Apparent diffusion coefficient of sodium phenobarbitone in ethylcellulose microcapsules: effects of capsule size

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Ethylcellulose microcapsules of sodium phenobarbitone with a thick wall were prepared and fractionated. The apparent diffusion coefficient of sodium phenobarbitone was measured for the transport of the drug from the core of microcapsules into the surrounding sink condition. The apparent diffusion coefficient decreased with decreasing capsule size. Apart from structured water in and around the capsule wall, the volume fraction of pores in the membrane has been suggested as the source of the observed trend.

The permeation process of a drug through the wall of a microcapsule is closely related to the composition of the wall and/or to the method of preparation of the microcapsules. The investigation of the permeability of microcapsules is more complex than that of ordinary polymer sheets since it could be influenced by the size of capsule (Kondo 1978). Ohta et al (1978) reported that the permeability coefficient of ethylcellulose microcapsules towards sodium hydroxide decreased with decreasing capsule size and Jalšenjak & Kondo (1981) found that the permeability of gelatin-acacia microcapsules followed the same trend.

In both of those papers the permeability coefficients of microcapsules towards electrolytes were measured on thin-walled microcapsules the wall thicknesses of which could be regarded as constant whatever the particle size of the microcapsules. The direction of the solute permeation was from the surrounding bulk solution *into* microcapsules.

We have investigated wall permeability towards sodium phenobarbitone for various capsule sizes when solute permeation takes place from the capsule core into the surrounding sink solution. Ethylcellulose microcapsules with thick membranes were used.

MATERIALS AND METHODS

Materials
Ethylcellulose had the viscosity of 50 cp for a 5% w/w solution in toluene–ethanol mixture (80:20) w/w. All materials were of reagent grade purity.

Preparation of microcapsules
Microcapsules with a core to wall ratio of 1:2 were prepared from ethyl cellulose solutions in cyclohexane at 80 °C, by the phase separation technique induced by a temperature change. The microcapsules were separated into suitable fractions by sieving mechanically with a nest of standard sieves and a shaking time of 10 min.

Assay of the total drug content
Triplicate samples of approximately 500 mg of microcapsules were accurately weighed, thoroughly triturated, and the powder suspended in 250 ml of water. The mixture was filtered through a sintered glass suction funnel (grade 3) to separate the shell fragments. A suitable dilution of the sample was made, and the pH was adjusted to 9·3 with dilute KOH. Sodium phenobarbitone was assayed spectrophotometrically at 240 nm.

The microcapsule membranes were collected, washed and dried under reduced pressure.

Determination of wall thickness
For thick-walled capsules, an encapsulated particle can be considered as two concentric spheres having the radius of microcapsule, r_{mc}, and the radius of core, r_c. The thickness of the wall, h, can be calculated from the volume relationships of the concentric spheres as follows. The mass of the wall, m_w, is given by:

$$m_w = N \left[\frac{4}{3}\pi \, r_{mc}^3 - \frac{4}{3}\pi (r_{mc} - h)^3 \right] d_w \quad (1)$$

* Correspondence.

where N is the number of capsules and d_w is the density of the wall material. The number of particles per sample weight, m_{mc} grams, is given by

$$N = \frac{3\, m_{mc},}{4\pi r_{mc}^3 d_{mc}} \qquad (2)$$

(d_{mc} = the density of microcapsules).
Hence the following equation is obtained:

$$h = r_{mc}\left[1 - \left(1 - \frac{m_w\, d_{mc}}{m_{mc}\, d_w}\right)^{1/3}\right] \qquad (3)$$

The thickness of wall can be calculated from the densities of wall and capsules, the mass of the wall material, m_w, in a sample of microcapsules weighing m_{mc} grams.

Densities were determined from the displacement volume of a known weight of the wall material, or a sample of microcapsules, using n-hexane as the displacement fluid.

Permeation studies
The permeation process under steady state condition may be characterized by means of Fick's first law. For a sample of spherical microcapsules the permeation rate is given by:

$$\frac{dm}{dt} = D_a\, A\, \frac{\Delta c}{h} \qquad (4)$$

where m is the mass of drug released, dm/dt is the steady state permeation rate at time t, Δc the difference in drug concentration between the inside, c_2, and outside, c_1, of the microcapsules, D_a the apparent diffusion coefficient, and h the membrane thickness. A the total surface area, is defined as the product of the number of capsules in a sample and the surface area of an individual capsule i.e. $A = N\, 4\pi r_{mc}r_c$. Under the experimental condition used, $c_2 \gg c_1$, and Δc becomes c_2.

For a plot of the mass of drug transferred against

time, the permeation rate is given by the slope dm/dt, and the apparent diffusion coefficient is:

$$D_a = \frac{(slope)h}{N\, 4\pi r_{mc}r_c c_2}\ [cm^2\ s^{-1}] \qquad (5)$$

Slopes were calculated by the least squares methods and as the other parameters of the equation were known, the apparent diffusion coefficients were calculated.

Measurement of permeation
A volume of 2000 ml of distilled water is stirred until a temperature of 37 °C is reached. With continuous stirring, a sample of 0·5 g microcapsules is added. A round bottomed flask fitted with a PTFE stirrer, a syringe fitted with a Millipore filter HA 0·45 μm and a stirring spead of 50 rev min^{-1} were used. 2 ml samples were removed at intervals. After dilution of the sample, the pH was adjusted to 9·3, and the amount of diffused drug is determined at 240 nm.

RESULTS AND DISCUSSION
The properties of microcapsules prepared and fractionated into size fraction are given in Table 1. The microcapsules were essentially spherical with a smooth outer surface. The core was evenly coated with ethylcellulose. For purposes of size fraction characterization, it was possible to estimate the average thickness of the film for the ideal case i.e. assuming perfect sphericity and film uniformity, by calculation. The densities of the microcapsules and the wall material increased with decreasing capsule size, but there is insufficient evidence to suggest the cause of this.

The study of the permeation of sodium phenobarbitone from microcapsules into the surrounding bulk solution showed a known pattern of core release (Fig. 1). A suggested overall permeation mechanism of the core material by solvent penetration consists of three rates: the rate of solvent penetration into the microcapsule, the rate of core dissolution

Table 1. Characteristics of ethylcellulose microcapsules.

Size fraction	r_{mc}/cm	r_c/cm	h/cm	d_w/gcm^{-3}†	d_{mc}/gcm^{-3}†	m_w/g*†	m_c/g*†	N*
1	0·0650	0·0431	0·0219	1·020	1·035	0·3489	0·1511	420
2	0·0450	9·0326	0·0124	1·190	1·067	0·3460	0·1540	1228
3	0·0325	0·0230	0·0095	1·257	1·198	0·3390	0·1610	2905

* Expressed per 0·5 g sample of microcapsules (i.e. m_{mc} = 0·5 g).
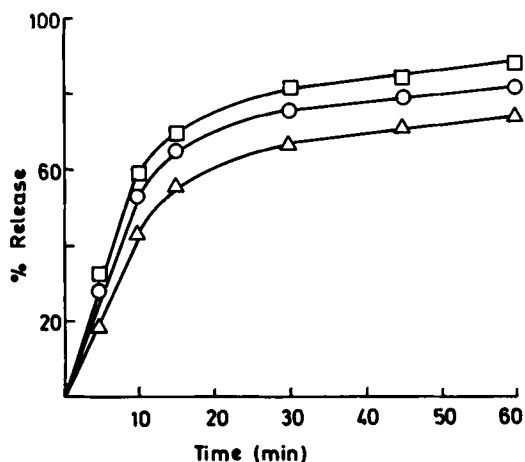† The mean value of three determinations.

FIG. 1. Plot of % drug diffused through the microcapsule membrane with time. Capsule fraction △1, ○2, □3.

and the rate of removal of core material into solution. In most systems now being studied, the rate of release of drug is controlled primarily by diffusion through a polymeric membrane. Thus the rate is determined, in general, by the solution to Fick's law (see Matthews 1975).

The permeation curves showed a linear part at the beginning of process and afterwards the plot showed a downward deviation from the straight line (Fig. 1). The linear relationship held for up to approximately 30% of the drug initially contained in the microcapsules. The calculation of the apparent diffusion coefficient in this paper was carried out with certain assumptions. If a drug is enclosed within an inert membrane, and if the drug concentration is maintained constant within the enclosure, then a steady state will be established during which the permeation rate will be constant providing the sink condition of the bulk solution are maintained. The most convenient method in achieving these demands is with a saturated solution of a drug with an excess of solid drug present in a microcapsule. The constant permeation rate ('zero-order') can be maintained as long as excess pure solid phase is present. Continual loss of drug or dilution by sorbed water will eventually produce a situation where the rate will fall. We assumed that a uniform concentration gradient in the membrane holds as long as the permeation rate is constant (Fig. 2). The solubility of sodium phenobarbitone in water is 0.333 g litre^{-1} since 0.5 g microcapsules containing approximately 0.16 g of sodium phenobarbitone, and a volume of the sink solution of
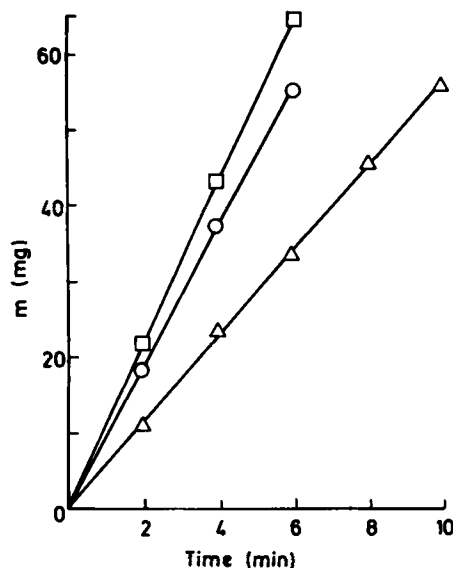

FIG. 2. Plot of amount of drug diffused into 2000 ml water, $m_{mc} = 0.500$ g. Capsule fraction △1, ○2, □3.

2000 ml were taken, sink conditions were observed and the difference in concentration of the drug inside and outside the microcapsules is equal to c_s. During the permeation process, the microcapsules remained essentially intact even after several hours of exposure to the dissolution medium. Although differential swelling of ethylcellulose in water might have taken place, we were not able to detect any alteration of the microcapsule wall, so we assumed the total surface area and the wall thickness to be constant during the permeation process. It appears that in our range of experiments all of necessary requirements are met, and therefore the apparent diffusion coefficient was calculated by using equation 5. The numerical values of D_a are given in Table 2. The apparent diffusion coefficient decreases with decreasing microcapsule size.

Table 2. Apparent diffusion coefficients for sodium phenobarbitone.

Size fraction	dm/dt × 10^4 gs^{-1}	D_a, × 10^7 cm^{2}s^{-1}	% M.D.*
1	0.929	4.13	7.2
2	1.511	2.48	6.8
3	1.776	1.86	5.3

* % difference of the most deviant result of four experiments from the mean.

These findings can be compared with the results of Ohta et al (1978) and Jalšenjak & Kondo (1981). In both of those papers the permeability coefficient was found to decrease with decreasing capsule size. Structured water in and around the microcapsule wall was suggested as the possible cause of the observed size effect, since the amount of structured water is greater in a dispersion containing microcapsules of small size in large numbers than in one containing microcapsules of a large size in small numbers (Ishizaka et al 1979; Jalšenjak & Kondo 1981). The permeability coefficient, P, can be converted to the apparent diffusion coefficient by using the equation (Takamura et al 1971):

$$D_a = P \, h. \tag{6}$$

The wall thicknesses of the thin-walled microcapsules such as the gelatin-acacia and the ethylcellulose capsules were supposed to be constant independent of the size of microcapsule (Si-Nang et al 1973; Ohta et al 1978; Jalšenjak & Kondo 1981). If this Assumption holds it may be concluded that the apparent diffusion coefficient for sodium hydroxide should also have the same trend as the permeability coefficient.

In present instance another explanation of the influence of capsule size on apparent diffusion coefficient of sodium phenobarbitone, together with structured water, could be proposed. Donbrow & Friedman (1975) have shown that a drug diffuses in the ethylcellulose film also by the solubility process in the membrane. On the other hand, it has been shown that the volume of pores in the wall of ethylcellulose microcapsules is small (Tateno et al 1978). Association of those findings with the rather high values of D_a (Table 2) we found, allows the postulation of parallel membrane and aqueous pore pathways for the transfer of the drug through the microcapsule wall. In such a case the apparent diffusion coefficient would be given by an equation:

$$D_a = (1-\alpha)D_m K + \alpha D_p, \tag{7}$$

where D_m and D_p are the diffusion coefficients in the membrane materials and the aqueous pores, respectively; α is the volume fraction of the pores in the membrane, and K is the membrane-solution partition coefficient of the drug. In our opinion the term $D_m K$ is not likely to depend on the capsule size and the increase of D_a for larger microcapsules is given by the relationship between α and $(1-\alpha)$. Support for this theory comes from the fact that the density of the deposited wall material (Table 1) is lower for larger microcapsules indicating higher porosity of their membranes.

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