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Preparation and Evaluation of Micro-Porous Ethylcellulose Capsule as Oral Sustained-Release Preparation of Theophylline

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ABSTRACT: Micro-porous ethylcellulose (EC) membrane capsules were prepared by dissolving polyvinylalcohol (PVA) particles from membranes which were made of a mixture of EC (a water-insoluble polymer). The pore size was approximately 400 μm. Since the dissolution rate of theophylline from the micro-porous EC membrane capsules was fast, gel-forming polymer, poly(acyclic) acid (Carbomer), was incorporated inside the capsule at 10, 20 or 30 mg. Using test capsules containing 100 μm of theophylline, *in vitro* dissolution studies were performed. By including Carbomer in capsule formulations, the dissolution rate of theophylline was decreased. However, there were not significant differences in dissolution rates between preparations containing the three different amounts of Carbomer. *In vivo* evaluation studies using beagle dogs showed that AUC, C_{max} and T_{max} were inversely proportional to the formulated amount of Carbomer. The capsule containing 20 mg of Carbomer gave plasma theophylline concentrations between 5 and 15 μg mL^{-1}, which reflect levels within the therapeutic window. The effect of food intake on the pharmacokinetics of theophylline was also studied with the same capsule. Food increased AUC, C_{max} and T_{max}, although plasma theophylline levels were maintained within the therapeutic range.
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Key words: micro-porous membrane; EC capsule; sustained-release; theophylline; beagle dog

Introduction

In the last 10 years, many new advanced drug delivery systems have been developed to more efficiently and specifically deliver drugs to the site of the target organ [1]. We have been studying one type of oral drug delivery system involving two kinds of colon delivery capsules: intestinal luminal pressure-controlled colon delivery capsules (PCDC) and time-controlled colon delivery capsules (TCDC). With these capsules, drug molecules are released in the colon rather than in either the stomach or small intestine [2,3]. Both type of capsules are prepared by coating the inner surface of gelatin capsules with a water-insoluble pharmaceutical polymer, ethylcellulose (EC). As one of the components of TCDC, an EC capsule body containing mechanically made micro-pores was prepared [4]. By increasing the number of micro-pores, sustained-release micro-porous EC capsules were prepared. The usefulness of the mechanically prepared micro-porous EC capsules as an oral sustained-release preparation was studied using cisplatin in beagle dogs, where the diameter of the micro-pores were 800 μm [4]. However, such a mechanical approach requires a great deal of effort in order to prepare large numbers of capsules. From the standpoint of industrial management, other technologies are needed for the production of micro-porous EC membrane capsules in bulk. One approach has been the production of micro-pores in EC membranes by chemical methods. Polyvinylalcohol (PVA), a water soluble polymer, particles were added to EC solution and micro-porous EC membranes were produced by dissolving PVA particles with warm water. Using this micro-porous EC membrane, micro-porous EC capsules were prepared. The capsules were evaluated by both *in vitro* dissolution studies and *in vivo* bioavailability studies using beagle dogs, where theophylline was used as a model drug for the sustained-release oral preparation.

Methods

Materials

Theophylline and N,N-dimethylacetoamide (DAA) were obtained from Kanto Chemicals Co. (Tokyo,

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Japan). EC (100G grade) was obtained from Shin-etsu Chemical Industry Co. (Tokyo, Japan) and the particle size was adjusted between 200 and 500 μm using stainless meshes. Poly(acrylic) acid (Carbomer, Carbopol™ 934NF) obtained from Chugai Boyeki Co. (Tokyo, Japan). Methanol (HPLC grade) was obtained from Kanto Chemical Co. (Tokyo, Japan). Sucrose, Tween 80 and Triton X–100 were obtained from Nacalai Tesque Co. (Kyoto, Japan). Size 00 hard gelatin capsules were obtained from Yoshida Shoten (Himeji, Japan). Male beagle dogs used in the study and standard solid commercial dog food were obtained from Nippon SLC Co. (Hamamatsu, Japan). All other materials were commercial products of reagent grade.

Preparation of Micro-Porous EC Membrane

Five millilitres of a 8% w/v solution of EC in DAA containing 300 mg PVA was cast evenly into petri dishes. Dishes were maintained in an incubator at 60°C for 5 min, and then were submerged in 1 L of chilled distilled water for 5 min in order to extract DAA. This washing was repeated five times. The polymer membrane thus formed was removed from the petri dish and was resubmerged, five times, in 1 L of warm distilled water at 60°C for 10 min in order to dissolve PVA. The micro-porous EC membrane was then air dried and stored in a vacuum desiccator with $CaSO_4$ for at least 72 h prior to use. The mean diameter of the EC membrane was measured by use of a micrometer with a microscope.

Preparation of Micro-Porous EC Capsule

From the micro-porous EC membrane, 2.5 × 3.0 cm, a micro-porous tube was made with the aid of concentrated EC solution (EC glue). EC capsule caps were prepared according to our method for preparing time-controlled colon delivery capsules [2]. Namely, size 00 gelatin capsules were filled with 20% w/v EC solution in a mixture of methanol and methylene chloride (1:4). By allowing the solvent to evaporate in a refrigerator for 12 h, the inner surface of the gelatin capsule became coated with an EC layer which was approximately 150 μm thick. EC capsule caps were obtained by dissolving the gelatin in these capsules in warm water (37°C). Caps were attached to EC membrane tubes with the aid of EC glue.

Test Preparations

Theophylline (100 mg), Carbomer (0, 10, 20 or 30 mg) and sucrose (300, 290, 280 or 270 mg) were thoroughly mixed with the aid of Tween 80 (100 mg). The resultant mixture was introduced into the micro-porous EC membrane capsule body, and the cap was attached to the body with EC glue.

Dissolution Test of the Capsules

Dissolution tests of the theophylline-loaded micro-porous EC membrane capsules were carried out according to the JP XIII method (paddle method). Test capsules held in a stainless sinker were introduced to 900 mL of JP 1st fluid (pH 1.2). The paddle was used with a rotation speed of 100 rpm. The dissolution medium was degassed by sonication at room temperature and maintained at 37°C throughout the test period. To simulate the transit from gastric to intestinal pH, samples of the 1st fluid were replaced 1 h later with JP 2nd fluid (pH 6.8). To determine the release of theophylline from the test capsule, 1.0 mL samples of the dissolution medium were removed for analysis every hour until 12 h, and, thereafter, at 24, 30, 36 and 48 h. Samples were subsequently replaced with fresh dissolution medium. The theophylline contents in the dissolution samples were measured by HPLC as described in the following section.

In Vivo Beagle Dog Studies

Administration in the Fasted Condition. Three adult male beagle dog, 10–12 kg, were fasted overnight for at least 16 h. Before drug administration, 0.5 mL blank blood samples were collected from the jugular vein. Test preparations were orally administered to beagle dogs at 10:00 h with 20 mL water. After administration, 0.5 mL blood was removed from the jugular vein at each sampling time. The blood sampling schedule was 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h after drug administration. Blood samples were drawn into heparinized micro-centrifuge tubes and immediately centrifuged at 12000 rpm for 5 min to obtain the plasma fractions (200 μL). The plasma samples were frozen immediately after collection and stored in a freezer at −20°C until analysis.

Administration in the Postprandial Condition. One hundred grams of solid food was given to each beagle dog at 09:30 h and 0.5 mL blank blood samples were collected from the jugular vein. Test preparations were orally administered to beagle dogs at 10:00 h with 20 mL water. After administration, 0.5 mL blood samples were removed from the jugular vein. The blood sampling schedule was 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15 and 24 h. Plasma samples were obtained and were treated as described above.

Analytical Procedures for Theophylline

Theophylline concentrations were measured by a HPLC method [5]. Briefly, to a 15 mL extraction tube, 100 μL of defrosted plasma sample, 1mL phosphate buffer (pH 6.0) and 5 mL ethylacetate were added. The tube was shaken and centrifuged at 3000 rpm for 20 min. After the aqueous phase had been aspirated off, the extract was removed, then

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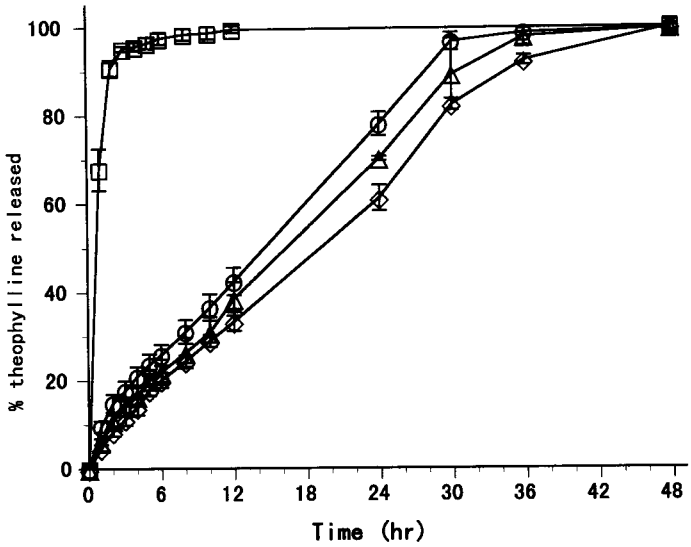

Figure 1. Dissolution profiles of theophylline (TP) from micro-porous EC capsules containing different amounts of Carbomer (□, 0 mg; ○, 10 mg; △, 20 mg; ◇, 30 mg). The formulated amount of theophylline was 100 mg. Each point represents the mean ± S.E. of three experiments

put in a clean glass tube. The organic liquid was evaporated to dryness at 45°C under a stream of nitrogen gas and the residue was dissolved in 200 μL of mobile phase of which 100 μL was injected into the HPLC system. The HPLC system used was a Shimadzu LC-10A pump (Kyoto, Japan) and UV detector (Shimadzu SPD-10A) connected to Shimadzu C-R4A Chromatopac. Samples were injected using a Waters WISP 710B automatic sample injector. The analytical column was a Chemcosorb 5-ODS-H (4.6 mm i.d. × 250 mm) and was maintained at 60°C for all separations. The composition of the mobile phase was methanol:water (12:88). The flow rate of the pump was 1.0 mL min^{-1}. Theophylline eluted from the column was detected by UV absorption monitored at 254 nm. Levels were estimated by comparing peaks obtained from standard samples to which were added known amounts of theophylline. A set of six or seven calibration standards was run with each series of unknown samples. The calibration was linear over 0–50 μg mL^{-1}.

Data Analysis

A non-compartmental pharmacokinetic analysis was applied to the plasma theophylline concentration–time data [6]. The terminal elimination rate constant, λ_z, was determined by a linear regression of at least three data points from the terminal portion of the plasma concentration–time plots. The area under the plasma concentration–time curve after oral administration, AUC, was calculated using the linear trapezoidal rule. The area under the first moment curve after oral administration, AUMC, was also calculated using the linear trapezoidal rule. The terminal elimination half-life, $t_{1/2}$ was determined by dividing ln 2 by λ_z. The mean residence time, MRT, was calculated as AUMC/AUC.

Statistics

All the values are expressed as their means ± S.E. unless otherwise noted. Statistical differences were assumed to be reproducible when $p < 0.1$ (two-tailed t-test).

Results

Dissolution profiles of theophylline from three kinds of test preparations are shown in Figure 1. In the case of capsules which did not contain Carbomer, approximately 90% of theophylline was released from the capsule into the dissolution medium within 2 h and, thereafter, theophylline was almost completely released from the capsule. When capsules were formulated with Carbomer, sustained-release characteristics of theophylline were obtained, although there were not significant differences in the dissolution curves between three kinds of capsules which contained 10, 20 and 30 mg of Carbomer. The percentage release of theophylline from the capsules containing 10, 20, 30 mg of Carbomer within 24 h were 78.0 ± 2.7 (S.E.), 70.2 ± 0.5 and 61.2 ± 2.9%, respectively. Figure 2 shows the relationship between $T_{50\%}$, the time when half of the formulated amount of theophylline was released from the capsule, and the formulated amount of Carbomer. The $T_{50\%}$ of theophylline capsules containing 10, 20 and 30 mg of Carbomer were 15.1 ± 1.2, 16.1 ± 1.2 and 19.5 ± 1.3 h, respectively. As shown in Figure 2, the release rate of theophylline decreased by increasing the formulated amount of

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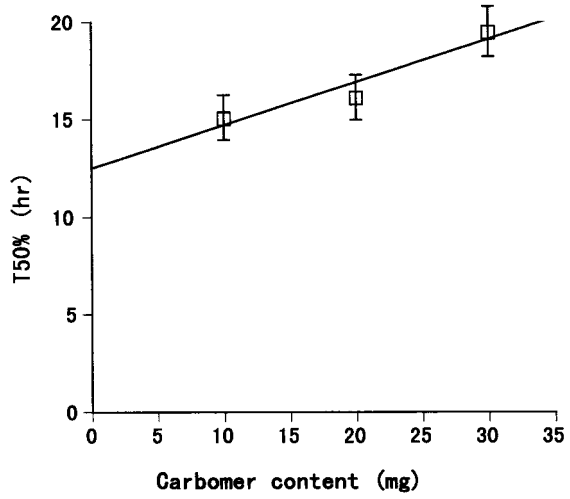

Figure 2. Relationship between $T_{50\%}$ obtained in dissolution studies and formulated amount of Carbomer in the micro-porous EC capsules (□, 0 mg; ○, 10 mg; △, 20 mg; ◇, 30 mg). Each point represents the mean ± S.E. of three experiments

Carbomer inside the capsule, although there were not significant differences in $T_{50\%}$ between these three capsules.

Next, the capsules formulated with Carbomer were used for *in vivo* evaluation in beagle dogs. At first, two types of theophyplline (100 mg) capsules formulated with 10 mg and 30 mg of Carbomer were studied and the results are shown in Figure 3 as the average plasma theophylline concentration–time profiles. As opposed to the *in vitro* dissolution studies, the plasma theophylline concentration–time curves showed significant differences between the two capsules. As the formulated amount of Carbomer increased from 10 to 30 mg, the peak theophylline concentration, C_{max}, decreased to approximately one-fifth. As the therapeutic window of theophylline in asthmatic patients were reported to be $5 \sim 15$ μg mL^{-1} [7], these two types of theophylline capsules are undesirable for clinical purposes. Therefore, the dose of theophylline was increased to 200 mg and the dog study was performed where the formulated amount of Carbomer was increased to 20 mg in correspondence with the theophylline dose. The result is also shown in the figure. With this capsule, the plasma theophylline concentrations were maintained within the therapeutic window. Pharmacokinetic parameter values were calculated with the non-compartmental method and the results are shown in Table 1, where MRT is known to be an important pharmacokinetic parameter for the evaluation of the sustained-release preparation. The MRT values did not show significant differences between the three capsules.

Finally, the effect of food on the plasma theophylline concentration–time curve was investigated with capsules containing 20 mg of Carbomer and the results are shown in Figure 4. As shown in Figure 4, C_{max} was slightly increased and T_{max} was considerably prolonged, although plasma theophylline concentration–time curves suggested sustained-release characteristics of theophylline. The pharmacokinetic parameter values in beagle dogs to whom test capsules were administered postprandially are also shown in Table 1. In the fed condition, approximately 1.5 folds higher AUC, C_{max} and T_{max} values were obtained as compared to the values obtained in the fasted condition study.

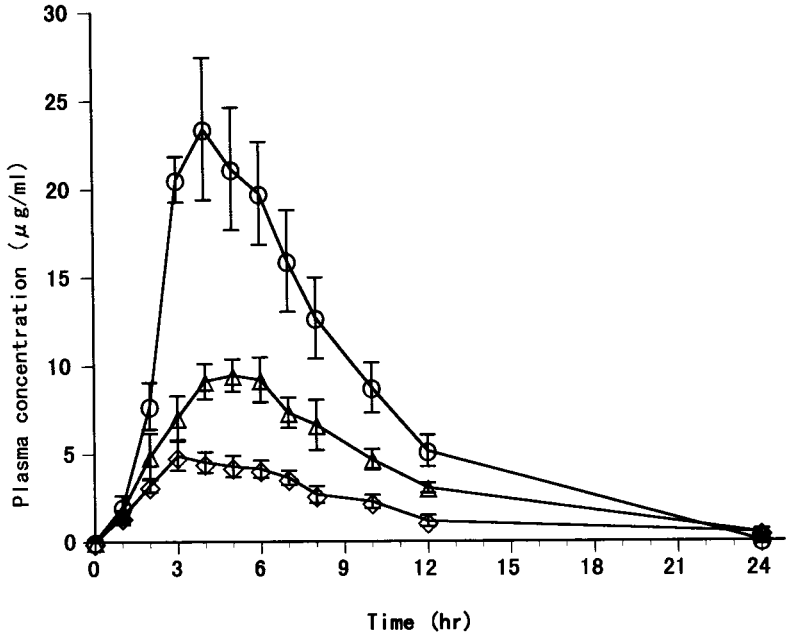

Figure 3. Plasma theophylline (TP) concentration–time curves after oral administration of micro-porous EC capsules containing theophylline and various amounts of Carbomer to beagle dogs. The formulated amounts of theophylline and Carbomer were: ○, 100 mg and 10 mg; ◇, 100 mg and 30 mg; △, 200 mg and 20 mg, respectively. Each point represents the mean ± S.E. of three experiments

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Table 1. Effect of Carbomer content and food on pharmacokinetic parameters of theophylline after oral administration to beagle dogs

Pharmacokinetic parameter	Carbomer content			
30 mg	10 mg	20 mg		Fasted
	Fasted	Fasted	Fed	
AUC ($\mu g \cdot h\ mL^{-1}$)	184 ± 28.0	92.0 ± 12.5	157 ± 24.1*	45.7 ± 6.28**
C_{max} ($\mu g\ mL^{-1}$)	24.0 ± 3.51	9.74 ± 1.56	13.1 ± 0.81*	5.00 ± 0.77**
T_{max} (h)	3.67 ± 0.33	5.00 ± 1.00	9.33 ± 1.33*	3.33 ± 0.33
$t_{1/2}$ (h)	1.92 ± 0.49	4.26 ± 1.37	4.87 ± 0.71	6.04 ± 0.74**
MRT (h)	7.00 ± 0.12	7.84 ± 0.61	7.65 ± 0.06	7.72 ± 0.50

Results are expressed as the mean $\pm$ S.E. of three animals.
* Significantly different from fasted condition ($p < 0.1$).
** Significantly different from 10 mg Carbomer content ($p < 0.1$).

However, there was not a significant difference in MRT between the two administration conditions.

Discussion

At the initial stage of the study, hydroxypropylmethylcellulose phthalate (HPMCP) was used to prepare micro-porous EC membranes. HPMCP has been used in the pharmaceutical industry as an enteric coating polymer [8]. HPMCP and EC were dissolved with the mixture of methylene chloride and methanol, and membranes were prepared by evaporating the solvent after casting into petri dishes. By dissolving the HPMCP with a 0.1N NaOH solution, the micro-porous EC membrane was produced and the micro-pore size was measured by use of a micrometer with a microscope. The mean diameter of the EC membrane was approximately 20 μm. Using HPMCP-EC membrane, micro-porous EC membrane capsules were prepared. However, the micro-pore size was so small that the permeability rate of the dissolution medium inside the micro-porous EC membrane capsules was slow. To overcome this problem, PVA was used in this study. In the case of PVA, PVA particles were not dissolved with the solvent. Therefore, the micro-porous PVA-EC membrane had a larger diameter than the HPMCP-EC membrane. The size of the micro-pores of the PVA-EC membrane was approximately 400 μm, about 20 times larger than that of the HPMCP treated EC micro-porous capsule. As the size of the micro-pores increased, the permeability of water from outside to inside the capsule was improved and the dissolution rate of theophylline to the medium increased as shown in Figure 1. To decrease the dissolution rate of theophylline from the micro-porous capsule, Carbomer, a gel-forming polymer, was formulated inside the capsule as in the case of cisplatin [4]. However, within the range of the formulated amount of Carbomer tested, from 10 to 30 mg, there were not significant differences in the *in vitro* dissolution rates between the three formulations. On the other hand, significant differences were observed in the *in vivo* studies using beagle dogs. As the formulated amount of Carbomer increased from 10 to 30 mg, both the AUC and C_{max} decreased and increases in $t_{1/2}$ were observed. Generally, orally administered preparations release drug molecules during passage through the gastrointestinal tract where physiological factors such as water content in the gastrointestinal tract, pH changes and peristalsis affect the release rate of drug molecules from the preparation [9]. However, *in vitro* dissolution tests cannot simulate such *in vivo* conditions fully—especially since the sink condition was attained in the *in vivo* situation, because the test preparation moved from the stomach to the rectum after oral administration. Therefore, the dissolution process in the test preparations and in the *in vivo* dissoloution test was thought to be different. Consequently, the discrepancy observed between *in vitro* dissolution studies and *in vivo* bioavailability studies may be attributed to such factors.

With the micro-porous EC membrane capsule containing 20 mg of Carbomer, the effect of food on the plasma pharmacokinetics of theophylline was studied. With postprandial administration, AUC, C_{max} and T_{max} increased. These results were ascribed to the prolonged gastric emptying time (GET) due to the concomitant food intake. The administered amount of solid food in this study was the same as used in our previous study where the effect of food on the gastrointestinal transit of a model drug, fluorescein (FL), in colon delivery capsules was studied [10]. By comparing the T_{is}, the time when FL firstly appeared in the systemic circulation, from colon delivery capsules administered in postprandial and fasted conditions, the difference was calculated to be 6.67 h. By considering the small intestinal transit time of capsules in beagle dogs, 2 h [11,12], it is likely that theophylline capsules remain in the stomach for at least 4.67 h and theophylline molecules are released there after oral administration. After that time, the test preparation transfers into the small intestine where the pH is

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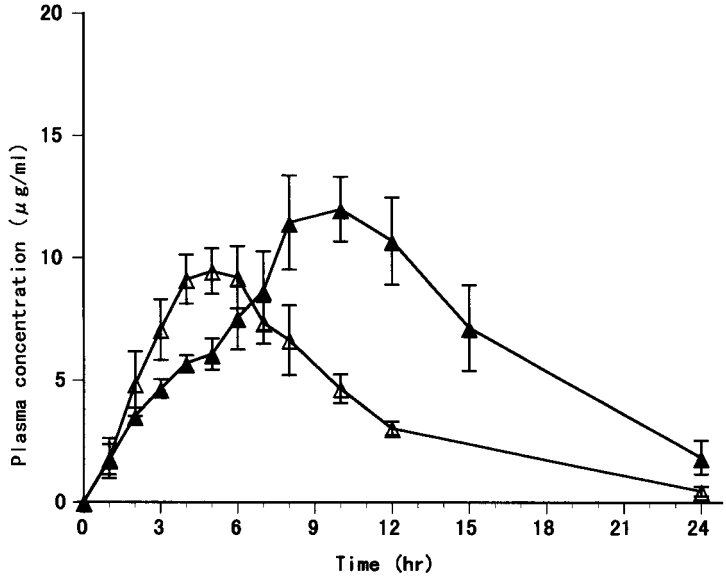

Figure 4. Effect of food intake on the plasma theophylline (TP) concentration–time curves after oral administration of micro-porous EC capsules containing theophylline (200 mg) and Carbomer (20 mg) to beagle dogs. (△, fasted; ▲, fed) Each point represents the mean ± S.E. of three experiments

considerably higher than that in the stomach and the gel-formation by Carbomer inside the micro-porous EC capsule reaches its ceiling [13,14]. Consequently, the drug release rate was thought to be increased and a prolonged T_{max} was obtained. On the other hand, as theophylline is a poorly water soluble drug, the solubility of theophylline was thought to be increased after postprandial administration and the bioavailability was thought to be increased [15]. When the test preparation was transferred to the colon where the water content was decreased due to reabsorption, the drug release rate was thought to be decreased. In this study EC was used as a core material of the micro-porous capsule. As EC is not biodegradable during its passage through the gastrointestinal tract, mico-porous EC capsules were recovered in the feces of the next morning even in the postprandial administration experiment. Therefore, theophylline preparations used in this study are thought to belong to a reservoir type sustained-release preparation [16].

Beagle dogs were used in this study in order to evaluate the micro-porous EC capsule as an oral sustained-release preparation. However, there are many differences in the physiological condition of the gastrointestinal tract between beagle dogs and humans [17,18]. The gastrointestinal transit time (GITT) of particles were reported to be 2.8 h in beagle dogs and 4.5 h in human volunteers [17–19]. Furthermore, the length of the gastrointestinal tract of beagle dogs is shorter than that of humans. Therefore, particles were reported to be delivered to the colon within 3 h in beagle dogs [18]. To overcome these problems, dogs whose gastrointestinal transit was adjusted by atropine are used to simulate the human [20]. Using such beagle dogs, micro-porous EC capsules will be evaluated in the next step.

In conclusion, micro-porous capsule made of EC was prepared with the aid of PVA. The pore size was approximately 400 μm. To decrease the dissolution rate of theophylline, a gel-forming polymer, Carbomer, was included inside the capsule at either, 10, 20 or 30 mg. Using test preparations containing 100 mg of theophylline, *in vitro* dissolution studies were performed. By including Carbomer, the dissolution rate of theophylline was decreased. However, there were not significant differences between the preparations containing three different amounts of Carbomer. *In vivo* evaluation studies using beagle dogs showed that AUC, C_{max} and T_{max} were inversely proportional to the formulated amount of Carbomer. The capsule containing 20 mg of Carbomer gave plasma theophylline concentrations between 5 and 15 μg mL^{-1}. The effect of food intake on the pharmacokinetics of theophylline was studied with this capsule. Food increased AUC, C_{max} and T_{max} as compared to administration in the fasting state.

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