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Evaluation of drug permeation through polymeric membranes as a model for release (II) ethylcellulose-walled microcapsules

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Summary

The importance of the use of ethylcellulose films as a model for drug release from microcapsules is demonstrated. The thermodynamics of the phase separation of polymer solutions, both for film formation and microencapsulation, can be interpreted by the Flory–Huggins theory. Both volume fraction of water and wettability of the model films in relation to water are affected by film casting techniques. The effect of casting methods on the permeation of theophylline through an ethylcellulose film has been demonstrated. The discrepancies in permeability between films and microcapsules are discussed.

Introduction

The potential use of a gelatin–acacia coacervate film as a diffusional model for release from microcapsules has been highlighted by Nixon and Wong (1989). The aim of this study is to use ethylcellulose model films to examine some controlling factors of drug release from the corresponding ethylcellulose-walled microcapsules. The interaction of the model films in water is studied because microcapsules are often used in an aqueous environment and dissolution from the dosage form always takes place under aqueous conditions.

Materials and Methods

Materials

Ethylcellulose (British Drug House, Lot No. 9008390 C2509); ethoxyl content 48–49.5%, viscosity of a 5% solution in 80:20 toluene; alcohol at 25°C approx. 14 CP. Sodium chloride (British Drug House, Lot No. 0411450) analar grade. Caffeine (McCarthy's H2503) anhydrous BP, theophylline (Fluka AG, 250462 784) anhydrous; cyclohexane (Fison's, BN104) SLR grade; chloroform (May and Baker) SLR grade; ethanediol (British Drug House, 9656270E) analar grade; pet-

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roleum ether (Fisons BN77, b.p. 1 W – 120 °C) SLR grade; toluene (May and Baker) SLR grade. Single distilled water was used throughout the study, with the exception that triple distilled water was used for contact measurement.

Preparation of ethylcellulose films

The methods used to prepare films can be divided into: solvent casting and temperature phase-separation techniques. The solvent casting technique used ethylcellulose in various solvent systems. Known weights of both solvent and solvent/non-solvent systems were cast. The use of non-solvent was to induce phase separation of the polymer. The compositions of the solvent/non-solvent systems were chosen from the phase diagrams of Nimmanit (1982) and Nixon and Meleka (1984).

The temperature-induced phase separation method has been described by various workers (Fanger et al., 1970; Jalsenjak et al., 1976) and a similar method was used here to prepare the free ethylcellulose films. The polymer was refluxed at 80 °C until dissolved and poured into a covered pyrex dish which was maintained at 80 °C on a thermostatic hot plate. After 5 min the hot plate was removed and the temperature of the casting substrate was allowed to decrease gradually. The dry film was peeled off after soaking in water overnight. The various compositions of the solvent systems and concentrations of ethylcellulose used are shown in Table 1.

TABLE 1

Composition of ethylcellulose film casting systems

System	Material	Composition (% w/w)
Solvent	(a) ethylcellulose	10
	toluene : alcohol (80 : 20)	90
	(b) Ethylcellulose	10
	chloroform	90
Solvent/ non-solvent phase separation	ethylcellulose	8
	chloroform	72
	ethanediol	20
Solvent/ non-solvent single phase	ethylcellulose	7
	toluene	87
	petroleum ether (100–120 °C)	6
Solvent/ non-solvent boundary of phase separation	ethylcellulose	8
	toluene	70
	petroleum ether (100–120 °C)	22
Solvent/ non-solvent phase separation	ethylcellulose	8
	toluene	48
	petroleum ether (100–120 °C)	44
Temperature-induced phase separation	ethylcellulose	0.1
	cyclohexane	to 100

Characterisation of ethylcellulose film

Morphology of ethylcellulose films by scanning electronmicroscopy All the prepared films, both before and after permeation studies, were examined by a scanning electron microscope (Philips EM501.B).

Determination of film densities An air pycnometer (Beckman Instruments Inc. Model 930) was used to determine the densities of the polymer films.

Determination of the volume fraction of water in the films The weight fraction of water present in the polymeric films was experimentally measured as W and the volume fraction, ϕ_w, in the film was calculated according to the method of Colton (1969):

$$W = \frac{\phi_w \rho_w}{\phi_w \rho_w + \phi_2 \rho_p}$$

$$\phi_w - \phi_2 = 1,$$

where ϕ_w = volume fraction of water; ρ_w = density of water; ϕ_2 = volume fraction of the polymer; ρ_p = density of the polymer.

W was obtained when the film was in equilibrium with the aqueous environment in the swelling study, as previously described (Nixon and Wong, 1989).

Assessment of film wettability The contact angle, as measured by the sessile drop technique

(Neumann and Good, 1979), was used to assess the wettability of the polymer films.

Permeation studies All experiments were performed at $37 \pm 0.5°C$, using Perspex diffusion cells (Wong, 1987). The permeabilities towards theophylline of ethylcellulose films prepared under different casting conditions were studied (Table 1).

Preparation of ethylcellulose microcapsules

A saturated solution with excess theophylline was used as a donor solution. The coating material, ethylcellulose, and the core material, theophylline, were used in a ratio of 1:1. Phase separation microencapsulation was induced by temperature change (Jalsenjak et al., 1976). A second technique used for microencapsulation was the solvent/non-solvent technique (Nixon and Meleka, 1984).

Characterisation of microcapsules

British standard sieves ranging from 63 μm to 2540 μm were used for particle analysis of the microcapsules. The surface morphology of the microcapsules was studied by scanning electron microscopy. The microcapsule density, drug content and wall thickness were determined by techniques previously described (Nixon and Wong, 1989).

Dissolution from microcapsules

Drug releases from the microcapsules were studied by a Copley dissolution system (Ultraspec TDS 4052 and Apple IIe Computer System), as described by Wong (1987).

Results and Discussion

In order to simulate the microencapsulation process, ethylcellulose films were prepared by both temperature change and solvent/non-solvent-induced phase separation.

The Flory–Huggins theory can be used to interpret the phase separation of polymer solutions (Flory, 1953). By adding a non-solvent, or lowering the temperature of a polymer solution, the Flory–Huggins interaction parameter increases above a critical value, indicating that the 'solvent' power of the system is lowered and polymer precipitation occurs.

Scanning electron micrographs (Fig. 1a, b) of ethylcellulose films demonstrated the dependence of the film structures on the casting operations. A rapid rate of dissolution and decrease in temperature of cyclohexane resulted in sudden precipitation of the ethylcellulose with incomplete fusion of the coacervate droplets (Fig. 1a). This resulted in a porous structure, which has recently been shown to occur for ethylcellulose microcapsules in some instances (Uno et al., 1984). When the rate of evaporation and the temperature of the

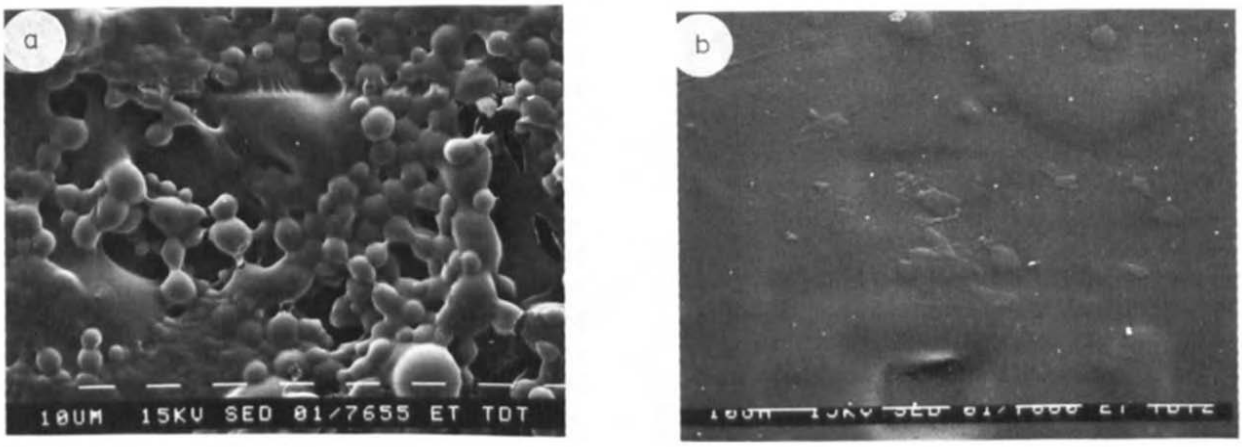

Fig. 1. Scanning electron micrographs of ethylcellulose films prepared by temperature-induced phase separation. (a) Upper surface view (840 ×). Incomplete fusion of ethylcellulose coacervate droplets due to rapid precipitation; (b) upper surface view (840 ×). Complete fusion of ethylcellulose coacervate droplets due to slow rate of dissolution and precipitation.

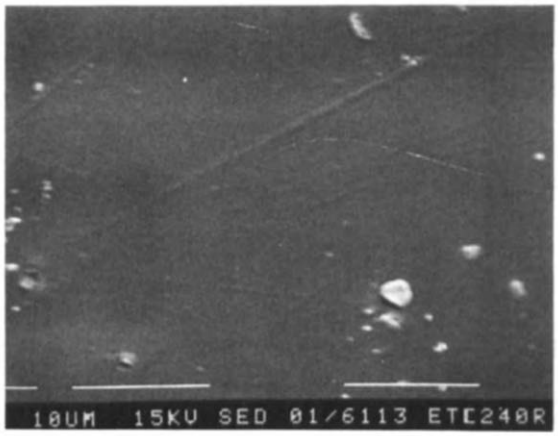

Fig. 2. Scanning electron micrograph of ethylcellulose film prepared by solvent casting (ethanol : toluene (20 : 80)). Non-porous reverse surface view (3000×).

cyclohexane was decreased gradually, complete fusion of the coacervate droplets was achieved (Fig. 1b). Micro-cracks, which can occur in cast films, may account for the unexpectedly high permeability found in some apparently dense ethylcellulose films. By contrast, ethylcellulose films prepared from cast solvents are generally non-porous and smooth (Fig. 2). The appearance of 'dense' films, prepared by solvent/non-solvent methods, was examined at a magnification of 5000×. Complete fusion of polymer coacervate droplets was observed.

The ethylcellulose films showed low degrees of hydration, as represented by the volume fraction of water (Table 2). The apparent higher volume fraction of water in the ethylcellulose film cast from the chloroform/ethanediol system could be due to the presence of unremoved ethanediol, whose hydroxyl groups could interact with the surrounding water. The ethylcellulose film prepared by the temperature-induced method also exhibited a higher volume fraction when related to the higher porosity of the film structure (Fig. 1a).

Contact angles, relevant to the ease of penetration of dissolution media into the microcapsules, were used to assess the wettability of the polymer

TABLE 2

Volume fraction, at 20 °C, of water and polymer for ethylcellulose films at swelling equilibrium

Casting conditions	Polymer density ($g\ cm^{-3}$)	Volume fraction of water	Volume fraction of polymer
Solvent cast: 10% w/w ethylcellulose in toluene : alcohol (80 : 20)	1.19	0.02	0.98
Solvent/non-solvent cast: composition of single phase region: ethylcellulose : toluene : petroleum ether (100–120 °C) (7 : 87 : 6)	1.20	0.06	0.94
Solvent/non-solvent cast: composition of boundary phase separation: ethylcellulose : toluene : petroleum ether (100–120 °C) (8 : 70 : 22)	1.20	0.07	0.93
Solvent/non-solvent cast: composition of phase separation region: ethylcellulose : toluene : petroleum ether (100–120 °C) (8 : 48 : 44)	1.20	0.07	0.93
Temperature-induced phase separation: 0.1% w/w ethylcellulose in cyclohexane	1.20	0.14	0.86
Solvent/non-solvent cast: composition of phase separation region: ethylcellulose : chloroform : ethanediol (100–120 °C) (8 : 72 : 20)	1.20	0.29	0.71

TABLE 3

Contact angles of polymeric model films of ethylcellulose

Casting conditions	Contact angles in degrees at 21°C between triple distilled water and polymer films
Solvent cast: 10% w/w ethylcellulose in chloroform	73.9±2.4
Solvent/non-solvent cast: composition of single phase region: ethylcellulose : toluene : petroleum ether (100–120°C) (7:87:6)	60.2±0.9
Solvent/non-solvent cast: composition of boundary of phase separation: ethylcellulose : toluene : petroleum ether (100–120°C) (8:70:22)	73.0±2.6
Solvent/non-solvent cast: composition of phase separation region: ethylcellulose : toluene : petroleum ether (100–120°C) (8:48:44)	72.0±2.5
Solvent/non-solvent cast: composition of phase separation region: ethylcellulose : chloroform : ethanediol (100–120°C) (8:72:20)	67.9±2.3
Temperature-induced phase separation: 0.1% w/w ethylcellulose in cyclohexane	69.5±2.8

Contact angle: mean±SD. Number of measurements = 6. Surface tension of triple distilled water at 21°C = 0.10736± 0.0012 N m^{-1}.

films. The data (Table 3) suggested that the contact angles for ethylcellulose films were influenced by the preparative conditions, which may affect the surface properties of these films.

The permeability of theophylline can be described by Fick's first law. Linear permeation curves were obtained after steady-state permeation was reached. However, two linear portions, of different slopes, were obtained for the permeation curves of films prepared by temperature-induced separation (Fig. 3). A similar observation was reported by Nasim et al. (1972). The present data suggest that the initial rapid permeation rate decreased with time as the film became saturated with the drug. This might be due to a rearrangement of the polymer molecules before diffusion reaches a steady state, or by the establishment of an aqueous-phase boundary resistance as the permeation proceeds due to saturation of the film or static layer. The effect of casting methods on the permeation of theophylline through ethylcellulose films has been demonstrated (Table 4). The permeability of the ethylcellulose films prepared by either solvent casting or solvent/non-solvent casting is very much lower in comparison to the films prepared by a temperature-induced phase separation method. The discrepancies in permeability are attributable to differences in film morphology and the volume fraction of water in the films. Films prepared by the temperature-induced method are more porous and amorphous, in contrast to films prepared by solvent casting because the latter allows time for alignments of polymer segments to form a dense crystalline structure. Permeation is considered to occur only via amorphous regions (Kesting, 1971; O'Neill, 1980).

The morphology of theophylline ethylcellulose-walled microcapsules depends on their size (Fig. 4a, b). The larger ones were aggregates of smaller microcapsules and may be classified as monolithic microcapsules. This observation applied to microcapsules prepared either by non-solvent addition or the temperature-induced method. The use of polyethylene glycol 400 as a wetting agent

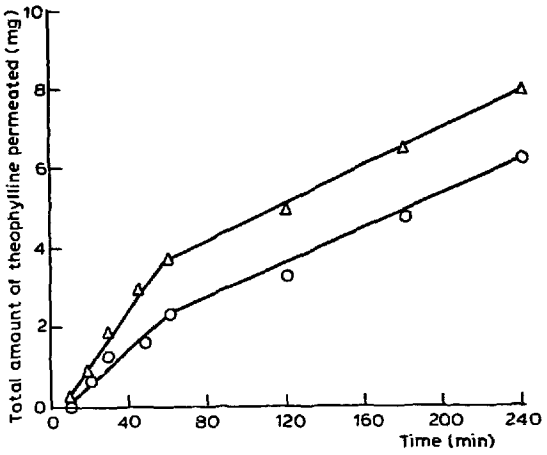

Fig. 3. Permeation of theophylline through ethylcellulose film (Clear Film) cast by temperature-induced phase separation. Film thickness, ○, 0.002 cm; △, 0.0045 cm. Donor concentration, 0.068 M (saturated theophylline in water with excess drug); temperature, 37°C.

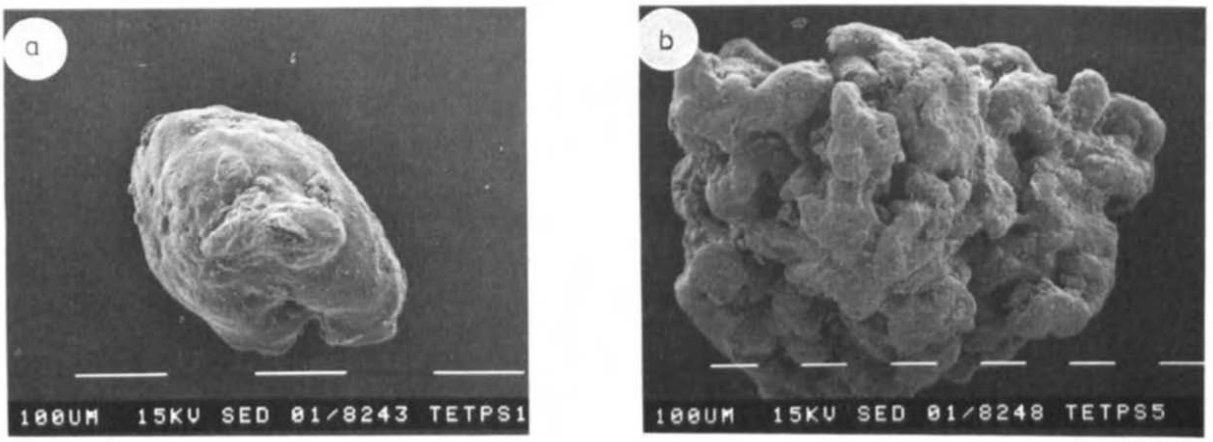

Fig. 4. Scanning electron micrographs of theophylline ethylcellulose-walled microcapsules prepared by temperature-induced phase separation. The structure of the microcapsules varies with their size. The larger microcapsules were aggregates of smaller microcapsules. Magnification: (a) 200 × ; (b) 1000 × .

to prevent the aggregation of ethylcellulose microcapsules did not cause any significant changes in the extent of aggregation or size distribution of the microcapsules.

The rate of drug release from microcapsules should depend on their surface area and wall thickness, according to Fick's first law. It is, therefore, essential to evaluate these physical parame-

TABLE 4

The effect of casting method on the permeability of ethylcellulose films towards theophylline at 37 °C

Casting conditions	Film thickness ($\times 10^4$ cm)	Apparent permeability ($cm^2\ s^{-1}$)	
		1st linear phase of release	2nd linear phase of release
Solvent cast: 10% w/w ethylcellulose in chloroform	88	1.1×10^{-11}	–
Solvent/non-solvent cast: composition of boundary of phase separation: ethylcellulose : toluene : petroleum ether (100–120 °C) (8 : 70 : 22)	73	6.4×10^{-12}	–
Solvent/non-solvent cast: composition of phase separation region: ethylcellulose : toluene : petroleum ether (100–120 °C) (8 : 48 : 44)	78	6.1×10^{-12}	–
Temperature-induced phase separation: 0.1% w/w ethylcellulose in cyclohexane	21	1.7×10^{-8}	6.0×10^{-9}

ters in relation to the overall size. They can be calculated according to Luu Si-Nang et al. (1973) and Benita and Donbrow (1982). A linear relationship between the size and wall thickness of theophylline/ ethylcellulose microcapsules was found (Fig. 5). The inverse relationship between the specific surface area and the microcapsule size is demonstrated (Fig. 6).

It should be recognised that the layer microcapsules are aggregates of smaller ones, the estimated wall thickness may not be the 'true' wall thickness and the specific surface area may be underestimated because of non-sphericity and, in turn, may differ from the surface area available for dissolution.

The drug release kinetics of theophylline/ ethylcellulose-walled microcapsules prepared by the temperature-induced technique depended on their size. The overall release kinetics were interpretable as either first order in behavior or of the type classified as 'Higuchi' matrix release. A

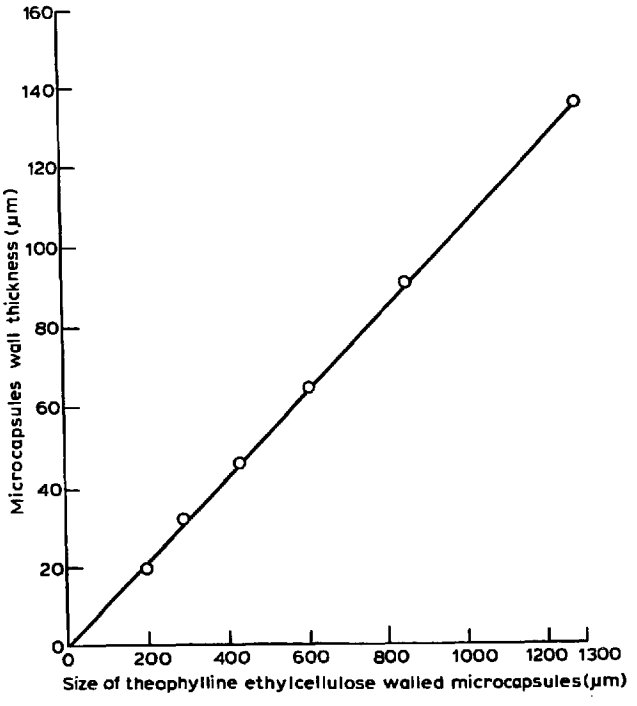

Fig. 5. Exhibition of the linear relationship between the size and wall thickness of the theophylline/ethylcellulose-walled microcapsules prepared by the temperature reduction method. No wetting agent was added; stirring speed of preparation, 1000 rpm.

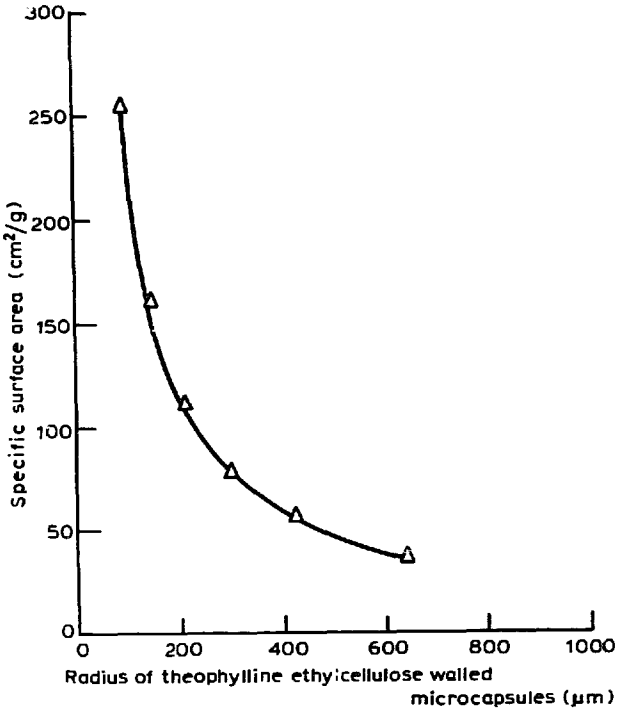

Fig. 6. The inverse relationship existing between the specific surface area and the size of theophylline/ethylcellulose-walled microcapsules. Core : wall ratio, 1 : 1; microencapsulation method, temperature-induced phase separation; no wetting agent added; stirring speed of preparation, 1000 rpm.

test based on the differential forms of the first order and square root time equation was used to distinguish the release mechanism (Benita and Donbrow, 1982). The plots of release rate against quantity released (Fig. 7) were non-linear throughout the release period for all microcapsule sizes, except the smallest mean size fraction (187 μm), which showed less aggregation and fitted first order release kinetics. The calculated membrane permeability of the ethylcellulose wall towards theophylline was 2.39×10^{-9} cm^2 s^{-1} at 37 °C and is higher than that of solvent-cast ethylcellulose films (10^{-11}–10^{-12} cm^2 s^{-1}), but similar to those prepared by temperature-induced phase separation (10^{-8}–10^{-9} cm^2 s^{-1}). The discrepancies between the permeability of model films and microcapsule walls suggest that the permeation properties of the microcapsule walls may be different from those of model membranes. Many factors may contribute to these permeability differences. Anderson et al. (1973) and Amann et al.

(1974) both pointed out that the crystallinity and permeability of a polymer can be affected by the use of different solvents and preparative conditions. Thus, the permeation of theophylline through ethylcellulose films could depend on the preparative conditions. The possibility of a larger proportion of the polymer from temperature-induced phase separation films being present in the form of amorphous structures, with either a greater porosity or a greater degree of 'free' water than is present in the model films prepared by solvent casting, could account for the higher permeability of the microcapsules prepared by the temperature-induced technique. The irregular shape of the microcapsules should also be considered. Mason et al. (1976) suggested that a non-uniform microcapsule wall thickness, coupled with macroscopic defects in the wall, could explain the differences between model films and the corresponding microcapsule permeability. In contrast, the release kinetics for microcapsules prepared by the 'Fanger' technique, with the addition of the wetting agent polyethylene glycol 400 during micro-

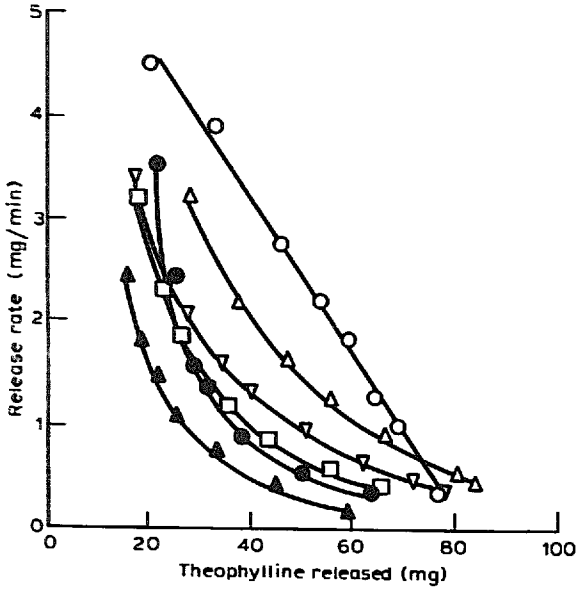

Fig. 7. Plots of the release rate against the amount of theophylline released from ethylcellulose-walled microcapsules (prepared without the addition of wetting agent). Mean microcapsule size (μm): ○, 187; △, 302; ▽, 427; □, 605; ●, 855; ▲, 1294. Dissolution medium, distilled water; pH, 5.5; dissolution stirring rate, 100 rpm; temperature, 37° C.

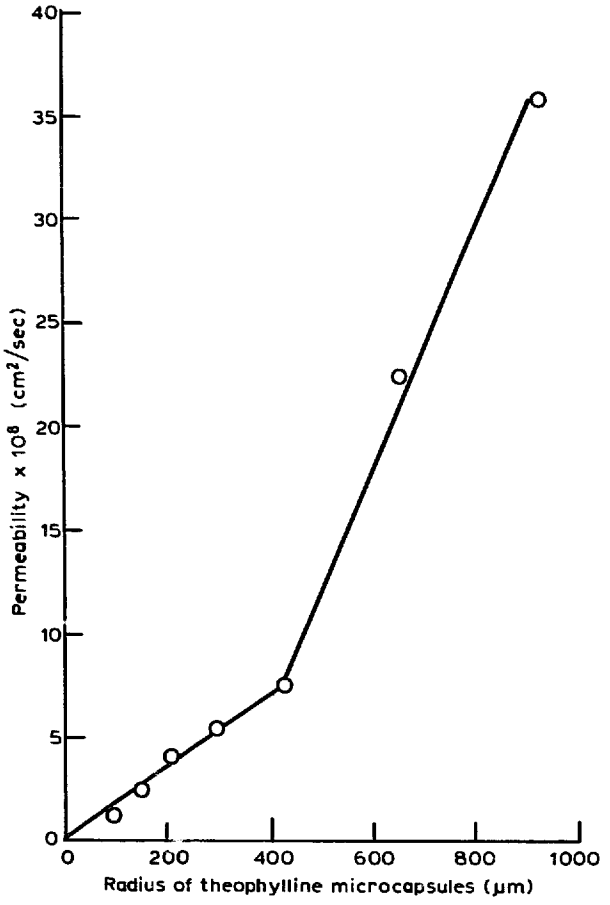

Fig. 8. Dependence of permeability on the size of the theophylline/ethylcellulose-walled microcapsules. Microencapsulation method: temperature-induced phase separation with the addition of polyethylene glycol 400 as a wetting agent. Dissolution medium, distilled water; pH, 5.5; dissolution stirring rate, 100 rpm; temperature, 37° C.

encapsulation, fitted the first order release pattern. The observed dependence of the permeability on size is shown in Fig. 8. Variations in density, porosity of the coating and 'structured' water in and around the microcapsule wall may provide some explanation of these results. The higher membrane permeability of these microcapsules, compared to those prepared without the presence of a wetting agent, might be due to the difference in porosity of the coating (Figs. 9 and 10). Dual diffusional pathways through the membrane and the co-existing aqueous pores have been postulated by Senjkovic and Jalsenjak (1980). Because of the wide size range of theophylline/ethylcellu-

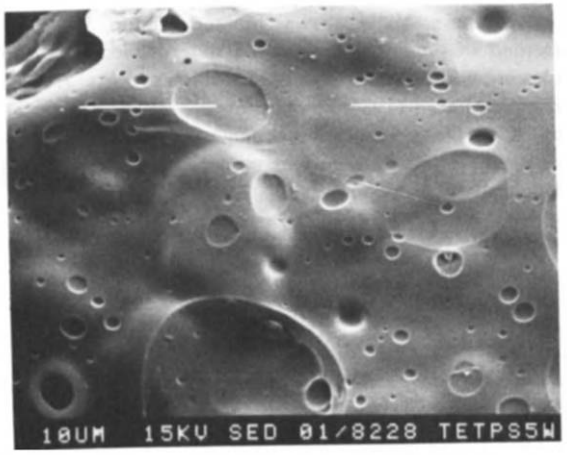

Fig. 9. Scanning electron micrographs showing pores and cracks created on the ethylcellulose-walled microcapsules after 4 h of dissolution (wetting agent added during microencapsulation). Magnification: 3300×.

lose-walled microcapsules prepared by non-solvent addition, it is difficult to differentiate the release kinetics. Herbig (1968) has indicated that the resultant release rate from a batch of microcapsules is the summation of the release rates of the individuals. Mixed kinetics might exist in the system under study. However, the use of ethylcellulose model films has highlighted the controlled factors of release from the corresponding ethylcellulose-walled microcapsules.

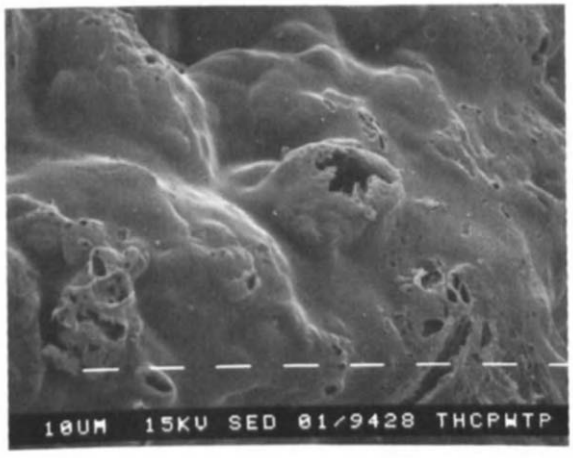

Fig. 10. Scanning electron micrographs of theophylline ethylcellulose-walled microcapsules after 4 h of dissolution (prepared without the addition of wetting agent). Magnification, 840×.

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