorption studies on salicylic acid and benzoic acid are listed in Table 3.

* Should this condition not be observed, transfer through the film might not remain zero order in all parts of the tract. Furthermore, the rate could then change for drugs varying in their degree of ionization in different parts of the tract. However, these are general conditions, being neither restricted to membranes nor likely to apply to sustained-release formulations.

Table 3. *Sorption of salicylic acid and benzoic acid by ethyl cellulose film.*

	Initial solute concentration M × 10^2	Weight of film (g)	Solute bound C_s moles litre^{-1}*	Free solute in solution C_1 moles litre^{-1}	Solubility coefficient S
Salicylic acid	1·5	2·0	0·55	0·0036	152·8
	1·0	1·5	0·47	0·0031	151·6
	0·5	1·0	0·31	0·0021	147·6
Benzoic acid	1·5	2·0	0·41	0·0070	58·6
	1·0	1·5	0·32	0·0055	58·2
	0·5	1·0	0·18	0·0032	56·2

* Film volume.

The solubility coefficient (S) values of salicylic and benzoic acids obtained from the sorption measurements are respectively, 151 ± 2·2 and 58 ± 3·1%. Because of the very low sorption of caffeine, its solubility coefficient in the film was obtained from the kinetic experiments. Characteristic permeation data may be used to calculate the diffusion coefficient in the film by means of the time lag equation of Barrer (1939):

$$D = l^2/6\,L$$

where D is the diffusion coefficient in the film (cm^2 s^{-1}), l is the thickness of the film (cm) and L is the time-lag intercept obtained by extrapolation of the steady-state slope to the time-axis of the permeation plot, converted into seconds. The intercepts obtained from the permeation of caffeine and salicylic acid through ethyl cellulose films of thickness 15·0 × 10^{-4} cm (s.d. 0·82, c.v. 5·4%) were 276 and 329 min, respectively.

Diffusion coefficients in ethyl cellulose obtained by this method were: for caffeine 2·26 × 10^{-11} cm^2 s^{-1}, and for salicylic acid, 1·96 × 10^{-11} cm^2 s^{-1}.

The relation between diffusion coefficient and permeability constant was given in equation (2). Using the D values from the time-lag method together with the previously calculated P values from the permeation experiments, the solubility coefficients were: caffeine, 1·94 and salicylic acid, 142. The salicylic acid value is in good agreement with that obtained by sorption, substantiating the use of Barrer's equation for the present system. The validity of the equation depends on the observance of Fick's Law and Henry's Law throughout the membrane. From the sorption data (Table 3), Henry's Law is observed by salicylic and benzoic acids over the concentration range used; though there is no information for caffeine, its film concentration should be some hundredth of that of salicylic acid and since there is also no evidence of chemical interaction, observance of the law is assumed. Fick's Law observance has been demonstrated for two of the substances using the plasticized ethyl cellulose films.

Since ethyl cellulose has a strong affinity for benzoic and salicylic acids but little for caffeine, it seemed possible that a hydrogen bond interaction might be involved. This was supported by some preliminary results of sorption experiments in which it was found that neither sodium benzoate nor sodium salicylate were taken up in measurable quantities, whereas sodium *p*-hydroxybenzoate, *p*-hydroxybenzoic acid and phenol were taken up rapidly. The last three have in common a hydrogen available for intermolecular H-bonding and though sodium salicylate might have been expected to behave similarly, its failure to do so could be due to preferential intramolecular bonding. However, the evidence is not conclusive and more work is being done.

Diffusion through pure ethyl cellulose film

The diffusion coefficients reported above for caffeine, salicylic acid and benzoic acid in ethyl cellulose are several orders lower than those estimated by Serota & others (1972) for the diffusion of four *N*-alkyl anilines through polyethylene film at 50° ($D \sim 10^{-8}$) and by Gonzales, Nematollahi & others (1967) for various aldehydes and ketones in polyethylene films at 40° ($D \sim 10^{-8}$). However, the latter obtained a much lower D value for benzoic acid at 40° ($5{\cdot}29 \times 10^{-10}$) which was possibly due to the formation of a dimer in the film. It is to be expected that D values would be lower in ethyl cellulose than in polyethylene because of the greater crystallinity of the former (Michaels & Bixler, 1961; Roff & Scott, 1971) and this is the probable reason for the low values obtained here. An alternative explanation is that the coefficients are lowered by hydrogen bonding of the acids with the ethyl cellulose during transfer, but since the same diffusion coefficients are obtained by the two methods, viz. the time lag method and the permeability constant data together with the solubility coefficients, and since the permeability constant showed no dependence on drug concentration, it is likely that the diffusion coefficients correspond to a transfer process through the film when the sites available for possible chemical interaction with the acid molecules are already equilibrated with "sorbed" molecules. Moreover, caffeine, a molecule which from its dimensions might be expected to have a similar diffusion coefficient to salicylic acid monomer, is incapable of forming a hydrogen bond with ethyl cellulose.

Diffusion of the acids in the form of dimers is less likely in ethyl cellulose than in polyethylene, and though caffeine dimerization is a well known phenomenon in water (Guttman & Higuchi, 1957), its extent in ethyl cellulose at 37° is likely to be low.

Mechanism of penetration through the mixed films

Hydrophilic polymers or other inserted substances could increase the permeability of hydrophobic films in several ways (Fig. 2):

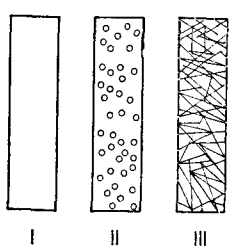

FIG. 2. Structural types of enhanced-permeability membranes. I Homogeneous. II Isolated hydrophilic centres or pores. III Interconnected hydrophilic network or capillaries.

(1) by changing the properties of the film matrix by altering the polymer configuration, changing the proportions of the crystalline and amorphous regions and increasing directly the hydrophilicity of the film. Such films would appear to be homogeneous or at least submicro-heterogeneous;

(2) by introducing increased porosity into the film;

(3) by forming capillaries or a hydrated network giving direct connection between the two sides of the film;

(4) by acting as carriers of penetrants by forming complexes having increased membrane solubility or diffusion coefficient.

These effects need not necessarily occur independendently.

PEG 4000 has been shown to undergo rapid leaching out (Donbrow & Friedman, 1974). Over 95% was recovered from the water within 15 minutes using 35 μm film containing 30% PEG (Donbrow & Samueloff, unpublished data) and release continued subsequently without appreciably affecting the values of the permeability coefficients, the PEG release following diffusion-controlled or first order kinetics (*cf.* Donbrow & Friedman, 1975). Loss of PEG would attenuate the barrier properties of the films by increasing their porosity or capillarity, the void volume being occupied presumably by water. Resultant changes in film volume, thickness, tortuosity or crystallinity do not appear to affect the observance of Fick's Law by thin films (see Table 1).

The low permeability of the 50% PEG films to sodium hydroxide and inorganic salts indicates that the diameter of the pores or capillaries which are present is insufficient to allow passage of these compounds. On the other hand, the larger molecules of the drugs studied in this work penetrated the film readily. However, there were large differences between the ratios of the diffusion coefficients of benzoic acid, salicylic acid and caffeine in water and the ratios of their permeability coefficients through the membranes (see Table 4). For example, the ratio of the diffusion coefficient of salicylic

Table 4. *Ratios of diffusion and permeability constants in water and membranes, based on correction for solubility in membranes.*

	Ratio of diffusion coefficients in water*	Ratio of permeability constants in film		Ratio of apparent diffusion coefficients in film ***
		% PEG in film	Ratio**	
Salicylic acid: caffeine	2·54			
		0	61	0·79
		10	135	1·73
		20	133	1·71
		30	103	1·33
		40	115	1·48
		50	100	1·28
Salicylic acid: benzoic acid	1·45	30	2·55	0·98
Benzoic acid: caffeine	1·75	30	40·5	1·35

* Diffusion coefficients in water: salicylic acid 1·6, benzoic acid 1·1, caffeine, 0·63 $\times$ 10^{-5} cm^2 s^{-1} (Desai, Singh & others, 1966; Schwartz, Simonelli & Higuchi, 1968).
** Calculated from the experimental results in this work.
*** Corrected using the solubility coefficients determined in this work and eqn 2.

acid to that of caffeine in water is 2·54 whereas the ratio of their permeability constants in ethyl cellulose containing 50% PEG is 100. Had the passage been through capillaries filled with water, the ratios should have been of the same order for water and for the "leached" membranes since the compounds were of similar molecular weight and similar dimensions (Renkin, 1954). Moreover, there is no sharp break in the ratio

value as the proportion of PEG is raised, which would have been expected had there been a transition from a homogeneous to a capillary type of transport.

Correction of the ratios of the permeability constants by dividing the P value for each compound by its solubility coefficient with respect to ethyl cellulose—water brings the ratios to values close to but slightly higher than unity (see Table 4). The corrected values in the last column represent the ratios of the apparent diffusion coefficients of the substances in the various films, treated as if the membranes were behaving homogeneously, in accordance with equation 2. This seems to indicate that it is the solubility difference in the matrix which is responsible for the permeability constant of salicylic acid being a hundredfold greater than that of caffeine in all the films.

The significance of the solubility factor is borne out by benzoic acid which has a lower affinity for the film than has salicylic acid. Its permeability constant ratios with respect to salicylic acid and caffeine differ greatly and correction for solubility in the film brings them both near to unity (Table 4).

The large solubility differences between the three substances in the ethyl cellulose matrix enables them to be used for a correlation test. Permeability constants are plotted against solubility coefficients in Fig. 3 for a 30% PEG film and there is clearly a linear relation.

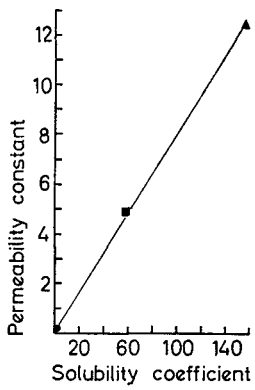

FIG. 3. Relation of permeability constants ($cm^2\ s^{-1} \times 10^8$) of ethyl cellulose films containing 30% PEG to solubility coefficients in ethyl cellulose, ● caffeine, ■ benzoic acid, ▲ salicylic acid.

Consideration may also be given to possible influence of the PEG as a carrier. Although the major part is leached out rapidly, small quantities might have remained and interacted in the film with salicylic and benzoic acids. Since a steady state condition was attained rapidly (under 20 min), it would seem that the PEG content of the film reached its equilibrium value or, if not, did not subsequently affect the permeation rate. Should complex be formed in the film between the PEG and drug, its concentration would be proportional to the PEG concentration in the film, if monomeric, or a power of it, if polymeric with respect to PEG, the reaction being expressed by an equation of the form:

$$n\ \text{Drug} + m\ \text{PEG} \rightleftharpoons \text{Drug}_n - \text{PEG}_m \quad \ldots \quad \ldots \quad \ldots \quad (7)$$

$$K = \frac{[\text{Drug}_n - \text{PEG}_m]}{[\text{PEG}]^m\,[\text{Drug}]^n} \quad \ldots \quad \ldots \quad \ldots \quad \ldots \quad (8)$$

where K is the formation constant. The diffusion rate of this complex would, from Fick's Law, depend upon the concentration gradient of the complex in the film, as well as the usual factors. Now, in the experiments on film thickness (Table 1), the equilibrium concentrations of PEG in the film are proportional to film thickness, other conditions having been held constant, assuming observance of the partition law. Hence the concentration of any such drug–PEG complex formed in the membrane at the drug solution interface should change by a factor of at least 3 to 4, over the thickness range used.* This should have increased the permeation rate by the same factor, had the complex been the predominant carrier mechanism, whereas the experimental results are in accordance with Fick's Law. Nor would a carrier process be in accord with the solubility relation of Fig. 3 unless the stability constants for the PEG interactions were equal, which would seem to be fortuitous.

In this connection, the interactions of PEG have been studied by Higuchi & Lach (1954) and Guttman & Higuchi (1956), who were unable to demonstrate the formation of complexes of PEG 4000 with benzoic or salicylic acids in aqueous solution. In non-aqueous solution, these acids show a stronger tendency to undergo dimerization than to form complexes with 5 to 7% diethyl ether (Forbes & Knight, 1959), hence they would not be expected to interact with PEG at low concentrations in ethyl cellulose.

These facts demonstrate that the permeation rates of these compounds in the mixed films are determined by a true diffusion-partition process in the membrane matrix. The linear relation of permeability constant to PEG 4000 concentration cannot thus be explained by a change over of mechanism to transfer via the pores in the high-porosity films but is due largely to a shortened effective path length resulting from reduced barrier thickness of film. Since the area of matrix available for permeation, measured perpendicularly to the flow direction, is reduced by increase of porosity, and the tortuosity is also thereby increased, the penetrant evidently passes through the pores at a much greater rate than through the ethyl cellulose matrix, the latter process constituting the rate-determining step. This is borne out by the high diffusion coefficients of these drugs in water, of the order of 10^{-5} cm^2 s^{-1}, compared to 10^{-11} cm^2 s^{-1} in the matrix. Theoretical prediction of the permeability constants of the solutes through the films treated as heterogeneous barriers using the equations developed by Higuchi & Higuchi (1960) does not lead to values of the same order as the experimental ones.

The near-linearity of the relation between the permeability constants of the penetrants and the PEG concentrations in the membranes, shown in Table 2, enables the permeability increases to be expressed by enhancement coefficients, E_p, representing the slopes in the equation:

$$P' = P_0 + E_p \cdot C_{PEG} \quad .. \quad .. \quad .. \quad .. \quad (9)$$

where P' = permeability constant of the mixed film, P_0 = permeability constant of pure ethyl cellulose film, C_{PEG} = % w/w PEG used in the film.

Enhancement coefficients obtained thus were $0{\cdot}36 \times 10^{-10}$ for caffeine, *ca* 16×10^{-10} for benzoic acid and 37×10^{-10} for salicylic acid using chloroform as solvent and mercury as substrate. Since these appear to be related to the solubility constants

* It is assumed that the quantity of film is insufficient to alter the drug concentration and that the film is not saturated with complex at the interface.

of the substances in the film matrix, it would be convenient to express the equation so as to show a diffusion coefficient enhancement, which may be done by means of equation (2), giving:

$$D' = D_0 + E_d \cdot C_{PEG} \quad .. \quad .. \quad .. \quad .. \quad (10)$$

where D' = apparent diffusion coefficient through the porous film ($D' = P'/S$); E_d = enhancement coefficient for diffusion through the porous films ($E_d = E_p/S$). By use of this treatment, E_d values of 0·19, 0·28 and 0·25 $\times$ 10^{-10} were obtained for caffeine, benzoic acid and salicylic acid respectively. Although the caffeine value is slightly lower than the others, the values are of the same order, and imply that the enhancement of permeability is a function of the drug solubility constant in the membrane, which is reasonable for the transfer mechanism proposed above. More systems would have to be studied, however, to establish this.

Prediction of E from P_0 values measured on the pure ethyl cellulose membranes did not give the experimental slopes, possibly because of differences in the crystallinity of the matrix due to plasticization by PEG.

Pharmaceutical implications

The use of such equations, together with parameters measured for the transfer of specific drugs through the membranes could open the way to the formulation of coatings of predictable release properties, in which the thickness of the coating and the introduced porosity could be balanced against each other to give the correct release rate for the drug from a sustained—release product.

For pharmaceutical use, equation (9) is the more practical, since the PEG concentration required to give a particular release rate is obtainable directly from it using the experimentally-determined E_p value in conjunction with a P' value obtained using equation (3); in calculating the latter, the appropriate release rate and the formulation parameters, viz. thickness and surface area of coating are used.

The treatment is independent of the mechanism of transfer through the membrane, depending only on the observance of linearities in equations (9) and (3).

However, equation (10) would be advantageous should E_d be constant for a specific mixed membrane system, since once its value is established, only measurement of the solubility coefficient and permeability constant of a drug in the membrane matrix material would be necessary for calculation of E_p and consequent use of equation (9). When $E_p . C_{PEG} \gg P_0$,

$$P' = E_p \cdot C_{PEG} \quad .. \quad .. \quad .. \quad .. \quad (11)$$

Similarly

$$D' = E_d \cdot C_{PEG} \quad .. \quad .. \quad .. \quad .. \quad (12)$$

As an example, for defining release rates to within 5% of a required rate, the simplified equations will account for 95% of the drug permeating when the membrane contains more than 25% PEG in the case of caffeine and above 14% PEG in the case of salicylic acid.

The values of the parameters reported in this work were established for films prepared under closely-controlled conditions. Use of other solvents, substrates or conditions may alter the parameters.

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