Porosity-Controlled Ethylcellulose Film Coating. V. Mechanism of Drug Release from Beads Coated with Porous Ethylcellulose Film

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The porous ethylcellulose (EC) film-coating technique was applied to prepare the film-coated (so-called capsule-type) controlled release dosage form of phenylpropanolamine hydrochloride (PPA), which was used as a highly water-soluble model drug. To prepare EC film-coated beads with various film-porosities, the PPA-loaded uncoated beads were spray-coated with an aqueous ethanolic or ethanolic solution of EC, and their drug release behaviors or drug release mechanisms were investigated. Although the amount of coating of the beads was equal, the PPA release rate differed according to the ethanolic concentration in the coating solution, that is, the lower the ethanolic concentration, the faster the release rate. The release profiles were normalized using a reduced time method to compare the profiles of different release rates. It was found that the profiles were well superimposed on the same curve, suggesting that the drug release obeyed the same mechanism. To examine the mechanism of drug release from the EC film-coated beads of PPA, drug release behaviors were investigated under the condition of various osmotic pressure differences. The drug release rate was decreased by decreasing the osmotic pressure difference. The contribution of an osmotic pumping to the drug release was estimated for the EC film-coated beads with different coating porosities. The driving force for drug release from the porous EC film-coated beads was found to be mainly an osmotic pumping mechanism, irrespective of film porosity.

Keywords porous film-coating; ethylcellulose; porosity; controlled release; drug release mechanism; osmotic pumping

Porous films are often utilized for capsule-type controlled release dosage forms. Such dosage forms consist of drug-containing core materials surrounded by porous films that control the drug release rate during the drug release process. Such films are usually formed from non-aqueous coating solutions of polymers which contain water-soluble pore-forming substances.[1-4]

We previously reported that a microporous film of ethylcellulose (EC) was formed from the EC–ethanol–water ternary mixture *via* phase separation and gelation of the polymer.[5] It was also found that a sprayed EC free film formed spontaneously during the spraying–drying process, and that the film-porosity could be modified by adjusting the ethanol or water content of the EC solution to an appropriate level.[6] Solute permeability could be changed according to the film-porosity.[6] These findings prompted us to establish a new porous EC film coating technique for the manufacture of controlled release dosage forms. The major advantages of this coating method are: i) it is not necessary to add any pore-forming agents into the coating film to make a porous film; and ii) it ensures a high productivity of the film-coated products without using anti-agglomeration agents, because tackiness of the polymer was extremely reduced during the film-forming process.[7] These advantages make the coating formulation simpler, and hence the coating process is much easier.

Drug release from the controlled release dosage form with polymeric coatings had been thought to predominantly obey the simple diffusion mechanism, in which drug molecules are diffused outside through the coating film. However, it has been revealed that osmotic pressure could be also another major driving force for drug release from these preparations. For example, Theeuwes reported an elementary osmotic pump for drug delivery for the first time, in which a drug contained in the osmotic core is pumped out at a constant rate with water flux through an orifice drilled in the semipermeable coating.[8]

In this study, spherical beads consisting mainly of phenylpropanolamine hydrochloride (PPA) and sucrose, which are highly water-soluble so they can generate high osmotic pressure, were coated with EC film with different porosities to investigate the drug release behaviors and the drug release mechanism. The purposes of the present study are: i) to examine the effects of solvent compositions or coating levels on release from EC film-coated beads; and ii) to confirm the effect of osmotic pumping on drug release from the EC film-coated beads and quantitatively estimate the contribution of the osmotic pumping effect. The effect of coating porosities on the contribution of osmotic pumping was also estimated for the first time.

Materials and Methods

Materials PPA (Alps Pharmaceutical Ind., Gifu, Japan) used was of JP grade and it was pulverized by a hammer mill before use. Sucrose sphere (Nonpareil-103, 24—32 mesh, Freund Industrial Co., Tokyo) was used as a core material of drug-loaded beads. Sucrose (Taito Co., Ltd., Japan) used as a binder was of JP grade. Hydrated silicon dioxide (Carplex, Shionogi & Company Ltd., Osaka, Japan) was used as an anti-electrostatic agent. EC (Ethocel standard premium, 45 cP, Dow Chemical Co., U.S.A.) was used as a coating polymer. All other chemicals used were of reagent grade.

Preparation of Uncoated Beads Uncoated beads of PPA were prepared by layering the powder blend of the drug and excipients using a CF-granulator (CF-360EX, Freund Industrial Co., Tokyo, Japan). Table I shows the formulation of uncoated beads. The powder blend was slowly applied on the Nonpareil seeds while they were continuously sprayed with a binder solution to obtain the drug-loaded beads. The granulating conditions were as follows: spray solution feed, 2—7 ml/min; spray air pressure, 0.8 kg/cm^2; blower rate, 150—250 l/min; blower temperature, 60 °C; rotating speed, 150 rpm. The beads produced were dried for 18 h at 45 °C. After drying, the beads were sieved to remove both the agglomerated beads and the fine particles.

EC Film Coating The uncoated beads were coated by spraying an aqueous ethanolic or ethanolic solution of EC with a CF-granulator. The EC concentration of the coating solution was 10%. The composition of ethanol/water of the coating solution was variously changed from

TABLE I. Formulation of Uncoated Beads

Component	Weight (g)
PPA	1125
Nonpareil-103	810
Hydrated silicon dioxide	9
Sucrose[a]	130

a) Sucrose was used as a binder. The binder solution was 40% aqueous ethanol containing 12.5% sucrose.

65/35 to 100/0 to control the film-porosity of the coating. The size of the beads was approximately 1 mm. The coating level (M_c) was defined as the amount of film deposited (M_f) *versus* the weight of the uncoated beads (M_b): $M_c = (M_f/M_b) \times 100$. The coating conditions were as follows: spray solution feed, 6 ml/min; spray air pressure, 1 kg/cm^2; blower rate, 100—200 l/min; blower temperature, 50 °C; rotating speed, 150 rpm. The film-coated beads were dried for 18 h at 45 °C before the dissolution testing.

Dissolution Studies Dissolution experiments were performed according to the JPXII paddle method in 900 ml of dissolution medium at 37 °C with constant stirring at 100 rpm. The dissolution media were water or an aqueous urea solution. The osmotic pumping effect on drug release was evaluated under various osmotic pressure differences generated by the urea solution. The urea concentrations were 1, 3 and 5 M. To determine the PPA amount released from the EC film-coated beads, aliquots were removed at specified time intervals and assayed with a spectrophotometer (UV-160, Shimadzu Co., Kyoto, Japan) at a wavelength of 258 nm.

Solubility Measurement To estimate the osmotic pressure difference between the inside and the outside of a film-coated bead, the saturated solubility of the components of the uncoated bead was measured. An excess amount of the PPA-loaded uncoated beads was dissolved in water or aqueous urea solution (1, 3 and 5 M) at 37 °C to prepare the saturated solutions. The PPA amount in the saturated solution (W_d) was determined by spectrophotometer. A 0.5 ml sample of each saturated solution (weight: W_t) was dried at 60 °C over P_2O_5 *in vacuo* for 3 h. The amount of water in the saturated solution (W_w) was determined by the weight difference before and after the drying. The amount of urea (W_u) was calculated by both the concentration of urea solution (1, 3 and 5 M) and W_w using the density of the urea solutions (1.012, 1.042 and 1.073 g/ml for 1, 3 and 5 M, respectively). Namely, the amount of urea dissolved in the saturated solution of the uncoated beads was assumed to be unchanged. The amount of sucrose (W_s) was arithmetically obtained from the amount of other components as $W_s = W_t - (W_w + W_d + W_u)$.

Results and Discussion

Effect of Ethanolic Concentration of EC Coating Solution or Coating Level on PPA Release Figure 1 shows the drug release profiles of the PPA-loaded beads, each of which was coated with aqueous ethanolic solutions or an ethanolic solution of EC. Although the coating level of the beads was equal at 10%, the release rate differed depending on the ethanolic concentration in the coating solution, that is, the lower the ethanolic concentration, the faster the dissolution rate. As mentioned previously,[7] when aqueous ethanol was used as a solvent of EC film coating solution, a porous film was formed through a phase separation process. In addition, its porosity was changed according to the ethanolic concentration in the coating solution. The porosity of the coating film can affect the drug release rate from EC film-coated beads of PPA, since the drug should predominantly permeate through the water-filled pores in the EC coating.

To determine whether the drug release mechanism might change according to the solvent composition of the coating solution, the release profiles shown in Fig. 1 were normalized by using the reduced time method.[9] The reduced time (T_r) is defined as $T_r = t/T_{50}$, where T_{50} is the time required to release 50% of the loaded drug. Figure 2 shows the result of superimposition analysis, which represents normalized drug release profiles using T_r. It was found that the release profiles were considerably superimposed, indicating that the drug release mechanism was essentially common and it was the release rate that differed.

The effect of coating levels on the PPA release rate was also investigated. Figure 3 shows the change of PPA release

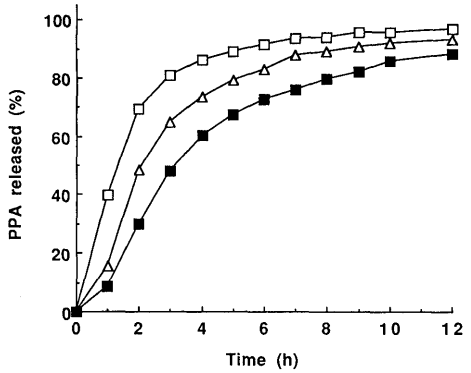

Fig. 1. Effect of the Ethanolic Concentration of an EC Coating Solution on PPA Release from EC Film-Coated Beads in Water

The coating level is 10%. Testing method: JP paddle method (100 rpm). Ethanolic concentration: □, 65%; △, 75%; ■, 100%.

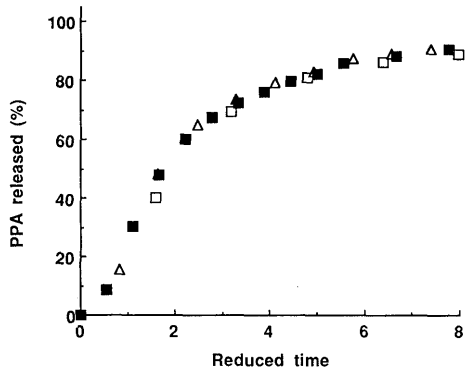

Fig. 2. Normalized Drug Release Profiles of EC Film-Coated Beads Prepared by EC Coating Solutions with Various Ethanolic Concentrations

The symbols representing the ethanolic concentration of the coating solutions are the same as in Fig. 1.

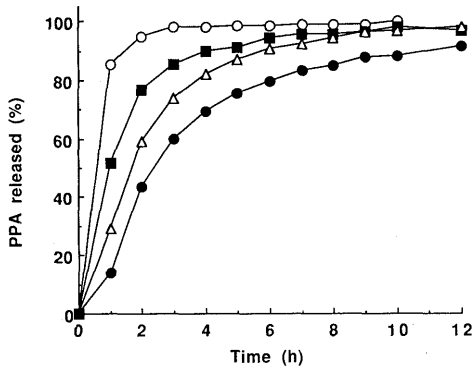

Fig. 3. Effect of Coating Level on the PPA Release of Porous EC Film-Coated Beads in Water

The ethanolic concentration of the EC coating solution is 75%. Testing method: JP paddle method (100 rpm). Coating level: ○, 4%; ■, 6%; △, 8%; ●, 10%.

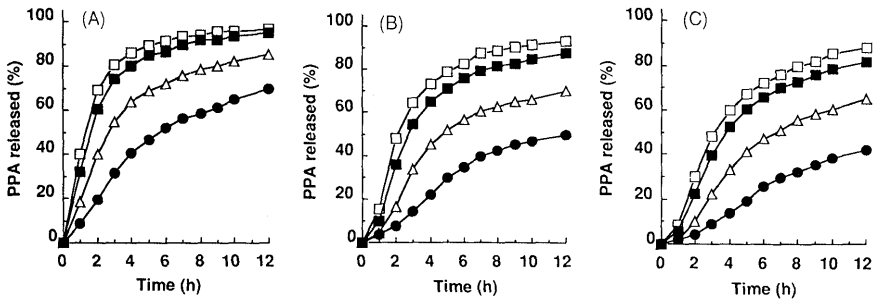

Fig. 4. Effect of Osmotic Pressure on PPA Release Profiles from EC Film-Coated Beads

Ethanolic concentration of coating solution: (A), 65%; (B), 75%; (C), 100%. Coating level: 10%. Urea concentration in dissolution medium: □, 0 M; ■, 1 M; △, 3 M; ●, 5 M.

profiles with coating levels, in which the EC film coating was conducted with a 75% aqueous ethanolic solution. As shown in Fig. 3, the release rate was delayed by an increase in coating levels.

According to Figs. 1 and 3, it was found that the porosity-controlled EC film coating method could be applied for the preparation of controlled release dosage forms of highly water-soluble drugs such as PPA, as well as for poorly water-soluble drugs such as theophylline.[7]

Contribution of Osmotic Pumping Mechanism to Drug Release A zero order drug release rate (dm/dt) at the steady state from a controlled release dosage form that is coated with a polymeric film can be expressed by an osmotic pumping term and a diffusion term as follows[8,10,11]:

$$dm/dt = (AS/h)L_p\sigma\Delta\pi + PAS/h \quad (1)$$

where A is the surface area of the device, h is the thickness of the coating film, S is the drug solubility, L_p is the hydraulic permeability of the coating film, σ is the reflection coefficient, P is the permeability coefficient of the drug through coating film, and $\Delta\pi$ is the osmotic pressure difference across the coating film. This equation implies that $\Delta\pi$ affects the drug release rate; a higher $\Delta\pi$ gives a higher dm/dt.

According to the method reported by Zentner *et al.*,[10,11] dissolution experiments for the EC film-coated beads of PPA with various porosities, which was prepared by EC coating solutions with different ethanolic concentrations (65, 75 and 100%), were conducted in various urea solutions (1, 3 and 5 M) which generated different $\Delta\pi$. The results are shown in Fig. 4. In all cases, the size of the beads hardly changed and the release rate of PPA decreased with increasing the urea concentration of the dissolution media. The decrease in the drug release rate can be attributed to two factors: a decrease in PPA solubility in the film-coated beads by an inversion of urea; and a decrease in the osmotic pressure difference by urea.

To approximately estimate the osmotic pressure difference across the coating film, it was necessary to determine the saturated solubility of each component of the PPA-loaded uncoated beads in water or in urea solutions. In this study, factors related to the deviation from the ideal were not considered. However, the solubility of each component of the uncoated beads in the presence of urea and other components, which had not been considered in other papers on drug release by osmotic pumping, was determined, because solubility can be a more influential factor in estimating the osmotic pressure. In addition, PPA was assumed to completely dissociate.

TABLE II. Solubility of Each Component and Osmotic Pressure Induced at 37 °C

Urea[a] (M)	Solubility			Osmotic pressure		
	PPA (M)	Sucrose (M)	Urea (M)	π_i[b] (atm)	π_o[c] (atm)	$\Delta\pi$[d] (atm)
0	1.25	1.74	0.00	107.8	0.0	107.8
1	1.27	1.72	0.33	116.7	25.4	91.3
3	1.16	1.64	0.93	124.3	76.3	48.0
5	1.27	1.31	1.43	134.2	127.1	7.1

a) Initial concentration of urea in the solution. *b*) Osmotic pressure of the inside of coated beads. *c*) Osmotic pressure of the outside of coated beads. *d*) $\pi_i - \pi_o$.

Table II lists the solubility of each component along with the value of osmotic pressure calculated by van't Hoff's equation as reported by Ozturk *et al.*[12] As listed in Table II, the solubility of PPA was almost constant irrespective of the urea concentration in the solution, indicating that the concentration difference of PPA between the inside and outside of film-coated beads should be constant. By contrast, the solubility of sucrose changed according to urea concentrations in the dissolution medium. The concentrations of urea in the saturated solutions differed from the initial concentrations of the urea solutions, since the volume of the solutions should increase with the dissolution of PPA and sucrose to each urea solution. The osmotic pressure difference was found to decrease as the urea concentration increased in the dissolution medium. According to these data, the change in PPA release rate, which is obtained by slope of the initial linear portion of each profile shown in Fig. 4, should be attributed to the change in osmotic pressure difference between the outside and inside of the film-coated beads.

According to Eq. 1, zero order release rates of PPA at the initial steady state in various urea solutions were plotted *versus* the osmotic pressure difference across the coating film (Fig. 5). Linear relationships were obtained for all the film-coated beads with the different coating porosities. This indicates that osmotic pumping is one of driving forces of PPA release from the EC film-coated beads. This is consistent with the results of other reports

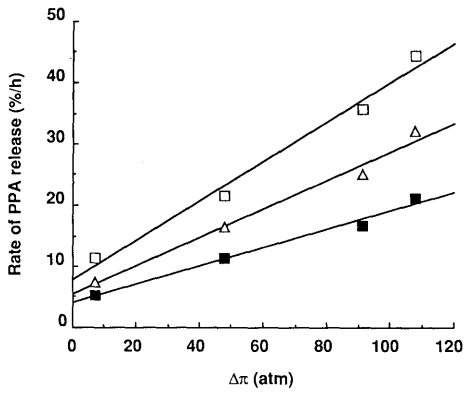

Fig. 5. Effect of Osmotic Pressure Difference on the Rate of PPA Release from EC Film-Coated Beads

Ethanolic concentration of coating solution: □, 65%; △, 75%; ■, 100%.

on tablets coated with cellulose acetate[10] or EC[11] and on pellets coated with EC-based film.[12] Since an organic solution or an aqueous dispersion of the polymer was used as a coating solution in these studies, the structure of the coating was apparently different from the porous EC coating film, which used an aqueous ethanolic solution as the coating solvent. The substantial EC portion in a porous EC film is thought to essentially have a semipermeable property, and pores formed during the film formation process by phase separation and gelation seem to have sufficient size distribution for water convection. Therefore, drug release can be driven by osmotic pumping as well as by simple diffusion. The two different mechanisms seem to contribute to drug release simultaneously.

Least-squares linear regression analysis for each line in Fig. 5 yielded a slope of 0.321%/h/atm for the 65% aqueous ethanol system, 0.234%/h/atm for the 75% aqueous ethanol system and 0.150%/h/atm for the ethanol system, respectively. According to Eq. 1, the slope of each line in Fig. 5 means $(AS/h)L_p\sigma$. It seems reasonable to regard fluid permeability ($L_p\sigma$) as a constant irrespective of film-porosity. Thus, the changes in the slopes in Fig. 5 are attributed to changes in the device surface area (A) and the coating thickness (h), which may be brought about by changes in film porosities.

When $\Delta\pi$ is equal to zero, drug release will occur only by diffusion; $(dm/dt)_{\Delta\pi=0}=PAS/h$. The intercept of the Y-axis of the linear lines gives the estimated value of the diffusive release rate according to Eq. 1. The F-value, which is the percentage of osmotic pumping contribution to the whole drug release rate in water, was estimated according to Eq. 2:

$$F=\frac{(dm/dt)_{\Delta\pi=107.8}-(dm/dt)_{\Delta\pi=0}}{(dm/dt)_{\Delta\pi=107.8}}\times 100 \quad (2)$$

where $(dm/dt)_{\Delta\pi=107.8}$ is the drug release rate in water.

Table III. Contribution of Osmotic Pumping in Drug Release for EC Film-Coated Beads in Water

Ethanol[a] (%)	Diffusive release rate (%/h)	Osmotic release rate (%/h)	Osmotic pumping contribution (F) (%)
65	8.9	29.3	76.7
75	6.2	18.8	75.2
100	3.6	17.1	82.6

a) Ethanolic concentrations of EC coating solutions.

Table III summarizes each drug release rate by different mechanisms and F-values of EC film-coated beads prepared using various coating solvents. The F-value for each preparation could be roughly estimated at 75—83%, which is almost constant irrespective of the solvent compositions of the coating solutions. This indicates that the drug release is mainly driven by an osmotic pumping mechanism rather than by diffusion, even though the film porosity changed. Accordingly, as also found by the reduced time method shown in Fig. 2, the drug release mechanism was found to be the same irrespective of the film porosity of the EC coating film.

In conclusion, the porous EC film-coating technique was applicable for the preparation of controlled release dosage forms of a highly water-soluble model compound, PPA. The release rate was controlled by film porosity as well as by the coating amount of EC. According to the reduced time method, the drug release mechanism seemed to be the same irrespective of film porosity, even though the PPA release rate changed. The drug release rate decreased with an increase in the osmotic pressure of the dissolution media. The drug release mechanism was found to be based mainly on osmotic pumping in each of the coated beads with different film porosities.

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