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COMMUNICATIONS

Cholic acids/salts as barriers to diffusing species: effect of pH

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Bile acids have been absorbed on a microporous polypropylene membrane and the diffusion of ionic and non-ionic compounds through the barriers obtained has been studied at different pH values. Results indicate that permeation rates are affected by environmental pH conditions and an explanation of this behaviour is proposed. This study represents an approach for a pH-controlled drug delivery system.

Sodium deoxycholate (SDC) and deoxycholic acid (DCA) have been studied as naturally occurring surface active agents (Feldman et al 1968; Feldman & Gibaldi 1969) and because of their capacity to form aggregates (Mukerjee & Cardinal 1976; Chang & Cardinal 1978; Thomas & Christian 1980) and inclusion compounds (Coiro et al 1982).

We report here on the diffusion of several substances, at different environmental pH conditions, through barriers of DCA on a polymeric support.

The polymer on which the cholic acids were absorbed was a microporous polypropylene membrane, previously used to study coupled transport through the pores (Baker et al 1977; Babcock et al 1980).

Materials and methods

Materials. The membranes used for the diffusion studies were of microporous polypropylene TF 200 (Gelman Instrument), pore size 0·2 μm, from which the Teflon support was removed. Membrane thickness was checked by micrometer. DCA, cholic acid, chenodeoxycholic acid, orange II and 4′-aminopropiophenone were purchased from Merck-Schuchardt. All other substances and reagents were supplied by Carlo Erba Co. HCl and phosphate buffers were used to give the appropriate pH values of the solutions. The ionic strength did not appreciably affect the diffusion rates of permeating species.

Methods. Impregnated membranes were prepared by soaking the polypropylene microporous membrane in 10 ml of ethanol containing 200 mg of bile acid overnight, after which the solvent was evaporated and the membrane dried under vacuum. Differences in weight before and after treatment showed that each membrane had 10 mg cm^{-2} of acid. For permeation studies, a two compartment diffusion cell described by Alhaique et al (1981) was used. Membranes were equilibrated overnight in solutions buffered at the same pH value as that of the subsequent diffusion experiment. Permeation rates were determined by spectrophotometric measurement of the diffusing species in the receptor compartment of the cell at the appropriate wavelength. The initial concentration of permeating species in the donor compartment of the cell was 2×10^{-3} M. Stirring and constant temperature (25 ± 1 °C) were maintained throughout.

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Results and discussion

The effect of pH on the permeation rate of salicylic acid/salicylate through the polymeric support and through bile acids-impregnated membranes is shown in Table 1 where the apparent diffusion constants, calculated from permeation experiments (Nogami et al 1970) are listed.

As expected, the untreated polypropylene membrane behaves as a lipophilic barrier permeable only to undissociated molecules. When the DCA-impregnated membrane was used as a barrier to the diffusing species, apparent diffusion constant values indicate the sharp increase in permeation rate detected at an environmental pH of 7·0; i.e. when it can be assumed that salicylic acid (pK_a 2·97) and DCA (pK_a 6·58) are in their ionized form. At pH 2·0, when permeating and absorbed species are both undissociated, a much lower permeation rate was observed, a minimum being reached at pH 5·0 when only the diffusing molecules are in their ionized form.

Chenodeoxycholic acid and cholic acid behaved similarly to DCA (Table 1), but at pH 7·0 no permeation of salicylate was detected with the cholic acid membranes because this bile acid dissolved easily in the water medium in these environmental conditions. Thus, the barrier behaved as the untreated polypropylene membrane. Table 1 also indicates that the diffusion through DCA barriers was faster than that observed with the other bile acids tested.

The comparison between diffusion through untreated and cholic acids-impregnated membranes clearly indicates that the results obtained are to be attributed to the bile acids absorbed on the microporous polymeric support. The remarkable increases in diffusing rates,

Table 1. Apparent diffusion constant ($D \times 10^8$ cm^2 s^{-1}) of salicylic acid/salicylate diffusing through the untreated polymeric support and through colic acids-impregnated membranes.

Type of barrier	Apparent diffusion constant pH 2·0	pH 5·0	pH 7·0
Untreated membrane	0·92	0·0	0·0
Deoxycholic acid	7·3	3·7	21·6
Chenodeoxycholic acid	2·1	1·3	4·9
Cholic acid	2·6	1·0	0·0*

* No permeation of salicylate: as the cholic acid leaves the polymeric support and dissolves in the buffer solution.

detected at pH 7·0 for DCA and chenodeoxycholic acid membranes, in spite of the same charge species being present on the membrane and the diffusing ion (salicylate), can be ascribed to the aggregate structures that bile salts may assume (Mukerjee & Cardinal 1976; Chang & Cardinal 1978), most probably within the pores of the polymeric support, inducing the membrane to behave as a sieve for diffusing species. The permeation at pH 2·0 and 5·0 takes place by a partition mechanism and shows a minimum at pH 5·0, i.e. when a charged species diffuses through an uncharged barrier.

In an attempt to differentiate the effect of pH on DCA membranes from the effect arising from ionization of the permeant, the diffusion of molecules not appreciably affected by pH conditions was studied. In Table 2 the apparent diffusion constants determined for orange II (always negatively charged in experimental conditions) and for phthalic aldehyde (uncharged) are reported for the different pH values.

Table 2. Apparent diffusion constant ($D \times 10^8$ cm^2 s^{-1}) through DCA membranes determined for different diffusing species at three pH values.

Diffusing species	Apparent diffusion constant pH 2·0	pH 5·0	pH 7·0
Orange II	0·5	0·7	4·9
Phthalic aldehyde	12·4	12·6	54·6
4′-Aminopropiophenone	6·5	11·5	1·5

Results indicate that both substances have an almost constant diffusion rate at pH 2·0 and 5·0, and there was an increase in permeation rate at pH 7·0. These findings give support to the mechanism previously proposed for salicylic acid diffusion and confirm that the effect of pH on permeation rate is to be ascribed to cholic acid membranes and not to the diffusing species (salicylic acid).

When an amine, i.e. 4′-aminopropiophenone (PAPP, pK_a 2·42), was used as a permeating species through DCA membranes under the same experimental conditions (Table 2), the variations of the apparent diffusion constant with pH show a different trend, being almost symmetrically opposite that of salicylic acid: PAPP is positively charged at pH 2·0 and uncharged at pH 5·0 and 7·0. In this instance the formation of aggregate structures can be disturbed by the presence of the amine and the diffusion takes place at all three pH values by means of a partition mechanism, thus a maximum diffusion rate was detected at pH 5·0, when an uncharged permeating species diffuses through the undissociated DCA membrane.

Diffusion experiments with saturated bile acids/salts solutions containing the permeating species and using untreated membranes as barriers, clearly indicate that the observed results are not to be ascribed to a coupling of the permeating molecules with DCA or SDC or to the bile salts acting as surfactants, because they had no effect on the permeation rate of the diffusing species. All the effects reported here are reversible and permeation rates determined with DCA-impregnated barriers freshly used, or with a membrane previously used in solutions buffered at different pH values, are reproducible with minor experimental variations. Furthermore, experiments after the equilibration of DCA membranes for 24–28 h in a pH 8·0 buffer solution show the same trend as that before such treatment, the amount of SDC released from the polymer always being negligible.

The results show how the permeation rate through DCA membranes can be affected by environmental pH conditions as well as the properties of the permeating molecules selected as model species.

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