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Influence of drug partition coefficient and pH value of sink solution on permeation from porous thick-walled ethyl cellulose microcapsules

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The permeation of barbitone sodium, benzoic acid, and salicylic acid from microcapsules into aqueous medium has been examined at different pH values. The apparent diffusion coefficients of drugs were linearly proportional to the ethyl cellulose/water partition coefficient of drugs, and the straight line parameters were dependent upon volume fractions of water-filled pores (i.e. capsule size), testifying to a previously proposed mechanism of drug permeation. The rate of drug permeation was also a function of the pH-value of the surrounding sink solution; the period of zero order release was longer at low pH because of the change of drug partition or solubility or both.

The use of ethyl cellulose to prepare microcapsules of water-soluble drugs has been investigated with the aim of controlling the release of drugs intended for gastrointestinal absorption. Among other properties of microcapsules, the release of encapsulated drugs into water has also been studied (Bakan & Anderson 1970; Jalšenjak et al 1976; Donbrow & Benita 1977; John et al 1979; Deasy et al 1980; Senjković & Jalšenjak 1981; Benita & Donbrow 1982), and various kinetics for the drug release have been proposed. Since the pH changes continuously along the gastrointestinal tract, knowledge of the effect of the sink solution pH on the drug permeability of ethyl cellulose microcapsules would be useful. However, release of sodium salicylate from ethyl cellulose microcapsules was investigated and was little affected by the pH of the external medium (Deasy et al 1980), while sodium salicylate is released from cellulose acetate microcapsules faster at high than at low pH (Madan & Shanbhag 1978).

The permeation process of a solute through a polymeric membrane is also related to the chemical nature of drug expressed by the membrane/water partition (distribution) coefficient, because it affects the profile of drug release from controlled release formulations (Baker & Lonsdale 1974; Flynn 1974). It has also been shown that the partition coefficient is partly responsible for governing membrane-controlled versus matrix-controlled permeation (i.e. in the case of a biphasic release profile) (Roseman & Yalkowsky 1976). Recently, it was proposed that the drug release from thick-walled ethyl cellulose microcapsules containing barbitone sodium might be explained in terms of a biphasic release profile with the zero-order release preceding the Higuchi type release (Vidmar & Jalšenjak 1982).

The microcapsules we have used in the present study have been shown to have a porous membrane, therefore our purpose was to find further details of the release profile of drugs with various membrane/water partition coefficients, when drugs are released from thick-walled microcapsules into sink solutions at different pH values.

MATERIALS AND METHODS

Materials

Ethyl cellulose (Dow chemical International GmbH, Frankfurt) had an ethoxyl content of 48·0–49·5%, and a viscosity of 10 cP for a 5% w/w solution in a toluene-ethanol mixture (80:20) w/w. All materials were of reagent or pharmacopoeial grade purity.

Microcapsules

The method of preparation, the release of drug into water medium at 37 °C, and the calculation of apparent diffusion coefficients, D_a, were carried out as described previously (Senjković & Jalšenjak 1981). The volume fractions of water-filled pores in membranes were 2·5, 1·1, and 0·54% for 1·13, 0·72, and 0·41 mm microcapsules, respectively (Vidmar et al 1982).

Assay of drugs

The assay of drugs was carried out spectrophotometrically after appropriate dilution of samples was

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made as follows: barbitone sodium at 238 nm (in buffer solution, pH 10), benzoic acid at 228 nm (in water), and salicylic acid at 296 nm (in water).

Drug properties

The diffusion coefficients of drugs in water, D_p, were calculated by an equation from Flynn et al (1974) using the van der Waals' volume of a drug. The following values were obtained 1·49, 1·68, and 1·65 $\times 10^{-5}$ cm^2s^{-1} for barbitone sodium, benzoic acid, and salicylic acid, respectively.

The solubilities of drugs in water at 37 °C found in usual handbooks are: 0·255 (barbitone sodium), 0·90 $\times 10^{-2}$ (benzoic acid), and 0·63 $\times 10^{-2}$ g cm^{-3} (salicylic acid).

The partition coefficients, K, for benzoic and salicylic acid are 58 and 151 (Donbrow & Friedman 1975). K for barbitone sodium was measured by equilibration of ethyl cellulose samples in buffered solutions of the drug in a way similar to the procedure of Donbrow & Friedman (1975). The mean value of 0·67 was obtained, and used in the analysis of the y-axis intercepts of D_a vs K functions. It should be noted that for a low partition, the range of the K-values obtained was rather broad (0·4–0·9). However, a simple calculation shows that even such a large error in the evaluation of K cannot affect the intercept evaluation to any significant level.

RESULTS AND DISCUSSION

The permeation curves (the amount of released drug vs time) showed a linear part at the beginning of process and afterwards a downward deviation from the straight line (Fig. 1). No lag time or 'burst' effect was noticed, indicating that a steady state was immediately achieved. Apparent diffusion coefficients were calculated from the zero-order part of the permeation curves. A period of the decreasing permeation rate followed the period of zero-order release. It was proposed that the period of the decreasing permeation rate could be described by Higuchi type kinetics (i.e. Q_t versus $t^{1/2}$) (Vidmar & Jalšenjak 1982). It is interesting to note the relative amount of drugs released at any given time, and time needed for 50% drug release. Barbitone sodium was released faster than benzoic acid, although its apparent diffusion coefficient is lower. These results can be misleading unless the respective solubilities of drugs in water are taken into account. Since a large sink solution volume (2000 ml) was used, sink conditions were observed, and therefore the available concentration gradient was higher for barbitone sodium because of its solubility.

It has been pointed out that the partition coefficient of a drug between membrane and aqueous phase, K, for a given release system, exhibits the widest extremes of values of any release system parameter among different compounds (Flynn 1974). Therefore, we have taken their numerical values into consideration when comparing the permeability characteristics of microcapsules (Table 1). The apparent diffusion coefficient, D_a, of a drug in the non-porous, homogeneous polymeric membrane is related to the partition coefficient by the expression: $D_a = D_m K$, where D_m is the diffusion coefficient of the permeant in the membrane-matrix (Baker & Lonsdale 1974). The membrane of the microcapsules investigated here cannot be regarded

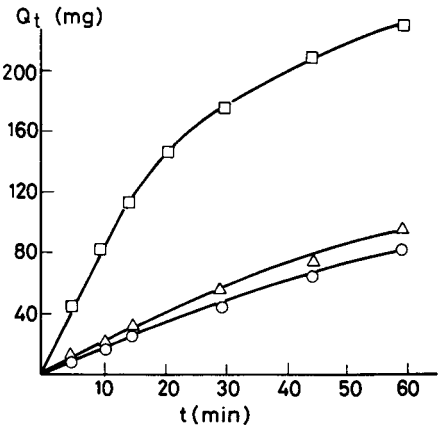

FIG. 1. Amount of drug released from microcapsules (d = 0·72 mm) vs time (500 mg sample, 2000 ml water, 37 °C): □, barbitone sodium; △, benzoic acid; ○, salicylic acid.

Table 1. Characteristics of ethyl cellulose microcapsules: apparent diffusion coefficient, D_a, and release half-time, t50%[a]

Substance	Size fraction, mm	$D_a \times 10^7$,[b] $cm^2 s^{-1}$	t50%,[c] min
Barbitone sodium	1·13	3·83	24
	0·72	1·78	22
	0·41	0·99	20
Benzoic acid	1·13	30·3	110
	0·72	18·7	70
	0·41	6·5	60
Salicylic acid	1·13	80·5	120
	0·72	38·2	80
	0·41	17·3	65

[a] Permeation from 500 mg microcapsules into 2000 ml of water at 37 °C.
[b] Calculated from the linear part of the permeation curves (Senjković & Jalšenjak 1981).
[c] Graphically extrapolated from the permeation curves.

as homogeneous, since it was shown that the volume fraction of water-filled pores in the ethyl cellulose membrane, α, varies depending upon microcapsule size (Vidmar et al 1982). As a consequence it follows that the permeation process is governed not only by the diffusivity in the membrane-matrix, but also through the water-filled pores. For this reason it is not possible simply to relate the values of apparent diffusion coefficients and partition coefficients, although it appears that they are linearly proportional (Fig. 2). Since all three lines show a positive intercept on extrapolation to the y-axis it would appear that an equation proposed previously (Senjković & Jalšenjak 1981) may be applied: $D_a = (1-a)D_mK + \alpha D_p$. But certain limitations are needed. The compounds used cannot be members of a group of closely-related substances, having similar numerical values of D_m. Therefore it is not possible to elaborate on the slopes of straight lines. The situation is different with the y-axis intercepts. (i.e. αD_p). The diffusion coefficients in water, D_p, (1·49, 1·68, and $1·65 \times 10^{-5}$ cm^2 s^{-1}) are close enough, and an 'average' diffusivity value ($\bar{D}_p = 1·61 \times 10^{-5}$ cm^2 s^{-1}) can be proposed. For the sake of control, the intercepts were calculated using the least-square method, the α-values (0·025, 0·011, and 0·0054) inserted, and the 'average' $\bar{D}_p$ value of three lines was found to be $1·60 \times 10^{-5}$ cm^2 s^{-1}, which was in very good agreement with $1·61 \times 10^{-5}$ cm^2 s^{-1}.

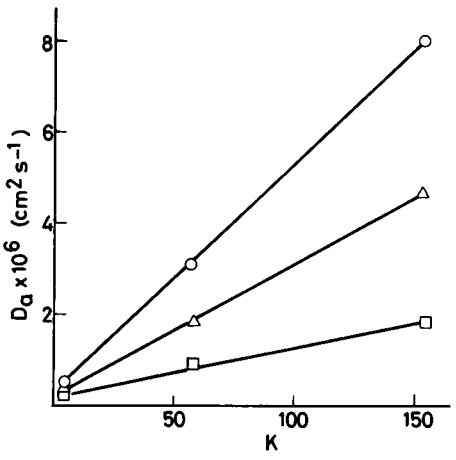

FIG. 2. Plots of apparent diffusion coefficient vs partition coefficient: ○, 1·13 mm; △, 0·72 mm; □, 0·41 mm.

The permeation of drug was measured at two additional pH values. The permeation curves of salicylic acid for the same capsule size at pH 2·0 and 7·0 given in Fig. 3 indicate that the permeation rate is dependent upon pH-values of the surrounding sink solution. The general shape of the curves is similar with the only difference being the duration of linearity, i.e. the critical time, when change of kinetics occurs. The difference can be explained by the effect of drug solubility in water and/or partition coefficient. The drug solubility affects the permeation process by influencing the concentration gradient as described before. Since values of the partition coefficient at different pH values were not measured, it was assumed that they were higher at low pH for weak acids. An increase in the partition coefficient of the same drug due to a lowering of the pH would decrease the permeation rate, because the proportion between unionized drug (diffusion through the membrane-matrix) and a mixture of ionized and unionized drug (diffusion through water-filled pores) is shifted towards the former. The effects of changing the drug solubility in water and the partition coefficient of the same drug due to a change in pH of the surrounding water medium cannot be separated, because a higher value of partition coefficient denotes a smaller solubility in water.

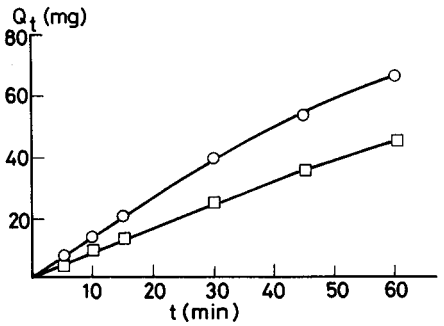

FIG. 3. Amount of salicylic acid released from microcapsules (d = 0·72 mm) vs time: ○, pH 7·0; □, pH 2·0.

The permeation from microcapsules of various sizes at different pH values is further complicated by the presence of different amounts of water-filled pores. The permeation of barbitone sodium was measured for two size fractions at pH 2·0 and pH 7·0 (Fig. 4). By using the equation given before, it is possible to calculate the proportion between the membrane-matrix controlled flux and the water-filled pores controlled flux. For the larger capsules about 96% of drug transport is taking place through pores, whereas for the smaller capsules it constitutes only about 82%. From the permeation curves given in Fig. 4 two tendencies become evident. First, the permeation rate is higher at pH 7·0, and second,

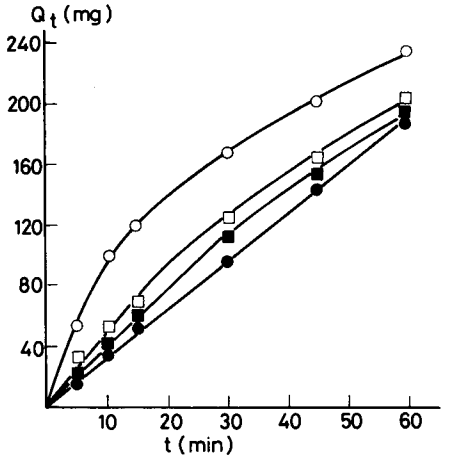

FIG. 4. Amount of barbitone sodium released vs time: pH 7·0 (○ 1·13 mm, □ 0·41 mm); pH 2·0 (● 1·13 mm, ■ 0·41 mm).

the difference between pH 7·0 and pH 2·0 is more pronounced for larger microcapsules. At pH 7·0, permeation of the ionized drug is taking place, mostly through water-filled pores, and the permeation rate is at its maximum for 1·13 mm microcapsules. At low pH, barbitone sodium, a salt of a weak acid, is converted inside the microcapsules into a far less soluble barbitone, and barbitone is released rather than barbitone sodium. Discussion, similar to the above may explain the relative position of the other curves.

In summary, the permeability characteristics of thick-walled ethyl cellulose microcapsules are not only dependent upon membrane properties (porosity among others), but also upon the medium pH-values, and the relevant properties of drug (pK_a, partition coefficient and solubility).

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