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# Volume of water-filled pores in the ethyl cellulose membrane and the permeability of microcapsules

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The volume fraction of the water-filled pores in the microcapsule membranes was calculated and the values from 0·55 to 2·5% were obtained. Differential scanning calorimetry of aqueous suspensions of microcapsules showed no structured water present in the ethyl cellulose membranes. The temperature effect on the apparent diffusion coefficient of a drug was investigated and the apparent activation energy of diffusion was calculated.

Previous investigations have shown that the permeability characteristics of low molecular weight solutes or drugs through the polymeric wall of microcapsules depend on the capsule size. It was found that the permeability coefficient decreases with a decrease in capsule size, and an explanation for the phenomena was given in terms of structured water in and around the microcapsules (Ohta et al 1978; Jalšenjak & Kondo 1981). An additional explanation was also suggested: namely, as the density of the wall material was found to be higher for smaller capsules, indicating smaller porosity of their membranes, the density (or alternatively porosity) of membranes was thought as the possible reason for the observed dependence of the apparent diffusion coefficient on the capsule size. Therefore, an equation was proposed for the calculation of numerical values for the apparent diffusion coefficient of drugs, $D_a$, through the microcapsule wall (Senjković & Jalšenjak 1981):

$$D_a = (1 - \alpha)D_mK + \alpha D_p \qquad (1)$$

where $D_m$ and $D_p$ are the diffusion coefficients in the membrane materials and the aqueous pores, respectively; $\alpha$ is the volume fraction of the pores in the membrane, and K is the membrane-solution partition coefficient of the drug.

Equation 1 implicates the existence of parallel diffusional pathways through the ethyl cellulose membrane, as follows: a drug can diffuse through the matrix of the membrane by a solubility process, as well as, through pores filled with water.

In the present work the studies were extended in order to calculate the numerical values of $\alpha$ and $D_mK$. In addition differential scanning calorimetry (DSC) data for membranes were obtained, and the temperature effect on $D_a$ was measured. The porosity of ethyl cellulose microcapsules were altered by addition of an hydrophilic polymer.

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## MATERIALS AND METHODS

### *Materials*

Ethyl cellulose was of 10 cP viscosity when dissolved in toluene-ethanol 80:20 w/w at 25 °C. Polyethylene glycol 4000 was purchased from Dow Chemical International GmbH, Frankfurt, and all other chemicals were of pharmacopoeial or reagent grade purity.

### *Preparation and characterization of microcapsules*

Ethyl cellulose microcapsules were prepared by a method described previously (Senjković & Jalšenjak 1981). Two batches of capsules with various core to wall ratios were prepared: sample A—sodium barbitone–ethylcellulose (1:1), and sample B—sodium barbitone–ethyl cellulose–PEG 4000 (1:0·9:0·1). The size fractions of microcapsules were obtained after sieveing with a nest of standard sieves.

PEG 4000 was used because it introduces an additional porosity into the system by rapid leaching out from ethyl cellulose membrane when the capsules are subjected to water (Donbrow & Friedman 1975). In the case of sample B capsules, it took less than five 5 min for the PEG 4000 to leave the capsules, as shown gravimetrically, after they had been subjected to release of their content into water at 37 °C.

The apparent diffusion coefficient and the density of microcapsule membranes were obtained as described by Senjković & Jalšenjak (1981). The permeability of sodium barbitone from the microcapsules (0·500 g) into the surrounding water (2000 ml) was measured under sink conditions at 22, 27, 37, 47, and 62 °C. The solubilities of the drug at various

temperatures, needed for the calculation of $D_a$, were found in usual handbooks.

*Assay of the drug*

Barbitone sodium was assayed spectrophotometrically at 238 nm. Appropriate dilutions of samples were made with a buffer solution (pH 10).

*DSC data*

The thermal behaviour of a concentrated microcapsule dispersion was measured with a differential scanning calorimeter (Rigaku Denki Co Ltd, Tokyo). The sample was cooled to −50 °C and then heated to 40 °C at a rate of 10 °C $min^{-1}$.

## RESULTS AND DISCUSSION

The apparent diffusion coefficients for two batches of microcapsules are given in Table 1. $D_a$ increases with an increase in the microcapsule size, as well as with the amount of polyethylene glycol 4000 used in the preparation of microcapsules. Since the hydrophilic polymer underwent rapid leaching out at the beginning of an in vitro experiment, it can be concluded that additional porosity was introduced into the microcapsules in a way similar to that shown by Donbrow & Friedman (1975) for ethyl cellulose films. Therefore the total space within the membrane occupied by water was increased, and consequently the higher values of $D_a$ were obtained for the sample B, than for the sample A of microcapsules.

Table 1. Characteristics of ethyl cellulose microcapsules: microcapsule density, $d_{mc}$, membrane density, $d_m$, and apparent diffusion coefficient of barbitone sodium, $D_a$.

| Average diameter, mm | A[a] $d_{mc}$, g $cm^{-3}$ | A[a] $d_m$, g $cm^{-3}$ | A[a] $D_a \times 10^{7}$[b], $cm^2$ $s^{-1}$ | B[a] $d_{mc}$, g $cm^{-3}$ | B[a] $d_m$, g $cm^{-3}$ | B[a] $D_a \times 10^{7}$[b], $cm^2$ $s^{-1}$ |
|---|---|---|---|---|---|---|
| 1·13 | 0·882 | 0·541 | 3·83 | 0·850 | 0·767 | 5·28 |
| 0·90 | 0·880 | 0·549 | 2·57 | — | — | — |
| 0·72 | 0·922 | 0·569 | 1·78 | 0·906 | 0·900 | 2·41 |
| 0·57 | 0·944 | 0·544 | 1·60 | — | — | — |
| 0·41 | 1·018 | 0·624 | 0·99 | 0·930 | 0·925 | 1·60 |
| 0·28 | 1·020 | 0·632 | 1·01 | — | — | — |

[a] Sample A: barbitone sodium–ethyl cellulose (1:1); Sample B: barbitone sodium–ethyl cellulose–PEG 4000 (1:0·9:0·1). [b] Measured from 0·500 g capsules into 2000 ml of water at 37 °C, and stirring rate 50 rev $min^{-1}$.

The density of membranes increases as the diameter of microcapsules, d, decreases because of smaller values of α, and in a hypothetical (theoretical) case for the diameter of capsules being equal to zero, α would also approach zero. In such a situation Equation 1 would reduce to $D_a = D_mK$, a relation well known from the studies of drug diffusion in pure homogeneous polymeric films.

On the other hand, dependency of the apparent diffusion coefficient on the capsule size shows curves with a considerable curvature (Fig. 1). In order to seek any useful empirical correlation between $D_a$ and the average diameter of capsules, d, we assumed that the curves are represented with a polynomial series, such as:

$$D_a = D_mK + a_1d^3 + a_2d^2 + a_3d + \ldots . \quad (2)$$

Indeed, computer analysis of the curve (sample A) gave equation 3 as the best fit for the data:

$$D_a = 0{\cdot}18 + 3{\cdot}57\ d^3 - 4{\cdot}75\ d^2 + 4{\cdot}04\ d \quad (3)$$

From the previous discussion it follows that when the capsule diameter approaches 0, and $\alpha \rightarrow 0$, $D_a$ becomes equal to $D_mK$ (i.e. $D_mK = 0{\cdot}18 \times 10^{-7}$ $cm^2$ $s^{-1}$), and therefore equation 1 can be used for calculation of α values. However, the calculation of $D_p$ is coupled with a problem: if structured water is present in the water-filled pores of the membrane, it would affect the permeability characteristic to an appreciable extent by decreasing its numerical value. For example, after the existence of structured water in the polyamide membrane of microcapsules had been reported (Ishizaka et al 1979), the dependence of the permeability coefficient and the apparent diffusion coefficient of thin-walled ethyl cellulose and gelatin-acacia microcapsules on the capsule size was ascribed to the amount of structured water (Ohta et al 1978; Jalšenjak & Kondo 1981).

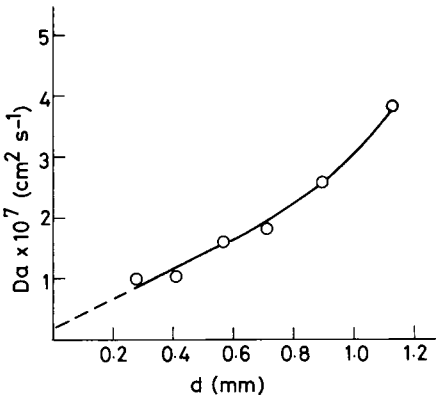


FIG. 1. Plot of apparent diffusion coefficient vs average capsule diameter (Sample A, 37 °C).

Fig. 2 is a thermogram of an aqueous suspension of ethyl cellulose microcapsules used in this work showing that no structured water exists in the membrane, or the amount of it is very small. For this reason the diffusion coefficient of sodium barbitone in the water-filled pores was calculated by an equation given in the literature (Flynn et al 1974). The diffusivity in water was obtained using the van

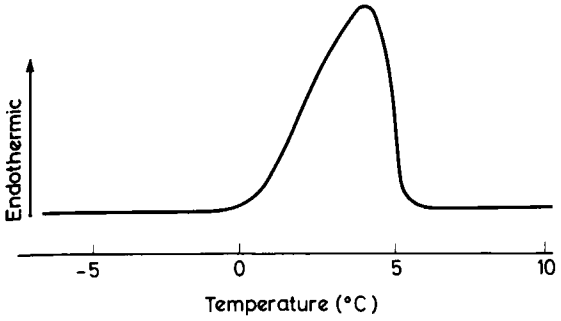


FIG. 2. Typical DSC thermogram of water in microcapsule membrane.

der Waals' volume of the drug, and the value of $1{\cdot}49 \times 10^{-5}$ cm$^2$ s$^{-1}$ was found.

On the basis of the measured values for $D_a$, and the calculated values of $D_mK$ and $D_p$, the volume fractions in membrane occupied with water, $\alpha$, were obtained and they are shown in Table 2. Rather low values obtained indicate a small volume fraction of the membranes occupied by the water-filled pores. It is interesting to compare the data presented here with the result obtained by Tateno et al (1978). On the basis of the electrophoretic measurement of polyelectrolyte-loaded microcapsules they evaluated the fraction of the total space within the ethyl cellulose membrane that is not available to counter ions, and the calculated values were found to be between 1 and 3%. Although, a different type of capsule (i.e. prepared with an interfacial polymer deposition technique) was used, the correlations between two sets of results is evident, especially when compared with the microcapsules of type A.

Table 2. Volume fraction of pores in the ethyl cellulose membrane of microcapsules.[a].

| Average diameter, mm | α, % A | α, % B |
|---|---|---|
| 1·13 | 2·5 | 3·4 |
| 0·90 | 1·6 | — |
| 0·72 | 1·1 | 1·5 |
| 0·57 | 0·95 | — |
| 0·41 | 0·54 | 0·95 |
| 0·28 | 0·55 | — |

[a] $D_p = 1{\cdot}49 \times 10^{-5}$ cm$^2$ s$^{-1}$; $D_mK = 0{\cdot}18 \times 10^{-7}$ cm$^2$ s$^{-1}$.

The B sample containing polyethylene glycol 4000 has higher α-values. The difference between the samples with and without polyethylene glycol 4000 would be expected to be even more pronounced, because of the high percentage of the hydrophylic polymer originally contained in the capsules. A possible explanation of this observation could be the method of microcapsule preparation does not rule out the possibility that a certain amount of the hydrophylic polymer is also contained in the microcapsule core mixed with the drug. In this case the porosity of a microcapsule, as a whole, should be influenced, and not only the membrane. The density data (Table 1) seems to confirm this explanation.

Permeation studies were conducted for one size fraction (d = 0·72 mm) at various temperatures, because Flynn et al (1974) have reported the temperature dependence of the permeability characteristics of complex barriers. The results obtained are shown in Fig. 3. The logarithms of the apparent diffusion coefficients are plotted against the reciprocal of the absolute temperatures. It was shown by Garrett & Chemburkar (1968) that the apparent activation energy of diffusion, $\Delta E_a$, is about 5 kcal (21 kJ) mol$^{-1}$ for diffusion in water, and as much as 10–15 kcal (42–63 kJ) mol$^{-1}$ or higher for many polymers. Therefore, $\Delta E_a$ were calculated from the apparent diffusion coefficients at the two temperatures considered. From the results in Table 3, it would appear that the transport mechanism of the

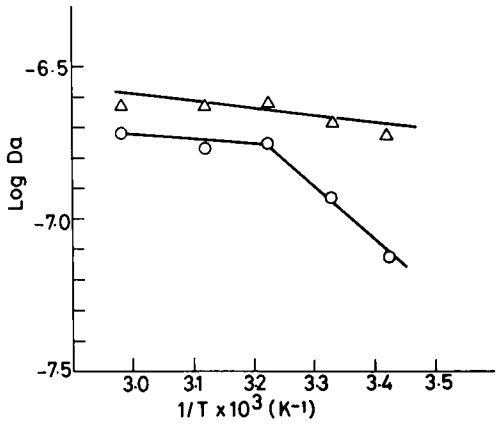


FIG. 3. Arrhenius plot of logarithm of apparent diffusion coefficient vs absolute temperature (d = 0·72 mm): ○, sample A; △, sample B.

Table 3. Activation energies of diffusion of barbitone sodium through ethyl cellulose membranes of microcapsules.

| Microcapsule sample | Temperature range, $(t_2 - t_1)$, °C | $\Delta E_a$, kcal mol$^{-1}$ |
|---|---|---|
| A | 62–37 | 0·6 |
| A | 37–22 | 10·9 |
| B | 62–22 | 1·0 |

drug in the membrane is different for the two samples of microcapsules at elevated temperatures. Whereas for the B sample the relationship $D_a$ vs 1/T is linear in the temperature range investigated (22–62 °C), this is not identical for the A sample. Two linear parts (with their respective energies of activation) indicate a change in diffusional mechanism. This difference stems from the fact that heterogeneity of the membranes was increased by the addition of the hydrophylic polymer during the preparation step. All the calculated energies are smaller than those in the case of diffusion in pure polymer films or in water, indicating the parallel pathways for the transport of the drug through the membrane.

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