# Effect of pH on salicylic acid permeation through ethyl cellulose-PEG 4000 films

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The use of mixtures of ethyl cellulose with PEG 4000 films for increasing the permeation rates of drugs through films has been demonstrated by Donbrow & Friedman (1975). The permeation mechanism was found to be controlled by diffusion through the film polymer matrix and the rate was a function mainly of the solubility of the drug in the polymer. Addition of the leachable hydrophylic component PEG 4000 had the effect of reducing barrier thickness of the ethyl cellulose film but did not change the mechanism, there being no evidence of formation of continuous capillaries, and the films were impermeable to inorganic salts.

This report presents final evidence that EC-PEG membranes act as lipid-like barriers permeable mainly to unchanged drugs, hence permeability coefficients of ionizable drugs are dependent on the pH of the drug solution. In this respect, these mixed porous membranes resemble synthetic homogeneous barrier membranes, which have also been found to be selective in their transfer of ionizable drugs as a function of pH (Garrett & Chemburkar 1968; Nakano 1971; Lovering & Black 1974).

Salicylic acid, was selected as the model ionizable drug. Membranes comprising 80% w/w ethyl cellulose and 20% w/w PEG 4000 were preferred using the same techniques and conditions as previously (Donbrow & Friedman 1975) except that Teflon-coated plates were substituted for glass and mercury substrates.

Rates of drug permeation were measured experimentally utilizing 12·55 $cm^2$ membranes held between the two chambers of a diffusion cell, one of which contained 60 ml quantities of buffered salicylic acid solution ($1 \times 10^{-2}$ M) covering the pH range 0·10 to 7·69. The other compartment contained 60 ml pH 7 aqueous buffer in which the drug was fully ionized, so preventing back permeation. Both solutions were preheated to 37° C and stirred during the experiment by means of a peristaltic pump (Buchler Model 2-6101) operated at a flow rate of 20 ml $min^{-1}$. The salicylic acid permeating the membrane at 37° C was measured spectrophotometrically at 296 nm at 15 min intervals using a 10 mm flow cell for a period of 10–12 h and experiments were triplicated. Concentration-time plots for drug transferred to the receiver compartment, were linear, after a short lag period, and the steady state slope gave the permeation rate, dc/dt, from which the permeability coefficient, P, was obtained using the relation: (Crank 1956)

$$P = \frac{dc/dt\ l.v}{A\ C} \qquad (1)$$

where $l$ is the thickness of the membrane and A the area in contact with the drug solution, the initial concentration of which is C; V is the volume of the sink solution.

The permeability coefficients of salicylic acid obtained from experiments at different pH values were found to be highly dependent on the pH of the drug solution within the range 0·1 and 7·69 (Table 1). They varied in value from $1{\cdot}054 \times 10^{-7}$ $cm^2\ s^{-1}$ at pH 0·1 to $2{\cdot}39 \times 10^{-9}$ $cm^2\ s^{-1}$ at pH 4·99. Taking 3·00 as the $pK_a$ of salicylic acid (Dippy 1939) 99·9% of the drug is unionized at pH 0·1 and 1·01% at pH 4·99. Fig. 1 shows the relationship between the permeability coefficient and pH: the pH value corresponding to half the asymptotic values of $0{\cdot}539 \times 10^{-7}$ $cm^2\ s^{-1}$ is 3·00 in agreement with the theoretical $pK_a$ of salicylic acid. From the data it is evident that the rate of permeation through the ethyl cellulose-PEG 4000 film is controlled by the concentration of unionized drug, a function of the pH of the solution and the $pK_a$ of the drug.

The concentration of unionized drug in solution, Co, is given by:

$$Co = C\{1 + \exp[2{\cdot}303(pH - pK_a)]\}^{-1} \qquad (2)$$

where C is the total drug concentration, the pH is that of the drug solution, and $K_a$ is the ionization constant of salicylic acid. Substitution into equation 1 yields:

$$P_a = \frac{dc/dt\ lV}{A\ Co} \qquad (3)$$

where $P_a$ is the actual permeability coefficient calculated from the concentration of unionized drug. Values of $P_a$ for the experimental points are included in Table 1. They are independent of pH and have a mean value of $1{\cdot}061 \pm 0{\cdot}068 \times 10^{-7}$ $cm^2\ s^{-1}$ (c.v. 6·10%) over the pH range of 0·1–4·47 (Table 1).

The permeability coefficient obtained using $1 \times 10^{-2}$ M sodium salicylate was $0{\cdot}0160 \times 10^{-7}$ $cm^2\ s^{-1}$ (Table 2) identical with that of salicylic acid in pH 6·64 and 7·69 buffer solutions. The drug is totally ionized in these solutions and the permeability coefficient is that of the salt ions in ethyl cellulose-PEG 4000 film.

The actual permeability coefficient of salicylic acid from water through pure ethyl cellulose film is 74·7

* Correspondence.

times greater than that obtained from sodium salicylate; $2.93 \times 10^{-9}$ and $3.92 \times 10^{-11}$ $cm^2$ $s^{-1}$ respectively (Table 2). In the 80% ethyl cellulose 20% PEG 4000 film studied, the ratio of $P_a$ values of salicylic acid and salicylate has a value of 70·8, indicating that the latter

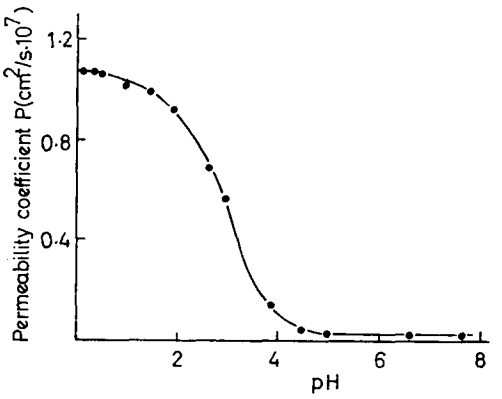


FIG. 1. Plot of permeability coefficient, P, versus pH for salicylic acid through 20% PEG 4000—ethyl cellulose film.

Table 1. Permeability coefficients of salicylic acid through 20% PEG 4000 80% cellulose film as function of pH. I Unionized salicylic acid concentration $C_0$ ($\times 10^3$); II. permeability coefficient[a] P ($cm^2$ $s^{-1}$ $\times$ $10^7$). III actual permeability coefficient[b] Pa ($cm^2$ $s^{-1}$ $\times$ $10^7$).

| pH | I | II | III |
|---|---|---|---|
| 0·10 | 9·987 | 1·054 | 1·056 |
| 0·32 | 9·979 | 1·069 | 1·072 |
| 0·49 | 9·968 | 1·055 | 1·058 |
| 0·95 | 9·911 | 1·014 | 1·022 |
| 1·48 | 9·700 | 0·982 | 1·012 |
| 1·92 | 9·232 | 0·927 | 1·004 |
| 2·62 | 7·058 | 0·697 | 0·988 |
| 2·95 | 5·287 | 0·560 | 1·060 |
| 3·86 | 1·213 | 0·136 | 1·122 |
| 4·47 | 0·320 | 0·0399 | 1·220 |
| 4·99 | 0·1012 | 0·0239 | 2·336 |
| 6·64 | 0·00229 | 0·0163 | |
| 7·69 | 0·000204 | 0·0155 | |

a. Calculated from the total drug concentration, C.
b. Calculated from the concentration of unionized drug, Co.

Table 2. Actual permeability coefficients, Pa of salicylic acid and sodium salicylate through pure ethyl cellulose and 20% PEG 4000—ethyl cellulose films.

| Drug | pH of soln[a] | Ethyl cellulose film | 20% PEG 4000—ethyl cellulose film |
|---|---|---|---|
| Salicylic acid | 2·52 | $2.93 \times 10^{-9}$[b] | $1.134 \times 10^{-7}$[b] |
| Sodium salicylate | 6·20 | $3.92 \times 10^{-11}$ | $0.016 \times 10^{-7}$ |

(a) Drug concentration $1 \times 10^{-2}$ M.
(b) Calculated from the concentration of unionized drug Co.

films behave as perfect ethyl cellulose films in spite of the introduction of porosity, which elevates the actual P values.

In contrast, Withington & Collett (1973) studying the rate of dialysis of salicylic acid through sieve-type cellophane membranes, reported a reduction of only 40% in the rate constant for the ionized drug (pH 5) compared with that for the unionized drug (pH 1).

The retention of the specific P ratio for acid and salt is a further sensitive test confirming previously cited evidence of non-penetration of small inorganic ions, and linear permeability coefficient-PEG concentration relationships, which indicate that these mixed EC-PEG films retain full barrier properties and do not contain capillaries allowing direct flow between the two sides of the film.

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