Porosity-Controlled Ethylcellulose Film Coating. I. Formation of Porous Ethylcellulose Film in the Casting Process and Factors Affecting Film-Density

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In an attempt to develop a new simple porous film coating technique for oral controlled release dosage forms, the pore formation of ethylcellulose (EC) in the casting process was investigated. When an EC–ethanol–water ternary mixture was cast, the porous film was spontaneously formed *via* the processes of coacervation and gelation of the polymer. The visual and microscopic observations revealed that pore formation proceeded on the basis of the phase separation mechanism, in which ethanol and water acted respectively as a solvent and a non-solvent for the polymer. Gelation, which is an important process for determining the density of the resultant film, occurred during evaporation when the decreasing ethanol concentration reached the critical concentration of about 62%. This value was almost constant irrespective of polymer concentration and molecular weight. The density of porous EC film was changed by formulation variables of the casting solution, such as ethanol or polymer concentration and organic solvent species. The permeation study of porous EC films was conducted using salicylic acid as the permeant. The permeability of salicylic acid was changed according to the film density; that is, the permeability coefficient exponentially increased with a decrease in film density, suggesting that the drug permeability of the cast film can be modified by controlling film density.

Keywords ethylcellulose; porous film; coating; phase separation; controlled release; permeability

Introduction

Ethylcellulose (EC) is probably the most widely-used water insoluble polymer in pharmaceutical film coating[1] because of the many advantages it affords formulators, such as good film formability, excellent physicochemical stability, minimum toxicity, *etc.* Especially, an increasing interest in the controlled release dosage form has led many researchers to attempt extending the use of EC to various dosage forms[2] and to develop new coating techniques like the recent introduction of aqueous latex dispersions of this polymer.[3]

The major aim of EC film coating is to provide an effective means for rate control of drug release; such dosage forms are commonly termed "capsule-type controlled-release systems,"[4] "diffusion-controlled reservoir devices"[5] or "membrane-moderated controlled release systems."[6] With such a system, the active material diffuses from the core materials through the rate-controlling film into the surrounding environment. Typically, such factors as film porosity, tortuosity, surface area and thickness play an important role in determining the rate at which the drug can pass through the coating.[7] Since such factors are naturally influenced by the structure of the film coating, it is very important to form a desirable structure of coating so as to provide the most suitable release rate of the drug concerned.

Many studies have been done in an attempt to modify the structure of EC film. Rowe demonstrated that the selection of an appropriate plasticizer helped to improve the barrier properties of EC coatings, resulting in a reduction in release rate of the drug.[8] Incorporation of some water soluble additives to EC is frequently attempted to enhance the permeability of the film.[9] In these systems, however, to obtain good reproducibility of the drug release rate, a lot of care must be taken regarding the distribution of additives in the film, because it affects the film structure and can thus cause a variation in the drug release rate.

Porous film coating, which potentially contains a tremendous number of small pores, may be a useful means of providing the precise control of drug release. Since this type of coating does not require the addition of any pore-forming additives, the formula of the coating solution would be simpler and the procedure of coating would be easier. In addition to facilitating the coating process, porous film coating may improve the reproducibility of the release rate.

The main purpose of our present work is to develop a simple, new porous film coating technique using EC without adding any pore-forming agents. In this paper, the pore-forming mechanism of the EC film cast from an EC–ethanol–water ternary system and factors influencing the density of film are examined. In addition, through the solute permeation study, the effect of film structure on drug permeability will be discussed.

Experimental

Materials Five viscosity grades of EC (Ethocel standard premium, 4, 10, 20, 45 and 100 cP, Dow Chemical Co., U.S.A.) were used as received. Ethanol and salicyclic acid were of a reagent grade and purchased from Katayama Chemical Industries Co., Ltd. (Tokyo, Japan). All materials were used without further purification. Deionized water purified by reverse osmosis was used throughout.

Preparation of EC Cast Film EC solution was cast on a teflon sheet fixed on a glass plate at 25 °C under controlled humidity. The solvent composition or the EC concentration of the solution was optionally changed according to the experimental purpose. After casting, the solution was placed so that the solvent could evaporate at room temperature for 3 h, and the film formed was dried at 45 °C for 18 h.

Measurement of Film Density Film thickness was determined at ten different positions on a specimen with the dimension of 4×4 cm using a micrometer dial gauge (Ozaki Seisakusho Co., Japan). The film density (d) was calculated from average thickness (X), film weight (W) and known film area (S) of the specimen as; $d = W/SX$.

Scanning Electron Microscopy (SEM) A scanning electron microscope (JSM-T100, JEOL Co., Ltd., Japan) was used to observe the morphology of EC cast film. Each sample was coated with gold by Ion Sputter (JFC-1100, JEOL Co., Ltd., Japan) before the SEM-observation.

Solubility Study of EC 2 g of EC (45 cP) was dissolved with 18 g of 70% aqueous ethanolic solution in a 50 ml test tube. Then 24 g of aqueous ethanolic solutions with various ethanolic concentrations were added to adjust the ethanolic concentration to the predetermined level, and thus the EC concentration was 4.55%. The tubes were then shaken violently for several hours and placed at 25 °C for 5 d. After equilibration was attained, the mixture was centrifuged to separate the liquid phase. An aliquot of the liquid phase was dried, and the residual EC was weighed to determine the amount of EC dissolved in the liquid phase.

Determination of Critical Concentration of Organic Solvent for Gelation (C_g) The titration method was applied. Water was added dropwise to 20 ml of EC (45 cP) organic solution in a 50 ml test tube with shaking at 25 °C. The titration was stopped when the EC solution abruptly changed to cloudy and EC gel was formed. The C_g value was calculated from the amount of organic solvent and the amount of water added.

Permeation Study The permeation experiment was performed using a two-compartment type glass diffusion cell, which was jacketed with water at 37 °C, and exposed area of a cast film was 7.069 cm^2. The film was placed between both compartments and fixed with a clamp. The upper surface of the film was faced to the receptor solution. Salicylic acid was used as the permeant. 200 ml of an aqueous solution of a drug (0.01 M) and 200 ml of water were put into the donor cell and the receptor cell, respectively. Continuous stirring with glass propellers at 100 rpm was performed in both compartments. The amount of drug transported through the film was assayed photometrically at predetermined time intervals.

Results and Discussion

Formation of Porous EC Film in the Casting Process To demonstrate the morphological characteristics of porous EC film, the appearances of EC cast films prepared from aqueous ethanolic solution and ethanolic solution were compared. As shown in Fig. 1, the cast film prepared from ethanolic solution was almost transparent and had quite a smooth surface, whereas the film prepared from the aqueous ethanolic solution was turbid and had a somewhat rough surface. SEM observation of the cross-section of both cast films revealed that the inner structure of films was considerably changed by the solvent used for casting; that is, the cast film prepared using 65% aqueous ethanol showed a thick and porous structure (Fig. 2A), whereas when ethanol alone was used, the resultant film had a thin and homogeneous structure (Fig. 2B). These results suggest that EC spontaneously formed a porous film during the film forming process after casting when a mixture of ethanol and water was used as the solvent.

The visual and microscopic observations of the film forming process revealed that the two films were formed in a completely different manner. When ethanol alone was used as the solvent, the casting solution was merely condensed during solvent evaporation until the polymer molecules were finally immobilized in a glassy state. Consequently, the resultant film was obviously transparent and did not contain any pores. On the other hand, when an aqueous ethanolic solution was used as the solvent, the porous film was formed through a more complicated process including coacervation and gelation.

Figure 3 is the schematic representation of the pore-forming process of the film prepared from the EC–ethanol–water ternary mixture, which is depicted according to our microscopic observation. When the polymer solution was cast, the solution was almost uniform at the initial stage. However, as the solvent evaporated, a large number of coacervation droplets appeared near the surface of the cast solution, and then gradually grew into contact with each other until they formed a gel-like coagulation phase. In the subsequent process of further evaporation, the gel phase gradually turned into the solid-state and finally yielded a xerogel with numerous opening pores. Cellulose acetate was known to form micro-porous films during the film-forming process on the basis of the micro-phase separation process.[10] This technique has been exclusively applied for manufacturing reverse osmotic membranes. The observed pore-forming process of EC film was quite similar to that reported by Kesting,[10a] in which porous cellulose acetate film was produced from a solution containing cellulose acetate, acetone, water and a swelling agent. Therefore, porous EC film was thought to be formed by basically the same mechanism. In the above case, ethanol and water acted as

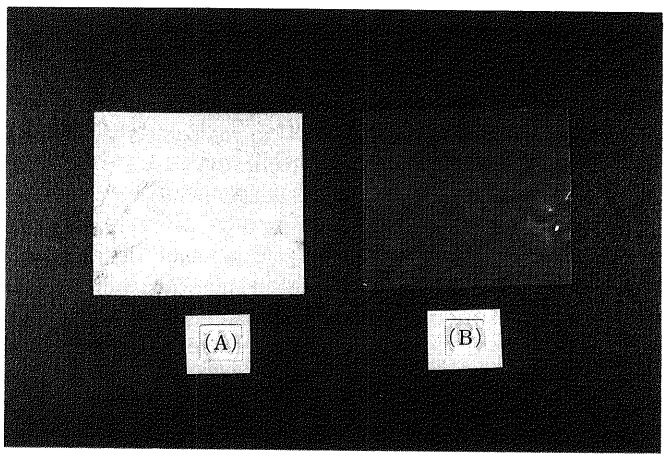

Fig. 1. Comparison of the Appearances of EC Cast Films

EC grade: EC 45 cP; solvent of EC solution used for casting: (A), 65% aqueous ethanol; (B), ethanol.

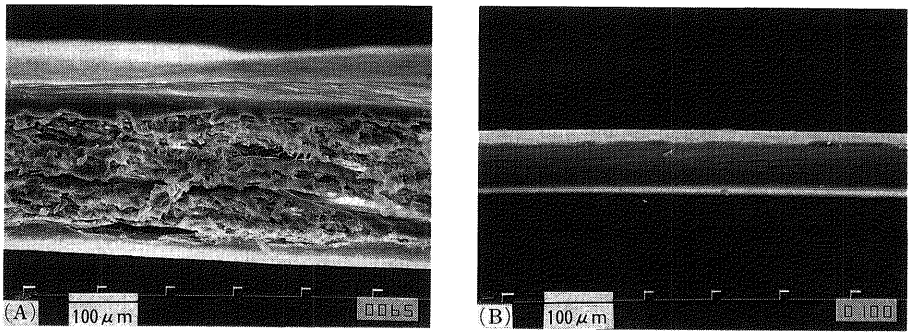

Fig. 2. Scanning Electron Micrographs of the Cross-Section of EC Cast Films

EC grade: EC 45 cP; solvent of EC solution used for casting: (A), 65% aqueous ethanol; (B), ethanol.

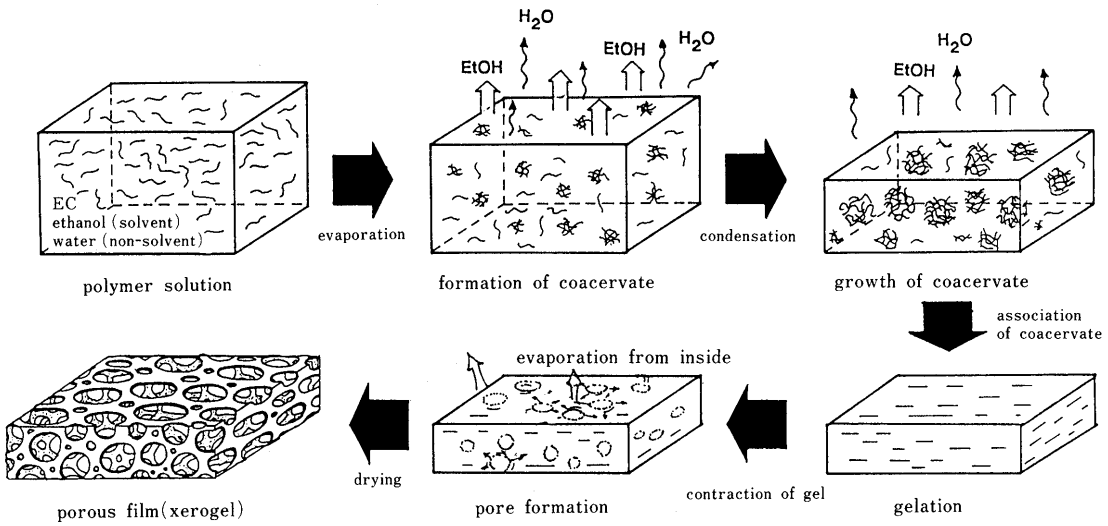

Fig. 3. Schematic Representation of Possible Pore-Forming Process

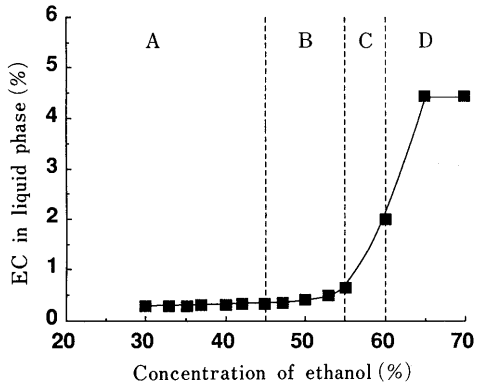

Fig. 4. Change of EC Concentration of Liquid Phase as a Function of Ethanol Concentration in EC–Ethanol–Water System at 25 °C

The total amount of EC in the liquid and solid phase corresponds to 4.55%. EC grade: EC 45 cP; separated EC phase: region A, solid; region B, gel and solid; region C, gel; region D, no solid (solution).

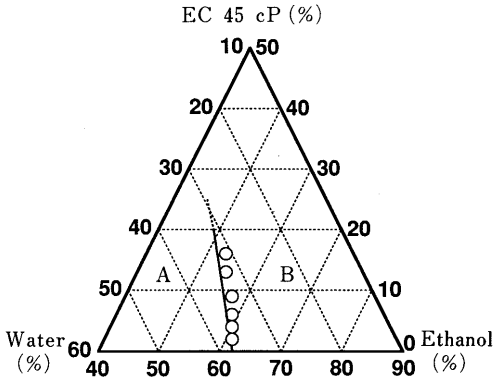

Fig. 5. Triangular Phase Diagram for EC–Ethanol–Water System at 25 °C

The line denotes ethanol : water (62 : 38). Region A, gel or solid; region B, solution.

a solvent and a non-solvent for EC, respectively. Since the evaporation speed of ethanol is much faster than that of water, the non-solvent concentration in the casting solution gradually increased as the solvent evaporated. Accompanied by this, the association of polymer molecules occurred to create coacervation, and the continuous growth of coacervation droplets resulted in the formation of a gel phase.

Gelation should be the most important process in porous film formation, because the precipitated gel phase almost decides the geometrical dimension of the resultant film. After gelation, since the reduction in volume is considerably hindered due to the structural rigidity of the gel phase, the subsequent solvent evaporation from the surface and the inside will make the film more bulky. Therefore, in discussing the pore-forming mechanism, it is important to understand what condition is necessary for the formation of the gel phase.

Figure 4 shows the change in EC concentration of the liquid phase in the EC–ethanol–water system. The polymer can dissolve in solvents with a higher ethanolic concentration, but at the ethanolic concentration of about 60%, the polymer was abruptly precipitated as a gel phase (observed as a semi-transparent jelly-like mass), and below about 50%, the polymer was practically insoluble. From this profile, the gel phase is thought to exist in the very narrow region of 55% to 60% of ethanol, and with a decrease in ethanol content, the gel phase gradually changed into a compact, fiber-like solid phase.

The formation of the gel phase happens so drastically that the critical ethanolic concentration for gelation, C_g, can be precisely determined by the titration of water to EC ethanolic solution. Figure 5 shows a triangular phase diagram for the EC–ethanol–water ternary system determined by the titration method. It was found that the value of C_g was almost constant at 62% irrespective of EC concentration. This diagram suggests that even if the composition of the EC–ethanol–water ternary mixture in the B region was used as the casting solution, the polymer molecules could eventually be precipitated as a gel phase during the film-forming process because the composition of the ternary mixture could move to the A region across the C_g line with solvent evaporation.

In order to see if the molecular weight (MW) of EC affects the C_g value, various grades of EC with different MW were determined for C_gs (Table I). It was found that the C_g value was almost the same level at around 62% irrespective of

Table I. C_g of Various Viscosity Grades of EC Measured at 25 °C

EC grade	C_g (%)
4 cP	58.6
10 cP	60.7
20 cP	61.8
45 cP	61.8
100 cP	61.9

Table II. C_g and Solubility Parameter (δ) of Various Water-Miscible Organic Solvent Systems

Solvent	δ ((cal/cm^3)$^{1/2}$)	C_g (%)	$\delta'^{c)}$ ((cal/cm^3)$^{1/2}$)
Dioxane	10.0[a)]	85.1	12.1
Acetone	9.8[a)]	80.2	12.0
Methanol	14.5[a)]	74.3	16.4
Ethanol	13.0[a)]	61.9	16.4
Isopropanol	10.0[b)]	57.1	15.0
n-Propanol	12.0[a)]	54.5	16.6

a) From reference 11*a*. *b*) From reference 11*b*. *c*) Solubility parameter at C_g.

MW, although the value became slightly lower with increasing MW. This similarity of C_g value is probably attributed to the fact that the content of ethoxyl groups of the polymers used is common at 48—49.5%.

The C_g value may change when ethanol is replaced by an alternative water-miscible organic solvent. Table II summarized the C_g values of various EC–organic solvent–water ternary systems. The C_g value varied from 54% to 85%, depending on the organic solvent used. Table II also listed the solubility parameter (δ) of each solvent system at C_g. The δ value of the mixture of organic solvent and water can be calculated from their volume fraction[11a)] using the solubility parameter of the individual solvent and water (23.4 (cal/cm^3)$^{1/2}$).[11)] According to the regular solution theory of Hildebrand and Scott, two substances whose δ values are equal to each other are completely soluble or miscible.[12)] It was thought that the solubility parameter at C_g(δ') should be identical irrespective of species of organic solvent, because EC began to be insoluble at C_g. However, the δ' values of alcohols were almost identical (15.0—16.6 (cal/cm^3)$^{1/2}$), but they were 3—4 (cal/cm^3)$^{1/2}$ higher than those of dioxane and acetone. Since the δ of EC is reported to be around 9.5 (cal/cm^3)$^{1/2}$,[12)] the data in Table II showed that the alcohol–water mixture can dissolve EC in spite of the larger difference of δ between the solvent and EC. The observed discrepancy is probably caused by the difference in hydrogen bonding ability between polymer and solvent.

Factors Affecting the Density of EC Cast Film As mentioned above, in the film-forming process from the EC–ethanol–water ternary system, the polymer inevitably precipitates as a gel-phase when the decreasing ethanolic concentration reaches C_g during solvent evaporation. Under this situation, the density of the resultant film, d, can be expressed as;

$$d = kW_p/V_g \quad (1)$$

where W_p is the weight of EC contained in the film, V_g is the volume of the gel phase precipitated, and k is the factor representing the shrinkage of the gel phase by drying. V_g can be roughly estimated from the difference between the initial volume of the cast solution, V_o, and the volume of the solvent lost until the gelation occurs, V_l, because most of residual solvent will be incorporated in the gel phase, that is;

$$V_g = V_o - V_l \quad (2)$$

V_g could be influenced by various factors, so the density of film could be affected by the formulation variables of the casting solution such as ethanol or polymer concentration and organic solvent species.

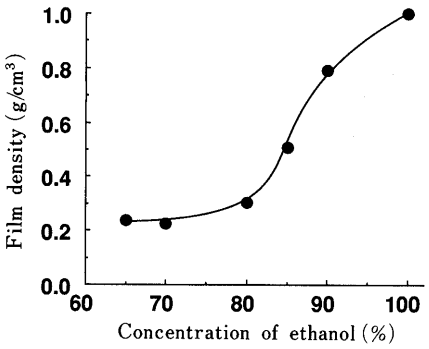

Fig. 6. Effect of Ethanolic Concentration on Density of EC Cast Film
EC grade: EC 45 cP; conditions: EC concentration, 5%; temperature, 25 °C.

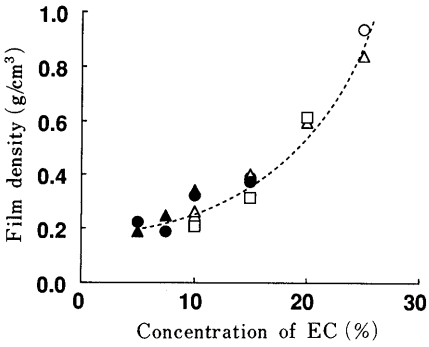

Fig. 7. Effect of EC Concentration on Density of EC Cast Film
Conditions: solvent, 70% aqueous ethanol; temperature, 25 °C. ○, EC 4 cP; △, EC 10 cP; □, EC 20 cP; ●, EC 45 cP; ▲, EC 100 cP.

In Fig. 6, the density of the cast film prepared from various EC–ethanol–water ternary systems was plotted against the ethanolic concentration of the solvent. Film density clearly decreased with decreasing ethanolic concentration, meaning that the casting solution containing more water allowed the resultant film to be more porous. This result suggests that the film density can be controlled in a rather wide range just by changing the ethanol/water composition of the solvent. This phenomenon is quite reasonable for the pore-forming mechanism. When a higher ethanolic concentration was used as the solvent, the cast solution had to be more condensed until the decreasing ethanolic concentration reached C_g during solvent evaporation. Since more solvent was lost, V_g should become smaller according to Eq. 2, resulting in higher film density according to Eq. 1.

Figure 7 shows the changes in film density relative to the polymer concentration in the casting solution, in which a 70% aqueous ethanolic solution was used as the solvent and five viscosity grades of EC with different molecular weight (MW) were examined. As is clear in the figure, film

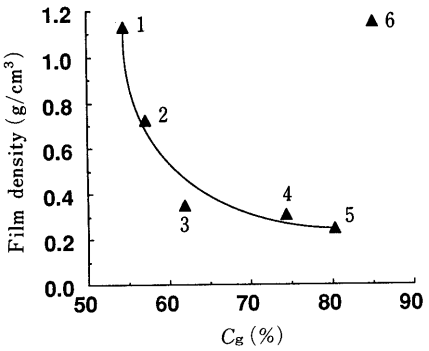

Fig. 8. Relationship between C_g of Various Organic Solvents and Film Density

1, *n*-propanol; 2, isopropanol; 3, ethanol; 4, methanol; 5, acetone; 6, dioxane.

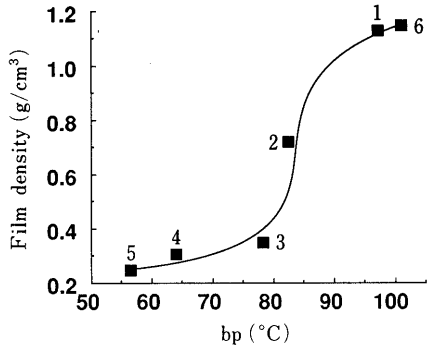

Fig. 9. Relationship between bp of Various Organic Solvents and Film Density

1, *n*-propanol; 2, isopropanol; 3, ethanol; 4, methanol; 5, acetone; 6, dioxane.

density considerably increased with the increase of polymer concentration, and film density was little affected by the MW of EC. These phenomena can also be explained by Eqs. 1 and 2. That is, since the C_g value is almost common irrespective of EC grade and polymer concentration in the EC–ethanol–water ternary system, V_g should be almost constant according to Eq. 2; therefore, d naturally increased with the increase of W_p according to Eq. 1.

Organic solvent species to be used in the casting solution also should influence the density of the cast film because different solvent systems provides different C_g (see Table II). In addition, the difference in boiling point (bp) between organic solvents can bring about a change in the total amount of solvent loss until C_g, because the balance of the evaporation speeds varies between solvent and non-solvent in each solvent system. Figure 8 shows the relationship between C_g and the density of the cast film prepared from various EC–organic solvent–water systems under the identical conditions. An organic solvent of a lower C_g value gives a higher film density. This relationship seems quite reasonable because V_g should decrease with decreasing C_g. However, dioxane gives high film density despite its highest C_g value. Dioxane has a little higher bp (101.1 °C) than water, whereas the other solvents had a lower bp. So, this may be caused by the high bp of dioxane. Figure 9 shows the relationship between the bp of an organic solvent and film density. It was shown that those solvents with a higher bp surely gave the higher film density. From these results, when a different solvent system is used, the film density is affected by the bp of the organic solvent as well as the C_g, even though it is still unknown which is the more influential factor.

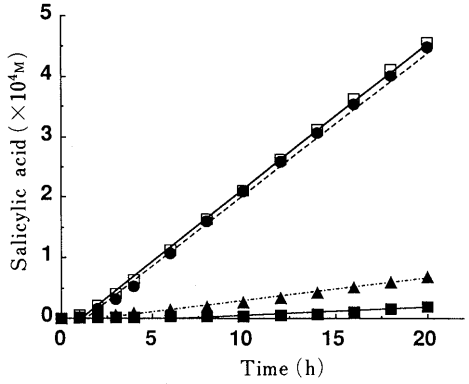

Fig. 10. Permeation Profiles of Salicyclic Acid through Various EC Cast Films with Different Densities at 37 °C

EC grade: EC 45 cP; film density (thickness): □, 0.46 g/cm³ (148.8 μm); ●, 0.51 g/cm³ (74.3 μm); ▲, 0.81 g/cm³ (71.5 μm); ■, 1.09 g/cm³ (58.1 μm).

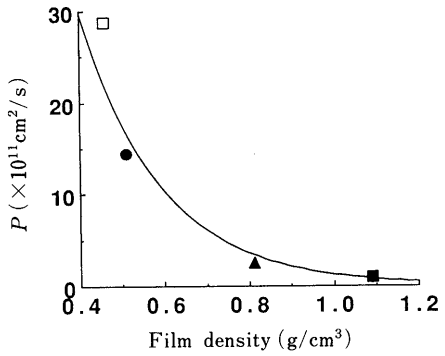

Fig. 11. Relationship between Film Density and Permeability Coefficient for Permeation of Salicylic Acid through EC Cast Films at 37 °C

Symbols are the same as in Fig. 10.

Drug Permeation through Porous EC Cast Film When porous EC film is utilized as a barrier of controlled drug release, it is significant to know the drug permeation property of the film. In order to characterize the drug permeation property of porous EC cast films, a permeation study was conducted using salicyclic acid as the permeant.

Figure 10 shows the permeation profiles of salicylic acid through various EC cast films with different densities. All the profiles exhibited straight lines. This means that drug permeation apparently obeyed Fick's law, so the drug permeation rate can be described according to the following equation:

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

where J is the flux (permeation rate per unit surface area of film), P is the permeability coefficient, C_d and C_r are the drug concentration in donor cell and receptor cell, respectively, and h is the thickness of the film. When C_d is far greater than C_r, Eq. 3 can be rewritten as:

$$J = PC_d/h \quad (4)$$

The P value was calculated for each film using necessary experimental data. The obtained P values were plotted against film density in Fig. 11. It was shown that the permeability coefficient exponentially increased with the decrease of film density, suggesting that the drug

permeability of the cast film can be modified by controlling film density. The permeability difference dependent on the film density indicated that the solute permeated predominantly through water-filled pores in the porous EC cast films.

Through the present fundamental study, we proved that the porous film was formed through a phase separation process when a mixture of solvent and non-solvent was used for the solvent of a polymer solution, and it was found that the density of the resultant cast film was influenced by various factors, including solvent composition, polymer concentration and solvent species. These findings imply the possibility of modifying the density or porosity of a cast film if an appropriate condition is established. Pharmaceutical spray coating has been used exclusively for the preparation of controlled release dosage forms. When the presented technique of porous EC film preparation is applied to actual spray coating for the formation of a drug diffusion barrier for capsule-type controlled-release systems, there are still some questions to be discussed, because some differences are involved in the film forming process between casting and spraying. For example, in actual spray coating, the evaporation speed of the solvent must be much higher than that of the casting process. In addition, in pharmaceutical coating, the rigidity of the porous film formed on beads or tablets may decrease by receiving continuous high mechanical stress in the coating machine. Although the pore-forming mechanism based on the phase separation will be essentially common, it is necessary to take into account such differences in the film forming conditions of casting and spraying. Further investigation will be extended to spray coating to see if a porous film can spontaneously be formed similarly to the casting process, and also to develop a new porosity-controlled film coating technique.

References

1) R. C. Rowe, *Pharmacy International*, **6**, 14 (1985); S. C. Porter, *Drug Dev. Ind. Pharm.*, **15**, 1495 (1989).
2) M. Donbrow and M. Friedman, *J. Pharm. Sci.*, **64**, 76 (1975); Y. Koida, M. Kobayashi and M. Samejima, *Chem. Pharm. Bull.*, **34**, 3354 (1986); M. Samejima, K. Noda, M. Kobayashi and S. Ishikawa, Japan. Patent 1-230513 (1989) [*Chem. Abstr.*, **112**, 104868*m* (1990)]; J. Akbuga, *Int. J. Pharmaceut.*, **76**, 193 (1991).
3) J. W. McGinity, "Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms," Marcel Dekker, Inc., New York, Basel, 1989, pp. 1—47.
4) T. Ishizaka, *Hyoumen*, **19**, 639 (1981).
5) J. R. Robinson and V. H. L. Lee, "Controlled Drug Delivery: Fundamentals and Applications," 2nd ed., Marcel Dekker, Inc., New York, Basel, 1987, pp. 181—186.
6) K. Tojo and K. Miyanami, *Powder Technol.*, **35**, 89 (1983).
7) N. A. Peppas and D. L. Meadows, *Journal of Membrane Science*, **16**, 361 (1983); I. Ghebre-Sellassie, R. H. Gordon, R. U. Nesbitt and M. B. Fawzi, *Int. J. Pharmaceut.*, **37**, 211 (1987); T. Hatanaka, M. Inuma, K. Sugibayashi and Y. Morimoto, *Chem. Pharm. Bull.*, **38**, 3452 (1990); G. Zhang, J. B. Schwartz and R. L. Schaare, *Pharm. Res.*, **8**, 331 (1991).
8) R. C. Rowe, *Int. J. Pharm.*, **29**, 37 (1986).
9) N. B. Shah and B. B. Sheth, *J. Pharm. Sci.*, **61**, 412 (1972); M. Donbrow and M. Friedman, *J. Pharm. Pharmacol.*, **27**, 633 (1975); T. Lindholm and M. Juslin, *Die Pharmazeutische Industrie*, **44**, 937 (1982); N. Hirashima, T. Kashihara, S. Hirai and N. Kitamori, *Yakuzaigaku*, **50**, 193 (1990).
10) *a*) R. E. Kesting, M. K. Barsh and A. L. Vincent, *J. Appl. Polym. Sci.*, **9**, 1873 (1965); *b*) K. Kamide, S. Manabe, T. Matsui, T. Sakamoto and S. Kajita, *Kobunshi Ronbunshu*, **34**, 205 (1977).
11) *a*) A. Martin, J. Swarbrick and A. Cammarata, "Physical Pharmacy," 3rd ed., Lea & Febiger, Philadelphia, 1983, pp. 272—313; *b*) R. C. Weast, M. J. Astle and W. H. Beyer, "CRC Handbook of Chemistry and Physics," 65th ed., CRC Press Inc., Boca Raton, Florida, 1985, p. C-701.
12) D. J. Kent and R. C. Rowe, *J. Pharm. Pharmacol.*, **30**, 808 (1978).