Porosity-Controlled Ethylcellulose Film Coating. III. Application of Porous Ethylcellulose Film Coating to Capsule-Type Controlled Release Preparation of Theophylline

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Porous ethylcellulose (EC) film coating technique was used in preparing a capsule-type controlled release dosage form, in which theophylline (TP) was used as a poorly water-soluble model drug. The TP-loaded uncoated beads were spray-coated with an aqueous ethanolic or ethanolic EC solution, and the drug release characteristics and productivity of each product were examined. When the aqueous ethanol was used as the solvent of the coating solution, a large number of micropores were formed in the coating, and the porosity of coating and drug release rate could be controlled by altering the ethanolic concentration in the coating solution. In addition, few agglomerates were produced in the coating process, even though there was no anti-agglomeration agent in the coating solution. The drug release rate from the coated beads could be changed by film porosity as well as film thickness. Superposition analysis revealed that the EC-coated beads with different film porosities or different coating levels had the same drug release mechanism. It was further found that the drug release behavior of the porous EC film-coated beads was not affected by any simulated physiological conditions such as pH, surface tension, ionic strength or paddle rotation speed, indicating that *in vivo* drug release should not be affected by such physiological conditions in the gastrointestinal tract.

Keywords porous film; ethylcellulose; film coating; capsule-type; controlled release; theophylline

Film-coatings have frequently been applied in preparation of controlled release dosage forms, which consist of a drug-containing core and barrier polymeric film. Cellulosic or acrylic polymers have been extensively utilized as the film-formers in pharmaceutical productions. Of those film-formers, ethylcellulose (EC) is probably the most widely used water-insoluble polymer, because it has good film-forming properties and provides a physicochemically and mechanically stable film.[1] However, because of its dense structure and hence lower water permeability, an EC coating sometimes makes it difficult to control the drug release rate of a poorly water-soluble drug. Therefore, to modify the permeability of EC film, various microporous film coating methods have been developed, in which water-soluble ingredients are incorporated into the coating layer.[2–4] In the conventional porous film-coating, the drug release rate depends on the amount of pore-forming ingredients incorporated, because the drug can permeate through the water-filled pores created after leaching the water-soluble ingredients from the coating film. Even though the coating structure may be successfully modified, however, such type of film-coating may make a coating formulation more complicated, and hence the production process to obtain a good reproducibility of drug release properties of the products becomes more difficult.

Previously, we found that a porous EC free film was spontaneously formed in a casting method from an aqueous ethanolic solution of EC during the film-forming process based on the phase separation principle; the density of the EC free film could be controlled by changing the ethanol/water ratio of the solvent.[5] Further, sprayed EC free film was used for a series of permeation studies and the drug permeability through the porous EC free films showed a certain relation with film porosity irrespective of drug solubility; this suggested that drugs permeate predominantly through aqueous pores of the sprayed EC free films.[6] All these findings imply the possibility of establishing a new, simple porous film coating method for the preparation of controlled release dosage without using any pore-forming substances.

The objective of the present study was to examine the applicability of the porous EC film coating technique to the preparation of capsule-type controlled release dosage forms. In this paper, the porous EC film coating was actually applied onto uncoated beads containing theophylline (TP) as a poorly water-soluble model drug. The coated products were prepared by spraying the aqueous-ethanolic solutions of EC with different solvent compositions and were compared in the structure of coating film, productivity and controllability of drug release rate. The productivity was evaluated by fraction of agglomerates in the coated product, whereas the controllability was evaluated by change of T_{50} (time required to release 50% of the loaded drug) per unit coating level. In addition, the *in vitro* drug release behavior of the highly porous film-coated product was evaluated under various simulated physiological conditions.

Experimental

Materials Anhydrous TP (Tokyo Kasei Kogyo Co., Tokyo) was used as a model drug and was pulverized by a hammer mill before using. Nonpareil-103 (24—32 mesh, Freund Industrial Co., Tokyo) was used as a core material to produce drug-loaded beads. Sucrose (Taito Co., Ltd., Japan) of JP grade was used as a binder or a filler. 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 TP-Loaded Uncoated Beads TP-loaded uncoated beads were prepared by layering the powder blend of the drug and excipients using a CF-granulator (CF-360EX, Freund Industrial Co.). Table I shows the formulation of the uncoated beads. The powder blend was slowly applied on the Nonpareil seeds while continuously spraying

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 agglomerated beads and fine particles.

EC Film Coating The uncoated beads were coated by spraying an aqueous ethanolic EC solution with a CF-granulator. The concentration of EC was 5%. The composition of ethanol/water of the coating solution was varied from 65/35 to 100/0 to control the porosity of the coating. 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 uncoated beads (M_b) as; $M_c = (M_f/M_b) \times 100$. Beads with various levels of coating were obtained by withdrawing small amounts at intervals during the coating process. 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 coated beads were dried for 18 h at 45 °C before the dissolution testing.

Dissolution Studies Dissolution experiments were performed according to the JP XII paddle method in 900 ml of dissolution medium at 37 °C. The composition of dissolution media or the paddle rotation speed was optionally changed depending on the experimental purpose. For example, 1st fluid (pH 1.2) and 2nd fluid (pH 6.8) for the disintegration test in JP XII were used to investigate the effect of pH on drug release. The paddle rotation speed was changed from 50 to 200 rpm to learn the effect of agitation. To determine TP amount released from the EC film coated beads, aliquots were removed at specified time intervals and assayed by a spectrophotometer (UV-160, Shimadzu Co., Kyoto, Japan) at a wavelength of 292 nm.

Scanning Electron Microscopy (SEM) A scanning electron microscope (S-2250N, Hitachi, Ltd., Tokyo) was used to observe the morphology of the surface of porous EC film coated beads. Each sample was sputter-coated with Pt–Pd alloy by an ion sputterer (E-102, Hitachi, Ltd., Tokyo) to reduce charging before the SEM-observation.

TABLE I. Formulation of TP-Loaded Uncoated Beads

Component	Weight (g)
Nonpareil-103	1000
TP	600
Sucrose (filler)[a]	1000
Sucrose (binder)[b]	300

a) Pulverized sucrose. *b*) Binder solution: 25% sucrose in 25% aqueous ethanolic solution.

Results and Discussion

Effect of Solvent Composition of EC Coating Solution on Morphology of Coated Beads Three batches of EC film-coated TP beads were prepared by spray-coating of EC aqueous ethanolic solutions with different ethanol concentrations (ethanol : water = 65 : 35, 70 : 30, and 75 : 25) on the same batch of TP-loaded uncoated beads (16—24 mesh); one batch was prepared by spraying EC ethanolic solution as an example of organic solvent-based coating. Scanning electron micrographs of the overall view of the obtained EC film-coated TP bead are shown in Fig. 1A, C, E, and G, and the fine structures of the coating surface of the same bead in Fig. 1B, D, F and H. Although there were no differences found in the overall view, the fine structure of the coated surface differed remarkably depending on the solvent composition of the EC solution used. Namely, when ethanol alone was used as the solvent, the resultant coating film was obviously smooth, and no micropores were found on the surface even at high magnification (Fig. 1H); on the other hand, when aqueous ethanolic solution was used as the solvent for the coating solution, a tremendous number of micropores were observed (Fig. 1B, D and F). It was also found that lower ethanolic content in the coating solution resulted in larger pore size in the coating. This SEM-observation proved that micropores could be formed during the coating process in the same manner as we reported previously with sprayed EC free films[6] when aqueous ethanolic solution was used as the solvent of EC.

Effect of Solvent Composition of EC Coating Solution on Productivity To demonstrate the influence of the porous film coating method on productivity, the yield and size distribution of each batch of coated products are summarized in Table II. Although the total yield of coated product was close to the theoretical value in every case, greater reduction in the fraction of agglomerates was found in the preparations using the solvent with lower ethanolic concentration. In fact, when the ethanolic

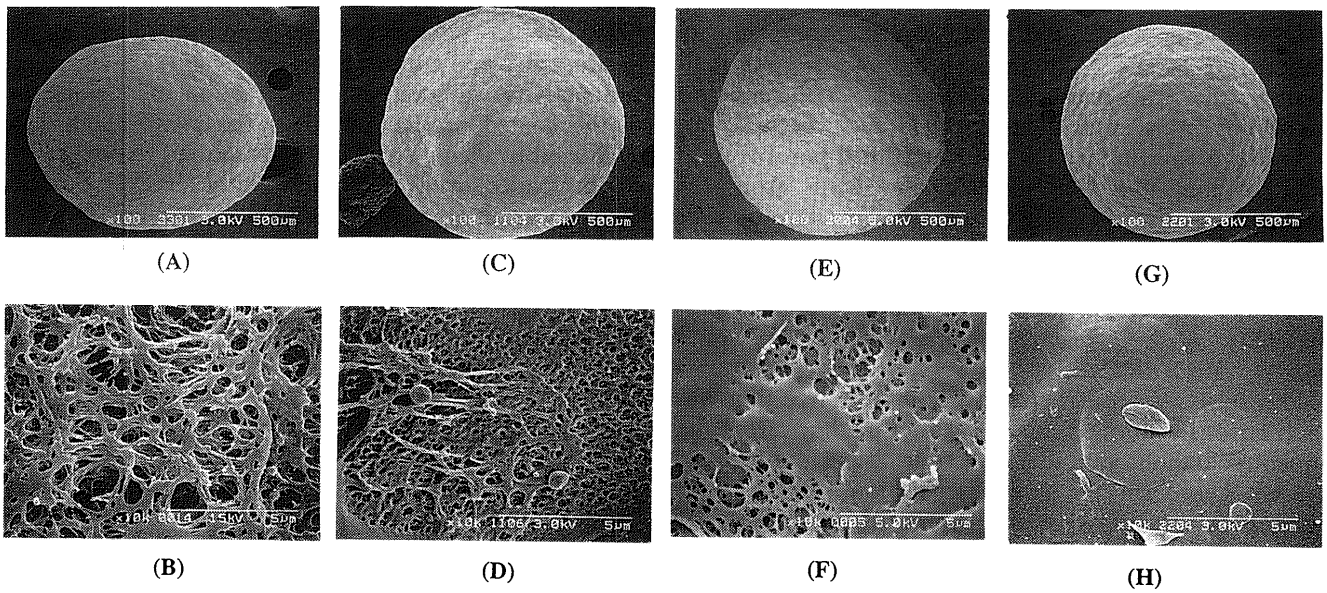

Fig. 1. Scanning Electron Micrographs of Overall Appearance (A, C, E, G) and Surfaces (B, D, F, H) of Porous EC Film Coated Beads

Solvent of EC solution used for coating: (A, B), 65% aqueous ethanol; (C, D), 70% aqueous ethanol; (E, F), 75% aqueous ethanol; (G, H); ethanol.

TABLE II. Effect of Ethanolic Concentration in EC Coating Solution on Productivity

Ethanolic concn. (%)	EC concn. (%)	Total yield (%)	Size distribution (%)	
			Agglomerates[a]	Single beads[b]
65	5	99.8	0.3	99.7
70	5	99.8	0.8	99.2
75	5	99.7	12.5	87.5
100	5	99.8	30.5	69.5

a) Above 16 mesh-size fraction. *b*) Under 16 mesh-size fraction.

concentration of the solvent was below 70%, agglomeration between beads did not occur in the coating process even though no anti-agglomeration agents were used. This phenomenon is quite interesting as it pertains to the film-forming mechanism and important from the viewpoint of industrial production as well.

The major reason why the fraction of agglomerates differed depending on the solvent used could be due to the difference in the film-forming mechanism. When ethanol alone was used as the solvent, the EC solution sprayed was condensed along with the solvent evaporation, and a highly viscous layer remained on the surface of the individual beads, which accumulated and formed agglomerates during the coating process. To prevent this agglomeration, the addition of an anti-agglomeration agent like talc is necessary in conventional organic solvent-based coating. On the other hand, when an aqueous ethanolic solution was used as the solvent, the film (porous film in this case) was formed *via* a different process. Namely, because the evaporation rate of ethanol is much faster than that of water, the ethanolic concentration of sprayed polymer solution would decrease during the drying process, and when it reached to a critical ethanolic concentration the polymer precipitated as a gel phase and finally formed a porous film as a xerogel. The gel phase formed in this process has a less tacky property so that it effectively prevents the occurrence of agglomeration. Another possible reason for difference in the fraction of agglomerates may be reduction of the generation of electrostatic force during the coating process due to high humidity created by water evaporation.

Effect of Solvent Composition of Coating Solution on Drug Release Figure 2 shows the drug release profiles of TP-loaded beads, each of which was coated with EC from a different aqueous ethanolic solution or from ethanol alone as the solvent. As can be seen, although the coating level of the beads was identical at 3%, the release rates differed greatly depending on the ethanolic concentration of the solvent in the coating solution; that is, the lower the alcoholic concentration, the faster the release rate. This result seems quite reasonable, because the EC coating from the solvent with lower alcoholic concentration provided a more porous film as seen by SEM (Fig. 1), and as was also mentioned previously with respect to sprayed EC free films,[6] most drugs permeate exclusively through the water-filled pores of the EC coating.

The drug release mechanism from such a capsule-type dosage form is known to involve an osmotic pumping process and a diffusion process.[7] To see whether the drug release mechanism could change when the solvent of coating solution was altered, all the release profiles shown in Fig. 2 were normalized using the reduced time method.[8] Reduced time (T_r) is defined as $T_r = t/T_{50}$, where T_{50} is the time required to release 50% of a loaded drug. The normalized profiles are plotted in Fig. 3. They were well superposed on the same curve, meaning that the drug probably was released obeying the same mechanism and that only release rate differed.

The effect of the coating level on drug release rate was also examined for all the coated beads prepared by spray-coating using different solvents. A typical example of the change in drug release profiles with coating levels is shown in Fig. 4, in which EC film coating was made using 65% aqueous ethanolic solution. As expected, the release rate was delayed by increase in the coating level. The normalized profiles by the reduced time method are also shown in Fig. 5, and most of them were well superposed on the same curve. From the dissolution studies

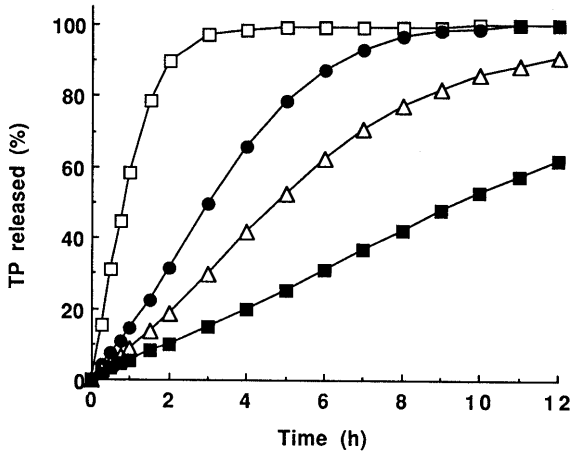

Fig. 2. Effect of Ethanolic Concentration of EC Coating Solution on TP Release from EC Film Coated Beads in Water

The coating level is 3%. Testing method: JP paddle method (100 rpm); ethanolic concentration: □, 65%; ●, 70%; △, 75%; ■, 100%.

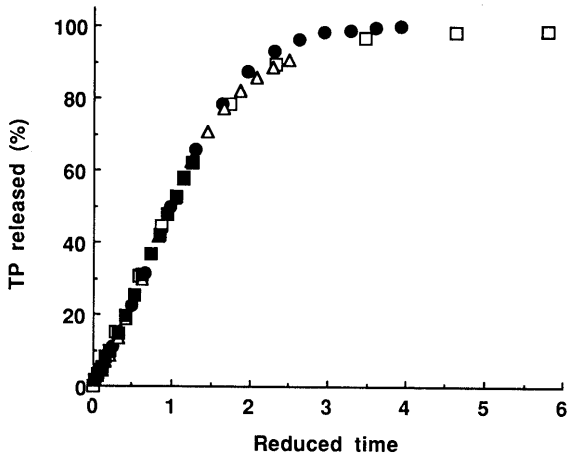

Fig. 3. Normalized Drug Release Profiles of EC Film Coated Beads Prepared by EC Coating Solutions with Various Ethanolic Concentrations

Ethanolic concentration of coating solutions: □, 65%; ●, 70%; △, 75%; ■, 100%.

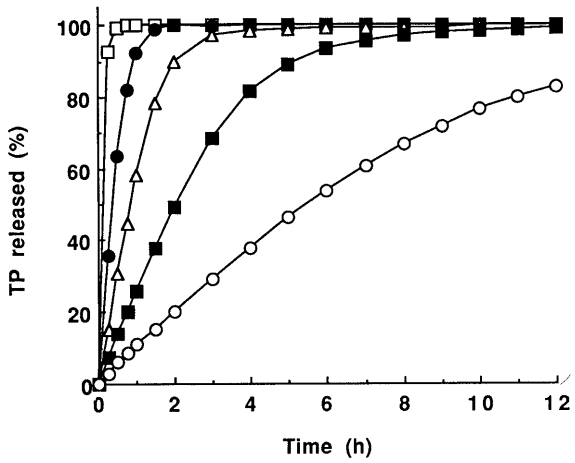

Fig. 4. Effect of Coating Level on TP Release from Porous EC Film Coated Beads in Water

The ethanolic concentration of EC coating solution is 65%. Testing method: JP paddle method (100 rpm); coating level: □, 1%; ●, 2%; △, 3%; ■, 4%; ○, 5%.

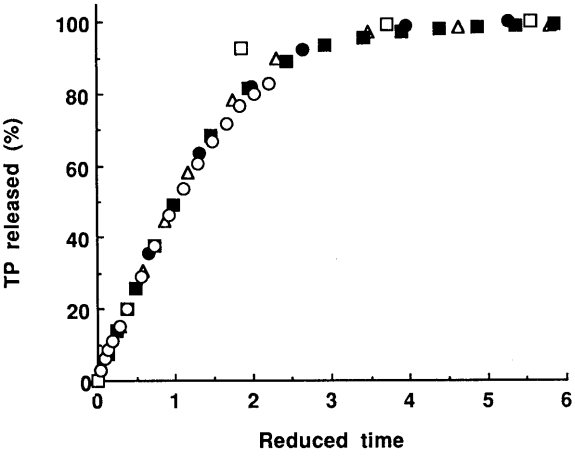

Fig. 5. Normalized Drug Release Profiles of EC Film Coated Beads with Various Coating Levels

Coating level: □, 1%; ●, 2%; △, 3%; ■, 4%; ○, 5%.

and the consequent superposition analysis, it can be concluded that, when the proposed porous film coating method was applied, the drug release rate could be controlled by changing either film thickness or the film-porosity without altering the drug release mode.

T_{50} value is plotted against coating level (M_c) in Fig. 6. Since the drug release is assumed to be controlled obeying the same mechanism, the reciprocal value of T_{50} can be a parameter representing drug release rate. Also, in this experiment the amount of coating is considered proportional to film thickness. Therefore, theoretically, T_{50} value should be proportional to coating amount according to Fick's law. Contrary to our expectation, however, a linear relationship was rarely found below 3% of coating level in every case. This suggests that permeability of the drug through the coating film is rather high when there is a small amount of coating because of coating imperfection, and steady permeation through a fixed film structure was achieved with increase in coating amount. The slope of the straight portion above 3% of coating level was thus regarded as the parameter

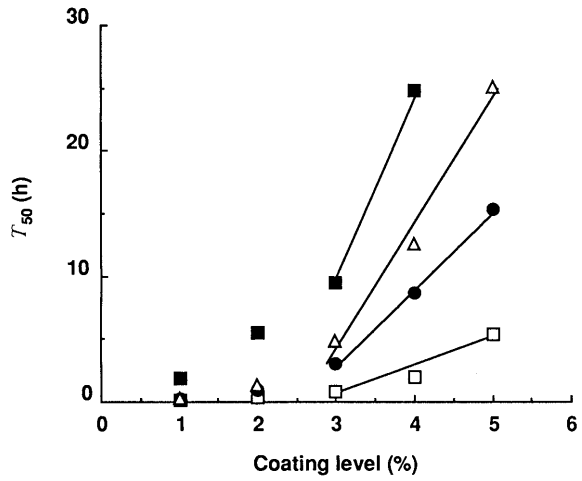

Fig. 6. Relationship between Time for 50% Drug Release (T_{50}) and Coating Level of EC Film Coated Beads Prepared by EC Solutions with Various Ethanolic Concentrations

Ethanolic concentration: □, 65%; ●, 70%; △, 75%; ■, 100%.

representing the change of drug release rate per unit coating level, and the calculated values for each ethanolic concentration in the coating solution were 15.5 h/% (100% ethanol), 10.1 h/% (75% ethanol), 6.2 h/% (70% ethanol) and 2.3 h/% (65% ethanol), respectively. The value of the slope greatly decreased with decreasing ethanolic concentration of the solvent. This is thought to be the result of the difference in structure of the EC film formed in the coating process; that is, lower ethanolic concentration of the solvent produced film of high porosity, and hence high permeability. This finding suggests the primary advantage of the proposed porous film coating technique in pharmaceutical productions. When the conventional organic solvent-based coating (ethanol alone, for instance) is applied to uncoated beads of a poorly water-soluble drug like TP, only a small amount of coating will make cause a drastic decrease in the drug release rate from the coated product as shown in Fig. 6. Therefore, with this method it is hard to precisely control the drug release rate at a desired coating level. In addition, due to the generally observed imperfection of film formed at a low coating level, drug release rate may be easily affected by a small variation in the surface state of uncoated beads. At the low coating level, EC acts as a film-former, and at the same time may smooth the surface roughness of the uncoated beads. Meanwhile, the porous EC film coating technique proposed here can solve the above-mentioned problems. That is, even though the surface roughness of uncoated beads affects film formation, the effect on drug release would be minimal, because the change of release rate per unit coating level becomes smaller in the porous EC film coating. Porous EC coating film may also effectively smooth the roughness, since the bulk of the porous EC coating film must be larger than that of the conventional organic solvent-base EC coating film. Accordingly, it is thought that the drug release rate can be controlled more precisely, and that the desired release rate can be obtained at a relevant coating level by the porous EC film coating method. Another advantage

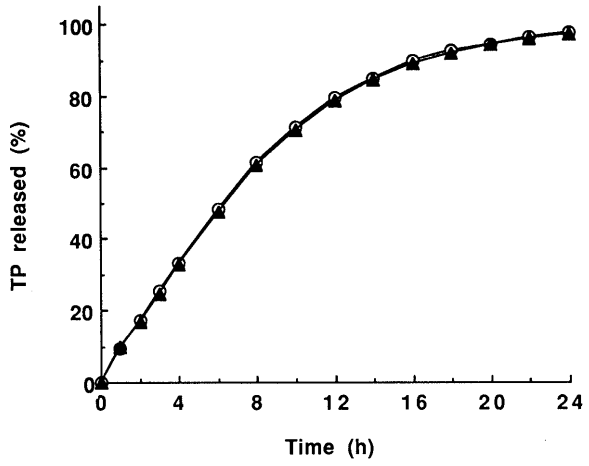

Fig. 7. TP Release as a Function of pH in the Dissolution Medium

Testing method: JP paddle method (100 rpm); coating level, 5%; ethanolic concentration of coating solution, 65%. pH in the dissolution medium: ○, pH 1.2; ▲, pH 6.8.

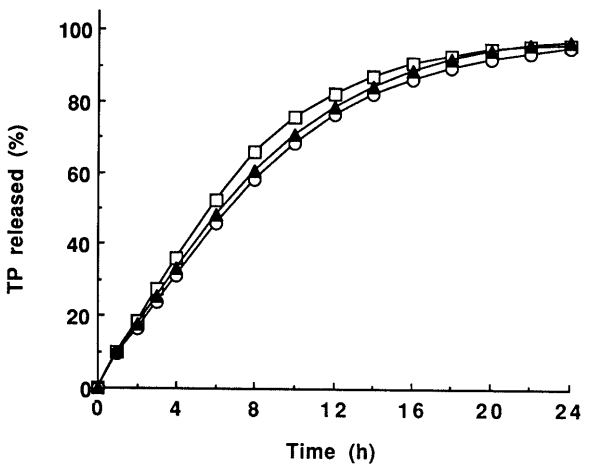

Fig. 8. TP Release as a Function of Agitation Speed in Water

The TP beads are the same as those used in Fig. 7. Testing method: JP paddle method; paddle speed: ○, 50 rpm; ▲, 100 rpm; □, 200 rpm.

of this coating method is that it allows modification of the drug release rate at a predetermined coating level just by changing ethanol–water composition of the solvent, in accordance with the solubility of the drug.

Drug Release Behavior under Simulated Physiological Conditions *In vivo* drug release from a pharmaceutical preparation may be influenced by various physiological factors including the mechanical force exerted by the digesting movement of the gastrointestinal tract and various characteristics of gastrointestinal fluid such as pH, surface tension and ionic strength.[9] Therefore, to develop a sustained release formulation, it is necessary to examine *in vitro* drug release under as many conditions as possible to predict every potential factor which may affect the rate of release *in vivo*.[9] The drug release behaviors of porous EC film coated beads were also investigated under various simulated physiological conditions. TP-loaded beads coated with 5% highly porous EC film, which were prepared from aqueous ethanolic solution (ethanol: water = 65 : 35) of EC, were used as the test sample.

The effect of pH of dissolution medium on the drug release from the TP-beads is shown in Fig. 7. The *in vitro* drug release profile is seen to be hardly affected by the pH of the dissolution medium. The ionic strength and surface tension of the dissolution medium were changed by dissolving sodium chloride (0—1.8%) and polysorbate 80 (0—1.0%) in water, respectively. Although the results are not shown in the figures, the ionic strength and surface tension did not affect the drug release from the coated beads. These results suggest that the porous EC film coating is potentially so stable that the drug permeability cannot be influenced by characteristics of the gastrointestinal fluid.

The effect of mechanical stress suffered during the drug release process was also examined. Figure 8 is a comparison of drug release profiles obtained from dissolution experiments conducted while varying the rotation speed of paddle from 50 to 200 rpm. The profiles show hardly any change irrespective of paddle rotation speed, suggesting that the EC film coating, even though highly porous, is still tough enough to withstand the mechanical stress imposed.

Through the series of dissolution studies described above, the EC film coated beads prepared using the porous film coating technique proposed appeared able to provide a stable drug release rate in the gastrointestinal tract without being affected by physiological conditions. This is probably attributable to the excellent physicochemical properties of EC and to the fact that the rate-determining step in the drug release of the capsule-type controlled release dosage forms, which is the film permeation process, is not affected by conditions of pH, ionic strength, surface tension or agitation speed, since none of these can change the porosity of the coated film.

Conclusion

To examine the applicability of the new porous film coating technique based on the phase separation principle, three batches of capsule-type controlled release beads of TP were prepared following tentatively determined procedures. The results revealed that a porous EC film could be successfully formed on the TP-loaded uncoated beads when aqueous ethanolic solution of EC was sprayed, and as expected, film porosity and drug release rate of the coated products were well controllable by modifying the ethanol–water ratio of the solvent. Also, through various *in vitro* dissolution studies under simulated physiological conditions, the coated products are thought to provide a stable drug release rate in the gastrointestinal tract. From all these results, the proposed new porous film coating method appears to afford an effective means for preparing capsule-type controlled release dosage forms, especially for poorly water-soluble drugs. Major advantages of this technique include precise control of the drug release rate and good productivity, without the addition of any pore-forming agents or anti-agglomeration agents.

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