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International Journal of Pharmaceutics 104 (1994) 95–106

international journal of pharmaceutics

Research Papers

Porosity-controlled ethylcellulose film coating. II. Spontaneous porous film formation in the spraying process and its solute permeability

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(Received 17 January 1993; Modified version received 26 July 1993; Accepted 11 September 1993)

Abstract

A new, simple porous film formation technique for the coating of capsule-type controlled release dosage forms was investigated. When an ethylcellulose-ethanol-water ternary mixture was sprayed, a porous film was spontaneously formed during the spraying process on the basis of the phase separation principle. Various factors influencing the porosity of the resultant sprayed film were examined. The film porosity increased considerably with decreasing ethanolic concentration, whereas the polymer concentration of the spraying solution had only a slight effect and the molecular weight of the polymer even less influence. Temperature and relative humidity also apparently affected the porosity of the resultant film. To assess quantitatively the effect of film porosity on solute permeability, permeation studies were performed using five model drugs with different lipophilicities; potassium chloride, theophylline, salicylic acid, sodium salicylate and diltiazem hydrochloride. The permeation rate increased considerably with increasing film porosity. An apparent relationship between film porosity and permeability could be expressed by a power function. These results suggested that solutes predominantly permeate through micro-pores of the films, and hence that the permeation rate depends on the film structure rather than on the physicochemical properties of the solute.

Key words: Ethylcellulose; Porous film; Phase separation; Porosity; Permeability; Controlled release

1. Introduction

Over the last few decades, much attention has been focused on fabricating oral controlled release dosage forms. The polymeric film coating technique has often been utilized for achieving sustained release of the active substance from pharmaceutical preparations (Ghebre-Sellassie et al., 1988). Ethylcellulose (EC) is probably the most widely used water-insoluble polymer in film coating (Rowe, 1985; Porter, 1989) due to its good film-forming properties that enable tough, flexible coatings to be produced.

Considering the authorized dissolution mechanism of the capsule-type controlled release dosage form, the permeability of the coating as well as

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SSDI 0378-5173(93)E0275-U

the solubility of the drug contained is the most influential factor on the drug release rate (Deasy, 1984). The porosity-controlled film coating technique has often been utilized for manufacturing sustained release preparations of poorly water-soluble drugs. The incorporation of water-soluble additives into the coating is a convenient means to modify the drug release rate (Lindholm and Juslin, 1982; Källstrand and Ekman, 1983; Ritschel and Udeshi, 1987; Munday and Fassihi, 1989). Aqueous colloidal polymer dispersions or latexes have attracted much attention due to problems associated with coating with organic polymeric solutions, e.g., high solvent costs, explosion hazards, potential toxicity, etc. These materials are also used for microporous coating (Appel and Zentner, 1991; Bodmeier and Paeratakul, 1991). In such systems, the desired release rate can be achieved by an appropriate combination of the water-insoluble polymer and the water-soluble pore-forming agents.

Recently, we found that EC could spontaneously form a porous film when an EC-ethanol-water ternary mixture was cast (Narisawa et al., 1993). The pore-forming mechanism was found to be based on the phase separation of the polymer, and the density of the resultant film could be modified by the altering ethanol/water ratios of polymer solutions. These observations suggest the possibility of developing a new, simple porous film coating technique without adding any pore-forming agents.

The final goal of our study was to establish a new porosity-controlled film coating technique widely applicable for the preparation of controlled release dosage forms. Following the previous fundamental study, our study was focused on the formation of a porous EC film in the spraying process. In the present paper, using the sprayed free films of EC as a more realistic model of actual film coatings, various factors influencing the porosity of resultant films, such as ethanolic or polymeric concentrations of spraying solution, and molecular weight of polymer, were examined. In addition, in order to characterize the drug permeability of sprayed EC films, through a series of permeation studies using various model drugs with different lipophilicity, a quantitative relationship between film porosity and permeability was investigated.

2. Materials and methods

2.1. Materials

Four viscosity grades of EC, 4, 10, 45 and 100 cP (Ethocel standard premium, ethoxy content: 46–48%) were supplied by Dow Chemical Co. (U.S.A). Ethanol, potassium chloride, sodium salicylate and salicylic acid were of reagent grade and purchased from Katayama Chemical Industries Co., Ltd (Tokyo, Japan). Anhydrous theophylline was also of reagent grade and purchased from Tokyo Kasei Kogyo Co. (Tokyo, Japan). Diltiazem hydrochloride used was of JP grade and produced by Tanabe Seiyaku Co., Ltd (Osaka, Japan). Deionized water purified by reverse osmosis was used throughout.

2.2. Film preparation

All the free films used were prepared through a spray-drying process. The spraying solution was prepared by dissolving EC in aqueous ethanol. The concentration of ethanol (65–100% (w/w)) or EC (2.5–10% (w/w)) was optionally altered according to the experimental purpose. The polymer solution was sprayed onto a teflon sheet fixed on the rotor of a CF-granulator (CF-360EX, Freund Industrial Co., Ltd, Tokyo, Japan), under the following predetermined conditions: rate of revolution of the rotor, 120 rpm; spraying time, 5 min; spray air pressure, 0.8 kg/cm^2. The films formed were dried at 45°C for 18 h.

2.3. Film porosity

Film porosity (ϵ) is generally defined according to Eq. (1):

$$\epsilon = 1 - D_f/D_c \quad (1)$$

where D_f and D_c are the film density and the density of EC, respectively. D_f is defined by the values of the geometrical volume (V) and weight (W_f) of the film specimen as $D_f = W_f/V$. In the

present study, the film specimen was cut to circular shape of 5.6 cm diameter. The thickness was determined at 10 different positions using a micrometer dial gauge (Ozaki Seisakusyo Co.). In all cases, the variance of film thickness at any one point did not exceed 10% of the mean value. ϵ was determined according to Eq. 2 from the weight and mean thickness of a dried film specimen of constant surface area (24.63 cm^2) and D_e:

$$\epsilon = 1 - (W_f/24.63h)/D_e \quad (2)$$

where h is the film thickness. D_e was determined as 1.13 by measuring the density of rigid and transparent cast films prepared from EC chloroform solution. To validate the above moethod of determination, ϵ values of some specimens were also determined from the volume fraction of water in the film according to Bindschaedler et al. (1987), and both the observed values were found to be closely consistent with each other.

2.4. Scanning electron microscopy (SEM)

A scanning electron microscope (JSM-T100, Jeol Co., Ltd, Tokyo, Japan) was used to observe the morphology of the surface or cross-section of sprayed EC films. Each sample was coated with gold using an Ion Sputter (JFC-1100, Jeol Co., Tokyo, Japan) before the SEM observation.

2.5. Viscosity measurement

The viscosity of various grades of EC aqueous ethanolic solutions (10% (w/w) EC in 70% (w/w) ethanol) was measured using a digital viscometer (type DVL-B, Tokyo Keiki Co., Tokyo, Japan) at 25°C. The measurement was conducted in a stainless vessel (28 mm diameter × 108 mm height) with 50 ml of each EC solution.

2.6. Measurement of rate of solvent evaporation from EC solution

10 g of EC solution was thermostated in a jacketed beaker (diameter: 5 cm) at 30, 40, 50 and 60°C by an external circulating bath, and the solvents of the EC solution were evaporated under a constant nitrogen gas flow at 1 ml/min. Evaporation was continued until sudden precipitation of gel-phase occurred. The total amount of solvents evaporated (W_t) was calculated from the difference between the weights before and after the evaporation experiment. The water content of the residue (W_{rw}) was determined by the Karl Fischer method, and the amount of water evaporated (W_w) was calculated from the difference between the initial amount of water (W_i) and W_{rw} as $W_w = W_i - W_{rw}$. The amount of ethanol evaporated (W_e) was calculated from $W_e = W_t - W_w$. The ethanolic concentration of the solvent remaining at gelation (C_r) was evaluated from the amounts of both solvents evaporated. The mean rate of evaporation of each solvent was calculated from the amount of solvent evaporated and the time required to form the EC gel.

2.7. Permeation study

The permeation experiment was performed using a two-compartment type glass diffusion cell, which was jacketed with water at 37°C, and the exposed area of a sprayed film was 7.069 cm^2. The film was placed between both compartments with a clamp. 200 ml of an aqueous solution of drug and 200 ml of water were put into the donor and receptor cells, respectively. The drug concentration of donor solution was 0.1 M for potassium chloride (KCl) and 0.01 M for the other four drugs. Continuous stirring with glass propellers at 100 rpm was performed in both compartments. The amount of drug transported through the film was assayed with a conductivity meter for KCl and a spectrophotometer for the other drugs at predetermined time intervals.

3. Results and discussion

3.1. Formation of porous EC films during the spraying process

To determine whether porous films can be spontaneously formed during the spraying-drying process, free films were prepared from EC-ethanol-water ternary mixtures of various compositions. The appearance of the resultant film dif-

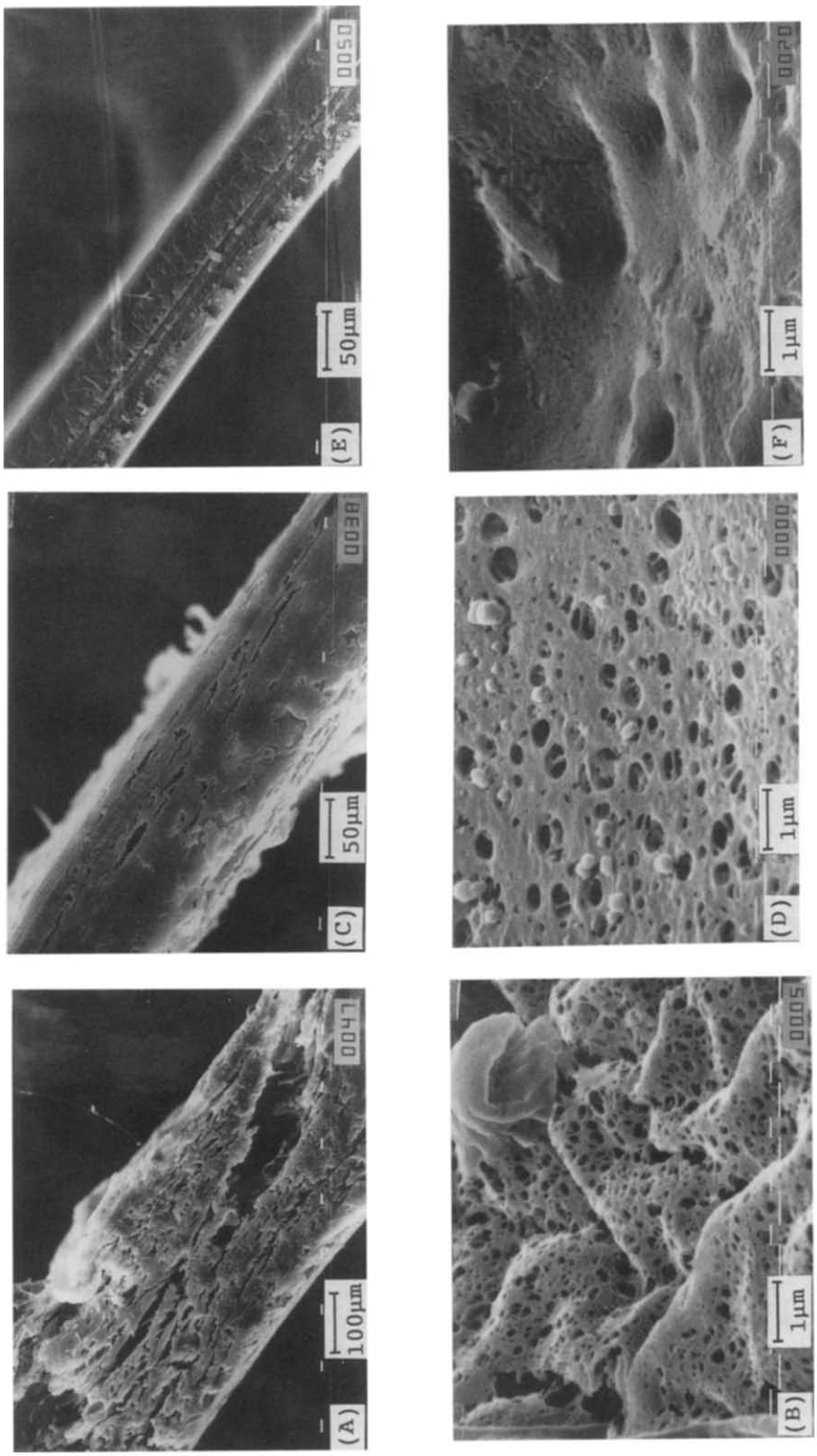

Fig. 1. Scanning electron micrographs of the cross-section (A,C,E) and surface (B,D,F) of sprayed EC films. EC grade: EC 45 cP; solvent of EC solution used for spraying: (A,B) 65% (w/w) aqueous ethanol; (C,D) 80% (w/w) aqueous ethanol; (E,F) ethanol.

fered depending on the solvent composition used. As a typical example, the morphological difference in cross-section and surface of sprayed EC films, prepared from ethanolic and aqueous ethanolic solutions (ethanol/water 65:35 and 80:20, w/w), was examined by SEM observation as shown in Fig. 1. When ethanol alone was used as the solvent, the resultant film was nearly transparent or translucent and micro-pores were found neither on the surface nor inside the film (Fig. 1E and F), suggesting that the film was completely homogeneous and the polymer molecules existed in the glassy state in the film. This is probably the typical structure of an EC film prepared by the routine organic-solvent-based coating method. In contrast, both of the films formed from the ternary mixtures were opaque and a tremendous number of micro-pores were observed on the surface (Fig. 1A and C). The diameter of the micro-pores was roughly estimated as ranging from 1 or 2 μm to less than 1 μm. Although an equal amount of EC solution was sprayed, the film thickness and the number of micro-pores increased with increasing water content in the polymer solution. These results clearly show that a porous EC film is spontaneously formed even during the spraying process as well as the casting process.

3.2. Various factors affecting the film porosity

In a previous report (Narisawa et al., 1993), we discussed the pore-forming mechanism of EC cast films from EC-ethanol-water ternary mixtures on the basis of the phase separation principle, in which the critical ethanolic concentration for gelation (C_g) was found to be about 62% (w/w). As shown later, since the rate of evaporation of ethanol is much faster than that of water, the solvent composition of the sprayed solution gradually changes, becoming less soluble for EC during the solvent evaporation process. When the ethanolic concentration decreased to less than the C_g, all the polymer molecules formed a gel-like coagulation phase. After gelation, due to the structural rigidity of the gel, further evaporation occurred from the inside of the gel phase and continuous association of the polymer molecules finally yielded a xerogel with a considerable number of opening pores. The concentration of EC at C_g in the spraying process seemed to affect film porosity as well as the formation of cast film. Therefore, various spraying conditions should be influential factors on film porosity.

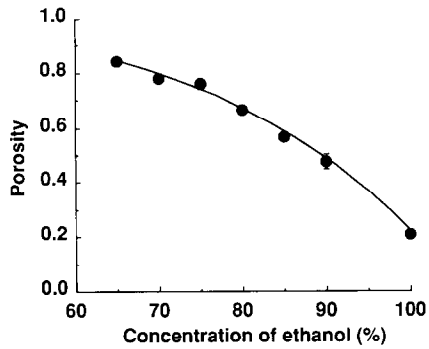

Fig. 2. Effect of ethanolic concentration on porosity of sprayed EC film. Conditions: EC grade, EC 45 cP; EC concentration, 10% (w/w); spraying solution feed, 10 ml/min; temperature, 30°C; relative humidity, 60%. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n = 5$).

Fig. 2 shows the relationship between the solvent compositions of the spraying solutions (EC-ethanol-water ternary system) and the porosity of the resultant film. As is clear in Fig. 2, when the ethanolic concentration of solvent decreased from 100 to 65% (w/w), the film porosity gradually increased from 0.21 to 0.84, indicating that a greater proportion of water in the polymer solution led to a more porous film. This suggests that the porosity of the sprayed EC film can be readily modified over a rather wide range in pharmaceutical coatings merely by changing the ethanol/water composition of the solvent. When more water is contained in the initial polymer solution, precipitation of the gel phase occurs earlier, therefore, the volume of the gel phase formed will be greater. Thus, a larger gel phase which contains more water can lead to a more porous film.

Although the observed relationship appeared to be quite consistent with the results obtained in cast films, the porosity values were slightly greater than those of cast films (when the corresponding polymer solution was cast, the porosity of the resultant film varied from 0.12 to 0.79). This

could be caused by a difference in the film-forming mechanism between both preparation processes (Allen et al., 1972; Spitael and Kinget, 1977; Porter, 1982). Namely, in the casting process, the evaporation of solvent is comparatively slow so that the films would be formed with sufficient rearrangement of polymer molecules, whereas in the spraying process, the solvent of the atomized polymer solution undergoes rapid evaporation on the substrate, so that the polymer molecules would be quickly fixed at the ultimate location (Lindholm et al., 1987). Consequently, a cast film generally gives a more dense structure compared with a film prepared by the spraying method. In addition, sprayed films are thought to be formed by layering of small pieces of films, each of which was formed by the finely atomized EC solution droplets. In such a case, small void spaces would inevitably be left between the spray-dried polymer films of unit constituents.

To examine the effect of the molecular weight (M_w) of EC on the film porosity, sprayed films were prepared using four viscosity grades of EC with different M_w values under identical spraying conditions. The viscosity of the spraying solutions and the porosity of resultant films are listed in Table 1. Although the viscosity of the polymer solution may be an influential factor on the droplet size and spreadability of the spraying solution, which may affect the quantity of void space formed in the unit films, only a minor change was found in the porosity of the resultant film. In the previous paper, we showed that the C_g value was almost independent of the M_w of EC and hence M_w did not affect the density of the cast film (Narisawa et al., 1993). Thus, the present result was consistent with that for cast films with respect to the effect of viscosity on film porosity.

Table 1
Effect of molecular weight of EC on film porosity [a]

EC grade	Viscosity (mPa s)	Porosity (mean ± SD) [b]
4	101	0.79 ± 0.022
10	227	0.82 ± 0.013
45	2285	0.76 ± 0.004
100	5940	0.75 ± 0.015

[a] Conditions: EC concentration, 10% (w/w); ethanolic concentration, 70% (w/w); temperature, 30°C; relative humidity, 60%.
[b] $n = 5$.

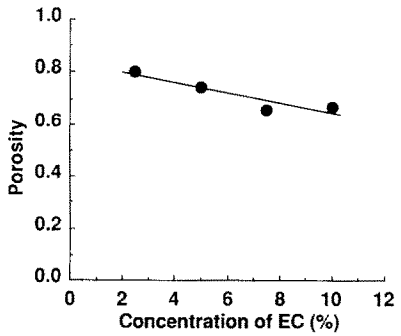

Fig. 3. Effect of EC concentration on porosity of sprayed EC film. Conditions: EC grade, EC 45 cP; ethanolic concentration, 70% (w/w); spraying solution feed, 20 ml/min; temperature, 30°C; relative humidity, 60%. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n = 5$).

Sprayed films were prepared with EC concentrations varying from 2.5 to 10% (w/w) using a 70% (w/w) aqueous ethanolic solution as solvent. Fig. 3 shows the change in porosity of the resultant films as a function of EC concentration. The porosity slightly decreased as EC concentration increased. Since C_g was found to be constant irrespective of EC concentration, when a solution containing a greater level of EC is sprayed, the concentration of polymer in the precipitated gel phase is expected to increase, resulting in a slight decrease in film porosity.

The temperature and environmental humidity must also be important factors influencing film porosity during the preparation process, since both can affect the volume of the EC gel phase at C_g (V_g) by altering the balance between the rates of evaporation of solvent (ethanol) and non-solvent (water). The free films were prepared by spraying the polymer solution at different temperatures (30, 35, 40 and 50°C). Fig. 4 depicts the effect of temperature on the porosity of the sprayed film. The film porosity decreased with increasing temperature.

This temperature effect was considered to be correlated with the difference in temperature de-

Table 2
Rate of evaporation and C_r values at various temperatures

Temperature (°C)	Rate of evaporation (g/min)		Ratio of evaporation rates [a]	C_r [b] (% (w/w))	EC_g [c] (% (w/w))
	Ethanol	Water			
30	0.089	0.018	4.93	60.9	8.42
40	0.161	0.038	4.23	61.3	8.97
50	0.227	0.054	4.20	60.9	9.18
60	0.269	0.068	3.97	60.8	9.59

[a] Ethanol/water.
[b] Ethanolic concentration of the solvent remaining at gelation.
[c] EC fraction in the gel phase.

pendency of the rate of evaporation of ethanol and water from the spraying solution of EC. Therefore, the changes in rate of evaporation of ethanol and of water from an EC-ethanol-water ternary mixture with temperature were assessed through a series of evaporation experiment. The results are shown in Table 2 along with the ethanolic concentration of the solvent remaining (C_r) and the EC fraction in the precipitated gel phase (EC_g). The C_r was almost independent of temperature and was almost coincident with the C_g (about 62% (w/w)) determined via the titration method (Narisawa et al., 1993). The results suggested that the change in C_r value with temperature could be negligible. Although the rates of evaporation of ethanol and water increased greatly with increasing temperature, the rate of evaporation of water was more strongly influenced by temperature than that of ethanol. Therefore, the ratio of the rate of evaporation of ethanol to that of water decreased. This indicates that, under higher temperature conditions, greater amounts of solvent must evaporate in order for C_g to be attained. Consequently, the volume of the gel phase should become smaller, resulting in lower film porosity. This was supported by the experimental observation that the EC_g values increased with increasing temperature. Besides the rate of evaporation, the rheological behavior of the precipitated gel phase may be another influential factor. The fluidity of the gel phase may increase with increasing temperature, so that the precipitated gel phase possibly deforms to a more dense structure under higher temperature conditions.

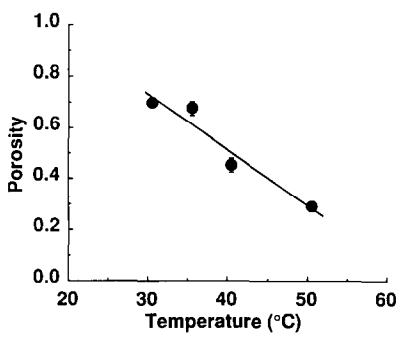

Fig. 4. Effect of temperature on porosity of sprayed EC film. Conditions: EC grade, EC 45 cP; EC concentration, 10%; ethanolic concentration, 75% (w/w); spraying solution feed, 10 ml/min; relative humidity, 60%. The absence of an error bar indicates that the standard deviation of the data was smaller than the size of the symbol ($n = 5$).

Table 3 lists the data on film porosity for preparation under different humidity (45 and 80% RH) at constant temperature. Even though a polymer solution with identical composition was sprayed, the porosities of the resultant films differed from each other. The film prepared under higher humidity showed a greater value than that prepared under lower humidity. This could be brought about by a difference in the rate of water

Table 3
Effect of humidity on film porosity [a]

Relative humidity (%)	Porosity
45	0.68
80	0.80

[a] Conditions: EC grade, EC 45 cP; EC concentration, 10% (w/w); ethanolic concentration, 70% (w/w); spraying solution feed, 10 ml/min; temperature, 30°C.

evaporation, since high water vapor pressure can hinder the evaporation of water whereas a smaller effect would occur in the case of ethanol. Therefore, under higher humidity, decreasing ethanolic concentration of the spraying solution will lead to C_g more rapidly during the evaporation process, resulting in greater porosity.

From these results, the conclusion was drawn that the pore-forming mechanism may be considered to be essentially common to both the casting and spraying process, even though the preparation method differs.

3.3. Effect of film porosity on solute permeability

When utilizing porous EC films as a barrier of capsule-type controlled release dosage forms, a knowledge of how the film porosity influences drug permeability or of the relation between both parameters is essential. Although several investigators have conducted drug permeation studies on various types of films (Shah and Sheth, 1972; Donbrow and Friedman, 1975; Spitael and Kinget, 1977; Benita et al., 1986; Dor et al., 1987; Lindholm et al., 1987), little is known about the quantitative relation between drug permeability and film structure. The porous EC films described here have a distinctive structure with a large number of micro-pores. Although all of the pores may not always act as permeation routes, the majority should contribute to drug permeation in various ways. Three pathways can be considered for drug permeation through the films: (1) the route through the continuous EC phase (diffusion-partition process); (2) the route via the micro-pores; or (3) through parallel routes (Rowe, 1985; Koida et al., 1987). A drug will permeate through either pathway depending on its physicochemical properties. A drug, which scarcely distributes to the polymer matrix phase, should permeate exclusively through water-filled pores. For studying pore-route permeation through porous EC films, KCl should be an appropriate model solute, since it dissociates completely in water and probably undergoes less interaction with cellulose membranes (Nambu et al., 1971).

Fig. 5 demonstrates the permeation profiles of KCl through various sprayed EC films with different porosities, which were prepared by changing the ethanol/water composition of the polymer solution from 65:35 to 90:10.

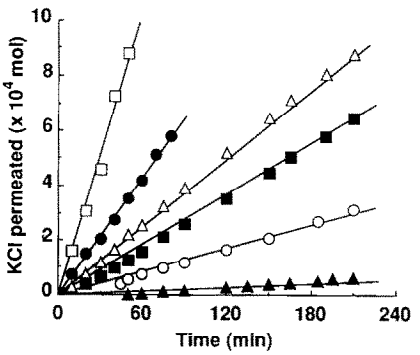

Fig. 5. Permeation profiles of KCl through sprayed EC films with different porosities at 37°C. EC grade: EC 45 cP; film porosity: (▲) 0.50; (○) 0.58; (■) 0.67; (△) 0.76; (●) 0.78; (□) 0.84.

Since all the profiles are indicative of a linear relation, the permeation process for linear flow under steady-state conditions may be characterized by Fick's first law (Jost, 1960). This can be expressed in the form:

$$dQ/dt = P(C_d - C_r)/h \quad (3)$$

where Q is the cumulative amount of drug which has permeated in time t through unit surface area of the film, P denotes the permeability coefficient, h is the thickness of the film, and C_d and C_r represent the drug concentrations of donor solution and receptor solution, respectively. Under the experimental conditions used at the beginning of permeation, $C_d \gg C_r$, hence, Eq. 3 can be rewritten as follows:

$$dQ/dt = PC_d/h \quad (4)$$

Thus, integration of Eq. 4 and expression as change in drug amount (Q) vs time yields:

$$Q = PC_d t/h \quad (5)$$

The profiles shown in Fig. 5 are in conformity with Eq. 5.

From the results of the KCl permeation study, dQ/dt values were obtained from the slope of the permeation profile (Fig. 5) according to Eq. 5 and P values were calculated using C_d and h according to Eq. 4 for each film. The values

Table 4
Results of permeation study of KCl at 37°C

Ethanol [a] (%)	h ($\times 10^4$) (cm)	ϵ	dQ/dt ($\times 10^9$) (mol/s per cm^2)	P ($\times 10^6$) (cm^2/s)
65	291.5	0.84	39.84	11.60
70	211.6	0.78	25.53	5.40
75	215.6	0.76	10.08	2.17
80	123.2	0.67	7.54	0.93
85	92.4	0.58	3.73	0.34
90	64.5	0.50	0.90	0.06

[a] Ethanolic concentration of EC solution used for preparation of sprayed EC films.

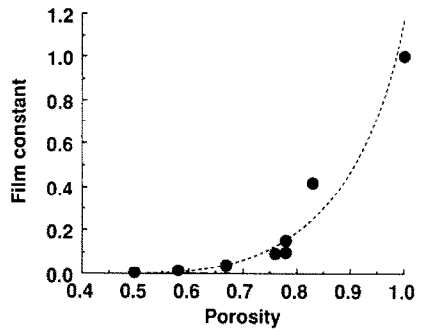

Fig. 6. Relationship between film porosity (ϵ) and film constant (f). The curve represents the relation defined by Eq. 9.

obtained are listed in Table 4 along with the dimensional parameters of the sprayed EC films used. It was shown that, even though the film thickness varied, higher porosity gave rise to greater permeability.

Since KCl is considered to diffuse exclusively through aqueous pores of the film, the solute diffusivity should be strongly influenced by the internal structure of the porous film. In such a case, P can be expressed as follows:

$$P = D_w \epsilon / \tau \quad (6)$$

where D_w is the diffusivity of the solute in water and τ denotes tortuosity (Peppas and Meadows, 1983; Ghebre-Sellassie et al., 1987). The film constant (f) is often used as a parameter representing the effect of film structure on the permeation behavior of a solute, and is expressed as a function of porosity and tortuosity as follows:

$$f = \epsilon / \tau \quad (7)$$

Consequently, Eq. 6 is rewritten as follows:

$$P = f D_w \quad (8)$$

The f value was calculated for each film using Eq. 8 from the P value listed in Table 4 and the D_w of KCl (2.28×10^{-5} cm^2/s at 37°C) (Nakagaki et al., 1962). The f values obtained were plotted against ϵ as shown in Fig. 6. According to Eq. 7, if τ is constant irrespective of ϵ, a linear relationship exists between ϵ and f. However, f increased considerably with increase in ϵ (Fig. 6), implying that a drastic change in τ had occurred with the change in ϵ. The τ values for each film calculated using Eq. 7 are listed in Table 5. The τ values were changed considerably (from 1.66 to 195.70) according to the change in ϵ (0.50–0.84). The relatively large τ value found may be understandable when taking the unique structure of the sprayed EC film into consideration. Namely, the sprayed film used here is believed to consist of a large number of small pieces of films, constituting a layered structure. In such a case, the water channels in the film, which are created by the connecting water-filled void space, should bend considerably along the layered structure. As the void space decreases, the branching of the pathway should decrease, resulting in the extremely greater tortuosity.

Although the relationship between f and ϵ may still involve several unknown factors, various functions were examined in order to determine a fit to the ϵ-f relationship shown in Fig. 6. As a result, the relation could be conveniently expressed as a type of power function: $f = A\epsilon^n$, where A and n are constants. Regression analy-

Table 5
Parameters representing the structure of EC sprayed film

Ethanol [a] (%)	Porosity	f ($\times 10^2$)	τ
65	0.84	50.88	1.66
70	0.78	23.68	3.31
75	0.76	9.53	7.97
80	0.67	4.07	16.52
85	0.58	1.51	38.53
90	0.50	0.25	195.70

[a] Ethanolic concentration of EC solution used for preparation of sprayed EC films.

sis including the diffusion coefficient ($\epsilon = 1$) provided the following experimental equation:

$$f = 1.18\epsilon^{8.55} \quad (R = 0.98) \tag{9}$$

where R is a determination constant of regression analysis, and the R value found indicates that all the data provide a close fit to the given regression line. Under ideal conditions, the value of A should be unity, since when $\epsilon = 1$, then theoretically $\tau = 1$, so that $f = 1$ according to Eq. 7. Although slightly larger, the A value obtained from this regression analysis was considered to be satisfactory. The exponent n indicates the degree of contribution of ϵ to f. The large value of n found indicates that the film has a rather complicated internal structure.

If a drug does not undergo any physicochemical interactions with the polymer and permeates only through aqueous pores, the P of the drug can be expressed by Eq. 10, which is deduced from Eq. 8 and 9:

$$P = 1.18\epsilon^{8.55} D_w \tag{10}$$

Taking the logarithm of both sides of Eq. 10 gives Eq. 11:

$$\log P = 8.55 \log \epsilon + \log D_w + 0.072 \tag{11}$$

In order to evaluate the feasibility of the proposed equation, and to examine whether the permeation mechanism differs depending on the drug species, another series of permeation studies were conducted using four model drugs: theophylline, salicylic acid, sodium salicylate and diltiazem hydrochloride which differ in lipophilicity. That is to say, log P_C is -0.09 (theophylline), 2.23 (salicylic acid) and 2.70 (diltiazem hydrochloride), respectively, where P_C is the octanol-water partition coefficient (Illum et al., 1983; Yalkowsky et al., 1983). The logarithm of the P value obtained was plotted vs the logarithm of ϵ of the films in Fig. 7 for each drug. The broken line in each panel corresponds to the predicted relation as deduced from Eq. 11. If the drug diffuses only through water-filled pores, the P value found should be on the predicted line. All the data seem to occur almost along the predicted line,

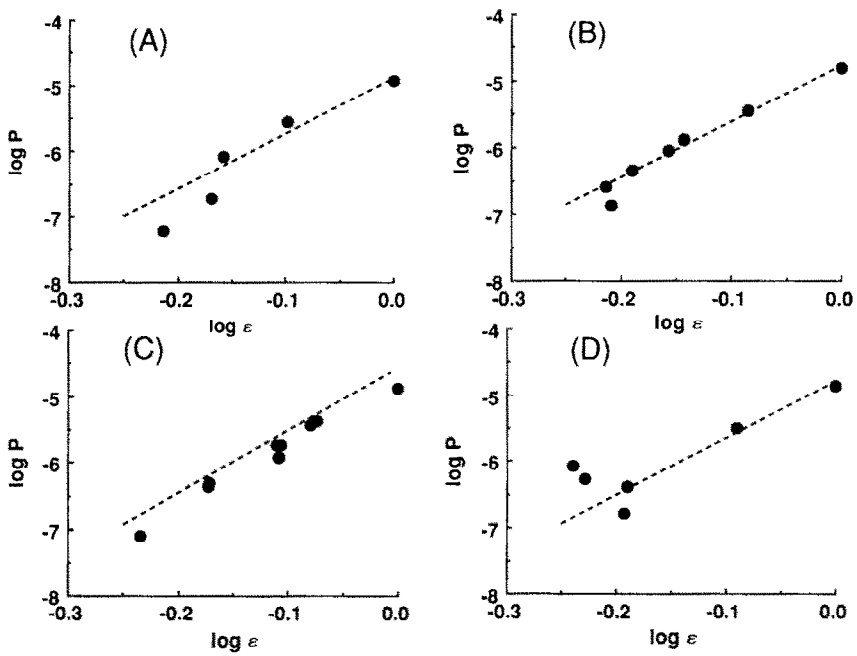

Fig. 7. Relationship between film porosity (ϵ) and permeability coefficient (P) for the permeation of theophylline (A), salicylic acid (B), sodium salicylate (C) and diltiazem hydrochloride (D) through sprayed EC films at 37°C. The broken line corresponds to the predicted relation as deduced from Eq. 11. D_w: theophylline, 1.20×10^{-5} cm^2/s; salicylic acid, 1.53×10^{-5} cm^2/s; sodium salicylate, 1.34×10^{-5} cm^2/s; diltiazem hydrochloride, 1.38×10^{-5} cm^2/s.

even though some fluctuations were involved. Therefore, the main permeation mechanism of either of the drugs is diffusion through aqueous micro-pores in the film. Although it is known that salicylic acid can readily be distributed into the EC matrix phase (Donbrow and Friedman, 1975), the permeation mechanism occurs predominantly via micro-pores. This is because diffusion in aqueous micro-pores can be considered to be much faster than that in the continuous polymer phase (Donbrow and Friedman, 1975; Conrad and Robinson, 1982).

4. Conclusions

Through the present study, porous EC films were proven to form spontaneously during the spray-drying process on the basis of the phase separation principle. The porosity of the resultant film can be most effectively controlled by selecting the appropriate composition of ethanol and water in the spraying solution. The EC concentration of the spraying solution, temperature and relative humidity also affect the film porosity. The permeation studies revealed that drugs predominantly permeate via water-filled pores in the film irrespective of the drug species, and that a certain relationship expressed by a power function exists between film porosity and drug permeability. These findings should be very useful in order to establish a new porosity-controlled film coating technique using EC for controlled release dosage forms.

5. References

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