Porosity-Controlled Ethylcellulose Film Coating. IV. Evaluation of Mechanical Strength of Porous Ethylcellulose Film

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The mechanical characteristics of porous ethylcellulose (EC) film as a barrier in a controlled release dosage form were investigated. Sprayed EC films with various porosities were prepared by changing the ethanolic concentrations in the EC spraying solution, and their film porosities (ε) and tensile strength (T_s) were measured. It was found that the T_s of EC films decreased with an increase in ε, and that the quantitative relationship between both parameters was considerably adapted to the equation proposed by Bal'shin. By using the permeability–ε and T_s–ε relations, the mechanical strength of two EC films with different porosities were estimated under the assumption that the drug permeation rate through the two films was equal. The result suggested that, when the permeation rate was equal, a film with higher porosity would have higher mechanical strength. This was also proved by a high-shear dissolution test for theophylline beads coated with EC film. The *in vivo* drug release behavior from porous EC film-coated beads agreed well with the *in vitro* drug release, indicating that the porous EC film-coated beads had sufficient strength to withstand the mechanical stress of the gastrointestinal tract, and that the porous EC film coating could be used as a barrier for controlled release preparations.

Keywords ethylcellulose; porous film; coating; mechanical strength; controlled release; *in vivo* release

Porous polymeric film has often been utilized as a diffusion barrier in membrane permeation-controlled gastrointestinal (GI) delivery systems.[1] In this kind of preparation, drug release rate is controlled by the thickness of the coating or the level of pore-forming additives used in the coating film which is formed around the drug-containing core material by the spray-coating technique.

Ethylcellulose (EC) is widely-used polymer in release rate-controlled film in sustained release dosage forms.[2] Previously, we developed a simple porous film coating technique without adding any pore-forming agents, in which the pore-forming mechanism was based on the phase separation of EC.[3] The porosity of the coating could easily be modified by altering the solvent composition of the polymer solution. This porous film coating technique was designed to provide appropriate void space in water-insoluble coating in order to promote the drug permeability. The release rate of physiologically active substances should be capable of being altered in a wide range, since the release rate can be controlled by the amount of void space (porosity) and by the amount of polymer (film thickness).

However, one major question to be discussed concerns the strength of the coating against physical impact, since it is believed that due to excessive void spaces, the rigidity of the coating is considerably decreased. There are several important physical impacts to be considered relating to release rate-controlled films. The internal pressure of microporous film-coated preparations due to osmosis is one of the physical stresses, because the drug release from them is reported to be osmotically driven.[4] On the other hand, the movement of the GI tract is also an external physical impact for orally administered preparations as they pass through the GI tract. If this GI impact was too strong, an unexpected rupture of the coating would cause dose dumping. In addition to these impacts, residual internal stresses within the film coating created by shrinkage of the film upon solvent evaporation by differences in the thermal expansions of the coating and the substrate, could cause flaws and cracks in film coating,[5] and they may affect the drug release rate. Furthermore, in pharmaceutical coating, a good film-forming property with adequately strong porous EC film is necessary, because continuous mechanical stress will be applied during the coating process involving manufacturing equipment.[3a]

The mechanical strength of EC film has been evaluated by several researchers. Arwidsson *et al.* extensively studied the effect of preparation conditions of free EC films on the fracture stress by tensile testing.[6] With respect to the solvent composition in their work, they reported that a water-containing solvent (maximum water content is 10%) provided a spongy, porous structure, resulting in lower fracture stress.[6c]

The objectives of the present work are: to quantitatively evaluate the change in tensile strength of EC films as a function of film porosity, and to examine the actual mechanical resistance of beads coated with porous EC film by investigating *in vitro* and *in vivo* drug release.

Experimental

Materials The EC used in this study was Ethocel 45 cP (Dow Chemical Co., U.S.A.). Anhydrous theophylline (Tokyo Kasei Kogyo Co., Tokyo) was of reagent grade and it was used after grinding by a hammer mill. Spherical sucrose particles (Nonpareil 103, 24—32 mesh) were used for the core material of drug-loaded beads and this component was purchased from Freund Industrial Co. (Tokyo). Sucrose (Taito Co., Ltd., Japan) was of JP grade. All other materials used were of reagent grade.

Film Preparation Free films were prepared from aqueous ethanolic solution through a spraying process as described before.[3b] The ethanolic concentrations of EC spraying solution were optionally changed in the range from 65% to 100% to obtain free films with various porosities. The spraying conditions were as follows: EC concentration, 10%; spraying solution feed, 10 ml/min; spray air pressure, 0.8 kg/cm^2; temperature, 30 °C. The resultant films were dried at 40 °C for 18 h. The film porosity (ε) is defined according to Eq. 1:

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

where D_f and D_e are the density of porous EC film observed and the density of EC, respectively. D_f is determined by the values of geometrical volume (V) and weight (W_f) of the film specimen as $D_f = W_f/V$. To determine the V value, the film thickness (h) of a dried film specimen (surface area: 24.63 cm^2) was measured by a micrometer. ε was determined according to Eq. 2:

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

D_e was determined to be 1.13 g/cm^3 by measuring the density of the rigid and transparent cast film prepared by an EC chloroform solution.

Tensile Strength Measurement A tensile testing machine (Autograph AGS-100A, Shimadzu Corp., Kyoto, Japan) equipped with a 10 kg-load cell was used to evaluate the mechanical property of the EC free films. The EC film, 10 mm wide and 25 mm long, was mounted between the grips in the tensile testing machine. The extension rate during the tensile testing was 5 mm/min. The load and extension were monitored, and the fracture load (N_f), which corresponded to the maximum load, was determined.

Beads Preparation A powdered mixture of pulverized theophylline (600 g) and pulverized sucrose (1000 g) was slowly applied to Nonpareil seeds (1000 g) in a CF-granulator (CF-360EX, Freund Industrial Co., Tokyo), and it was continuously sprayed with 1200 g of the binder solution (25% aqueous ethanol containing 25% sucrose) to obtain drug-loaded, uncoated beads. The conditions used were as follows: spray solution feed, 2—7 ml/min; spray air pressure, 0.8 kg/cm^2; blower rate, 150—250 Nl/min; blower temperature, 60 °C; and rotating speed, 150 rpm. After drying at 45 °C for 18 h and sieving the beads to remove both agglomerates and fine particles, an aqueous ethanolic solution of EC (EC concentration, 5%; solvent, 65% aqueous ethanol) or ethanolic solution of EC (EC concentration, 5%) was sprayed onto the drug-loaded uncoated beads in a CF-granulator. In this paper, the coating level (M_c) was defined as the amount of film deposited (M_f) *versus* the weight of the uncoated beads (M_b) as: $M_c = (M_f/M_b) \times 100$. The coating conditions were as follows: spray solution feed, 6 ml/min; spray air pressure, 1 kg/cm^2; blower rate, 100—200 Nl/min; blower temperature, 50 °C; and rotating speed, 150 rpm.

***In Vitro* Drug Release Studies** The *in vitro* drug release studies were performed by the JP XII dissolution testing method No. 2 (paddle method) at 37 °C with constant stirring at 100 rpm in 900 ml of the dissolution medium. The dissolution media were water, JP 1st fluid (pH 1.2) and JP 2nd fluid (pH 6.8). To evaluate the effect of mechanical impact on drug release from the EC film-coated beads, a modified dissolution test was also performed, in which the dissolution medium containing 400 polystyrene beads (diameter, 6.35 mm; specific gravity, 1.05 g/cm^3) was used. Aliquots were withdrawn at pre-determined time intervals and assayed with a spectrophotometer (UV-160A, Shimadzu Co., Kyoto, Japan) to determine the drug concentration.

Prediction of Drug Release in the GI Tract Two male beagle dogs (weighing 10—12 kg) were used. The dogs were fasted for 20 h before drug administration, while receiving water *ad libitum*. Small bags (size: 5 × 10 mm) made of polyester net containing 100 mg of EC film-coated beads were orally administered with 30 ml of water at pre-determined time intervals to the beagle dogs. The polyester net was flexible enough to freely deform, so that the film-coated beads contained would not be protected from the mechanical stress caused in the GI tract. Twenty-four hours after the first administration, the dogs were sacrificed and the entire GI tract was removed, then opened. Each beads-containing bag was recovered immediately from the GI tract. The appearances of the beads were investigated by a stereo microscope (SZH-141, Olympus Optical Co., Tokyo). The beads in the polyester net bags were washed with ice water immediately after the recovery. The washed beads were then dissolved in 100 ml of 80% (v/v) aqueous ethanol by violent shaking for 20 min at room temperature. The aqueous ethanol solution was filtered. Then 1 ml of the filtrate, 1 ml of the internal standard solution (20 μg/ml) and 8 ml of mobile phase were mixed, and 20 μl of the mixed solution was subjected to HPLC (Type LC-6A, Shimadzu Co., Kyoto, Japan) to determine the amount of residual drug. By subtracting the residual drug content from the initial content, the amount of drug released for various time intervals could be determined to predict *in vivo* drug release behavior.

Assay of Theophylline by HPLC 7-(2-Hydroxyethyl)theophylline was used as an internal standard. A mixture of 0.1 M sodium acetate–acetonitrile (10 : 1) was used as the mobile phase. A reverse-phase column (Nucleosil $5C_{18}$, 4.6 × 150 mm, Chemco Scientific Co., Ltd., Osaka, Japan) was used and UV detection for quantification was performed at 273 nm. A linear detector response was observed over the concentration range of interest.

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 a Pt–Pd alloy by an ion sputterer (E-102, Hitachi, Ltd.) to reduce charging before the SEM-observation.

Results and Discussion

Relationship between Tensile Strength and Film Porosity The mechanical properties of polymeric films are usually evaluated by tensile testing.[6] The tensile strength is defined as the tensile stress per unit cross sectional area at film fracture, as given by Eq. 3:

$$T_s = N_f/A_0 \quad (3)$$

where T_s is the tensile strength, N_f is the fracture load and A_0 is the original cross sectional area. According to Eq. 3, the T_s values of EC films with various porosities, which were prepared by changing the ethanolic concentration of the EC solution,[3b] were determined by tensile testing. Figure 1 shows the relationship between T_s and ε. As shown in Fig. 1, the T_s values obtained were drastically decreased with an increase in film porosity. Since the film porosity relates to the quantity of EC occupied in a cross sectional area of the film, a higher porosity indicates a smaller amount of EC per area, which results in a lower T_s value. In addition to this, there may be some differences among the EC matrices of these porous films with different porosities. Namely, an ethanol solution of EC will give rise to a glassy EC matrix, which may be different from that arising from an aqueous ethanolic solution of EC, since in the latter case, the film is formed through phase separation to provide a fibrous xerogel of EC.[3a]

Concerning the quantitative relationship between mechanical strength and porosity for porous materials, Bal'shin *et al.* proposed the equation expressed as a power function form,[7] which can be expressed by the following equation:

$$\sigma_p = \sigma_o(1-\varepsilon)^\alpha \quad (4)$$

where σ_p and σ_o are the mechanical strength of a porous material and corresponding non-porous material, respec-

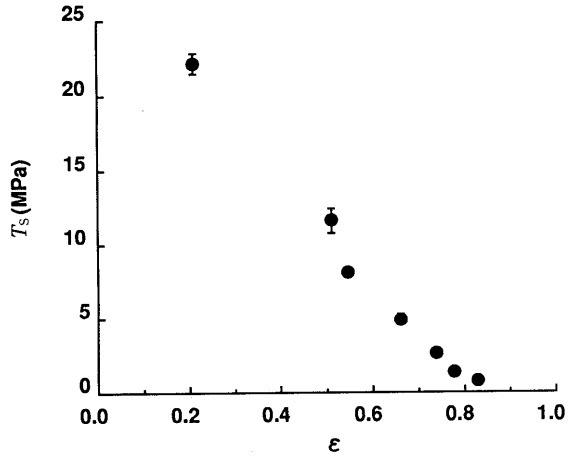

Fig. 1. Relationship between Tensile Strength (T_s) and Film Porosity (ε) (Mean ± S.D., $n = 3$)

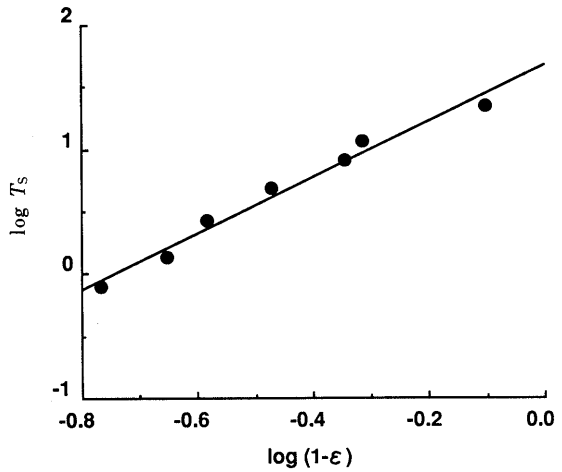

Fig. 2. Plot of log T_s *versus* log$(1-\varepsilon)$ According to Bal'shin's Equation (Eq. 4)

tively. α is the constant. Then, log T_s *versus* log$(1-\varepsilon)$ was plotted (Fig. 2). As shown in Fig. 2, a linear relationship between log T_s and log$(1-\varepsilon)$ was obtained ($R=0.989$), indicating that Bal'shin's equation was well adapted to the mechanical strength of the porous EC film presented.

Eq. 5 was obtained by the regression analysis of the plot shown in Fig. 2:

$$T_s=47.90(1-\varepsilon)^{2.26} \tag{5}$$

According to Eqs. 3 and 5, the fracture load of EC porous film can be expressed by Eq. 6 as a function of film porosity:

$$N_f=47.90(1-\varepsilon)^{2.26}A_0 \tag{6}$$

Comparison of Mechanical Strength of Films with Various Porosities under an Equal Permeation Rate When porous EC films are applied as the diffusion barriers of controlled release dosage forms, the change in mechanical property, as well as the change in drug diffusivity with film porosity, must be taken into consideration. To compare the mechanical properties of porous EC films with different porosities under the assumption that the permeation rate of each film was identical, model calculations were performed using free films to estimate the difference in film strength. The direction of solute permeation and tensile testing for such free films are schematically represented in Fig. 3.

As previously reported,[3b] the higher film porosity gave higher drug permeability. Therefore, to provide an equal release rate, more porous film requires a greater amount of EC. However, it is still unknown whether EC films with higher porosity have an advantage over those with lower porosity with respect to mechanical strength. The solute permeability through a porous EC film can be expressed by Fick's law as follows:

$$J=P\Delta C/h \tag{7}$$

where J is the flux of the solute (permeation rate per unit surface area), P is the permeability coefficient, h is the film thickness and ΔC is the concentration difference across the film. Water-filled pores in a porous film play an important role in solute permeation, and the permeability

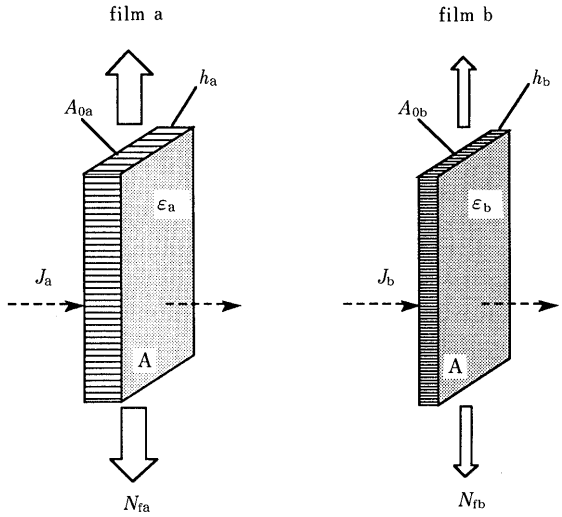

Fig. 3. Illustration of Direction of Drug Permeation and Tensile Testing for EC Free Films (Film a, Film b) with Different Porosities $(0<\varepsilon_b<\varepsilon_a<1)$

N_f, tensile load; J, flux; A_0, cross sectional area; h, film thickness; ε, porosity; A, permeation area.

coefficient can be expressed as:

$$P=\varepsilon D_w/\tau \tag{8}$$

where D_w is the solute diffusion coefficient in water and τ is tortuosity.[8] Although τ can be changed with porosity, our previous report[3b] showed that the P value of porous EC film could be also expressed in a power function form irrespective of the properties of solutes as given by:

$$P=1.18\varepsilon^{8.55}D_w \tag{9}$$

The flux ratio of two films (film a, film b) with different porosities $(0<\varepsilon_b<\varepsilon_a<1)$, such as those shown in Fig. 3, is expressed as Eq. 10, which is derived from Eq. 7:

$$J_a/J_b=P_ah_b/P_bh_a \tag{10}$$

where suffix 'a' and 'b' represent the parameters of each corresponding film, respectively. On the other hand, the ratio of the fracture load of film a and film b with different porosities is expressed as Eq. 11, which is derived from Eq. 3:

$$N_{fa}/N_{fb}=T_{sa}A_{0a}/T_{sb}A_{0b} \tag{11}$$

If the two films with different porosities have an equal flux ($J_a=J_b$), Eq. 12 was derived from Eq. 10:

$$P_a/P_b=h_a/h_b \tag{12}$$

Since the width of each free film was constant (10 mm), $h_a/h_b=A_{0a}/A_{0b}$. Eq. 13 was obtained from Eq. 12:

$$P_a/P_b=A_{0a}/A_{0b} \tag{13}$$

Then Eq. 14 was derived from Eq. 11 and Eq. 13:

$$N_{fa}/N_{fb}=T_{sa}P_a/T_{sb}P_b \tag{14}$$

Eq. 14 can be rewritten as a function of ε using Eq. 5 and Eq. 9 as given by:

$$N_{fa}/N_{fb}=\varepsilon_a^{8.55}(1-\varepsilon_a)^{2.26}/\varepsilon_b^{8.55}(1-\varepsilon_b)^{2.26} \tag{15}$$

According to Eq. 15, the ratio of fracture load (N_{fa}/N_{fb})

was calculated for various films with different porosities, in which the porosity of the reference film (ε_b) was assumed to be 0.3, because the porosity of EC sprayed film produced from good solvent was 0.2—0.3. The change of N_{fa}/N_{fb} against various ε_a ($0<\varepsilon_b<\varepsilon_a<1$) under the condition $J_a=J_b$ is shown in Fig. 4. The values of $\log(N_{fa}/N_{fb})$ are found to always be greater than zero, namely, the N_{fa} values are always greater than N_{fb} values in every ε_a, indicating that films with a higher porosity can provide a higher fracture load when equal flux is given. According to the results shown in Fig. 4, it was found that films with higher porosity have a higher fracture load under an equal permeation rate, although more EC is required.

Effect of Mechanical Impact on *in Vitro* Drug Release from Porous EC Film-Coated Beads The film-coated beads are usually subject to various mechanical stresses during their passage through the GI tract, such as internal osmotic pressure or external mechanical impact due to GI movement as mentioned before. To examine the mechanical resistibility of the actual dosage form coated with porous EC film, modified *in vitro* dissolution tests were conducted using theophylline beads coated with a high-porosity EC film as the model dosage form.

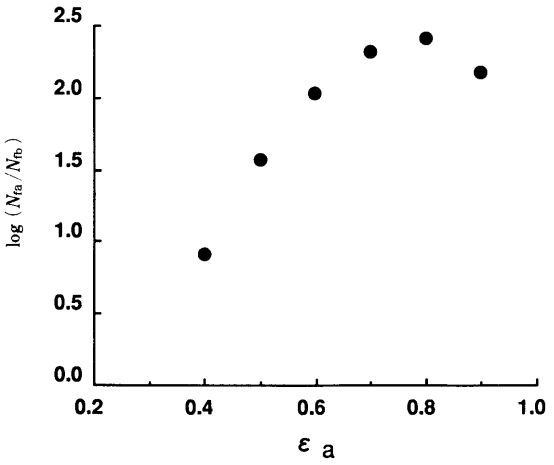

Fig. 4. Comparison of Fracture Load of Porous EC Films with Different Porosities under Equal Permeation Rate

The ratio of fracture load, N_{fa}/N_{fb} was calculated for each film with various porosities (ε_a) under the condition, $0<\varepsilon_b<\varepsilon_a<1$ and $\varepsilon_b=0.3$.

Figure 5 shows the scanning electron micrographs of the surface of the EC film-coated beads tested. When an aqueous ethanolic solution was used as the solvent for the coating solution, the coating showed a porous structure. On the other hand, an ethanolic solution of EC gave non-porous coating.

Although there is little information on the mechanical impacts in the GI tract, the liquid-stirring effect around the dosage form and the physical destruction effect are thought to be predictable mechanical impacts which can affect drug release from the controlled release dosage form. Recently, a study on the rational *in vitro* dissolution test for a controlled-release matrix tablet using polystyrene beads, which generates mechanical destruction or frictional force, was reported.[9]

Figure 6 shows the theophylline release behaviors from EC film-coated beads tested by a modified dissolution test method. The coating levels at the weight base of the beads was 4% for the high-porosity film coated beads and 1% for the non-porous film coated beads, and these two kinds of beads have almost an equal release rate (time for 50% drug release: 2 h). The film-coated beads seemed to undergo a grinding effect by the polystyrene beads during the dissolution test. As shown in Fig. 6, when the drug release rate in the modified dissolution test was compared with a common dissolution test (JP paddle method), almost no changes occurred on the drug release rate from the high-porosity film coated beads, but that from the non-porous film coated beads increased somewhat in the presence of polystyrene beads. These results demonstrate that the porous film coating is more resistant against mechanical destruction or friction force than the non-porous film coating under the condition that the release rate is equal, as estimated by Eq. 15.

***In Vivo* Evaluation of Mechanical Strength of Porous EC Film-Coated Beads** To evaluate the mechanical strength of the porous EC film *in vivo*, theophylline beads coated with a porous EC film (coating level, 4%; solvent, 65% aqueous ethanol) were orally administered in a polyester net bag to two beagle dogs at pre-determined time intervals, and the *in vivo* drug release behavior was predicted

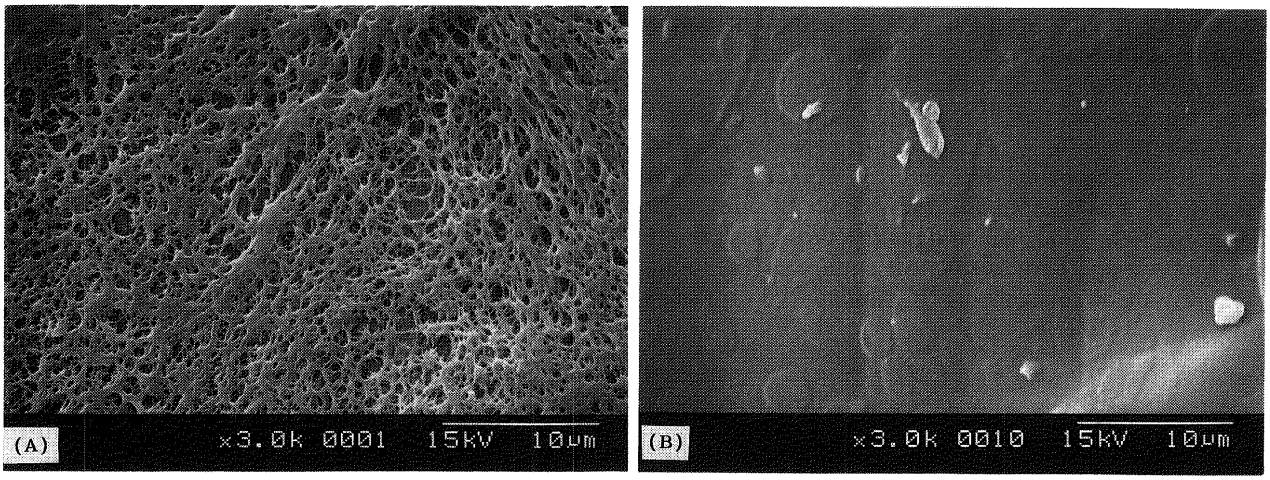

Fig. 5. Scanning Electron Micrographs of the Surface of the EC Film-Coated Beads

Solvent of the coating solution: (A), 65% aqueous ethanol; (B), ethanol.

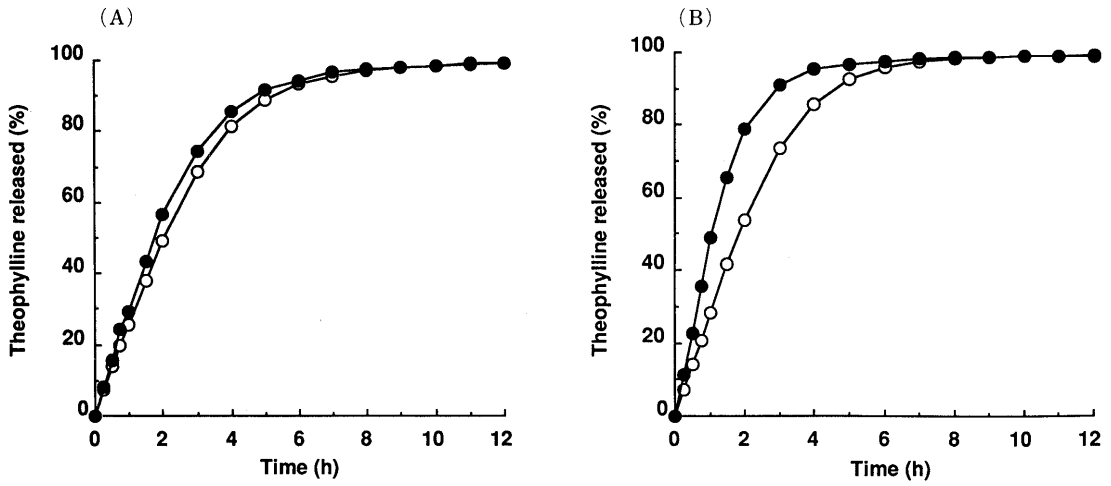

Fig. 6. Effect of Physical Stress Caused by Polystyrene Beads on Theophylline Release from High-Porosity (A) or Non-porous (B) EC Film-Coated Beads

Solvent of the coating solution and coating level: (A), 65% aqueous ethanol and 4% coating; (B), ethanol and 1% coating; conditions: Number of polystyrene beads, 400 beads; dissolution medium, water; method, JP paddle method (100 rpm); temperature, 37 °C; key: ○, without polystyrene beads; ●, with polystyrene beads.

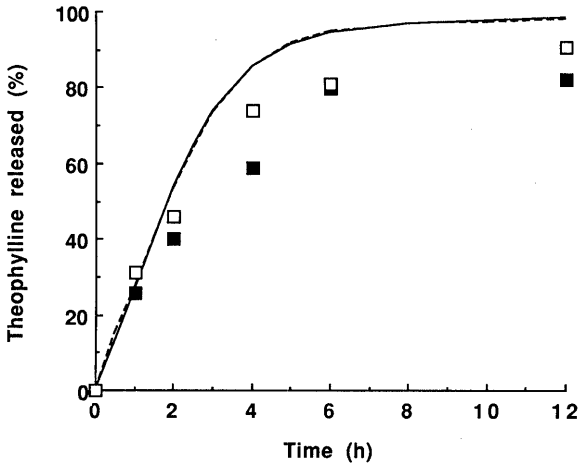

Fig. 7. Comparison of *in Vivo* Release with *in Vitro* Release of Theophylline from Porous EC Film-Coated Beads

Solvent of coating solution, 65% aqueous ethanol; coating level, 4%; key: ——, *in vitro* (pH 1.2); – – –, *in vitro* (pH 6.8); ■, *in vivo* (dog 1); □, *in vivo* (dog 2).

by the residual amount of theophylline in the beads recovered from the GI tract. Although the presence of foods with the beads in the GI tract may also affect the mechanical strength of the film-coated beads administered, the experiment was performed under fasting conditions. Figure 7 shows a comparison of the *in vivo* release with the *in vitro* release of theophylline from the porous EC film-coated beads until 12 h after the first oral administration. The *in vivo* release behavior was in good agreement with the *in vitro* release behavior. In addition, according to stereo microscopic observations, although some beads became slightly deformed, it was found that none of the beads recovered ruptured in the GI tract. These results indicate that the porous EC film coating can be used as a barrier for controlled release preparations, because it seems to have the strength to withstand the mechanical stress in the GI tract.

Conclusion

The mechanical characteristics of porous EC film were evaluated by using free films and film-coated beads *in vitro* and *in vivo*. It was found that the relationship between mechanical strength and porosity of EC free film was expressed as a power function according to Bal'shin's equation, and that a higher film porosity gives a higher fracture load under an equal permeation rate. This relationship was also confirmed by an *in vitro* high-shear dissolution test of EC film-coated beads with different film porosities. In addition, good *in vitro*/*in vivo* correlation was obtained in the drug release behaviors from high-porosity film coated beads. Accordingly, the porous EC film presented was found to be useful as a release rate-control film for capsule-type controlled release preparations with respect to mechanical strength.

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