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Preparation of enteric coated timed-release press-coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting

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Abstract

As a new oral drug delivery system for colon targeting, enteric coated timed-release press-coated tablets (ETP tablets) were developed by coating enteric polymer on timed-release press-coated tablets composed of an outer shell of hydroxypropylcellulose and core tablet containing diltiazem hydrochloride (DIL) as a model drug. The results of the in vitro dissolution tests in JP 1st fluid (pH 1.2) and JP 2nd fluid (pH 6.8) indicated that these tablets showed both acid resistance and timed-release. To clarify whether ETP tablets could have been of use in the gastrointestinal tract, ETP tablets with a layer of phenylpropanolamine hydrochloride (PPA) (a marker of gastric emptying) between the enteric coating layer and outer shell were prepared, and were administered to beagle dogs. The gastric emptying time and lag time after gastric emptying were evaluated by determining the times at which PPA and DIL first appeared in the plasma (TFA_{PPA} and TFA_{DIL}, respectively). TFA_{PPA} and TFA_{DIL} were about 4 and 7 h, respectively. This value of TFA_{PPA} indicated that ETP tablets displayed acid resistance in the stomach as well as in JP 1st fluid. Subtraction of TFA_{PPA} from TFA_{DIL} gave a value of about 3 h which agreed well with the lag time determined by in vitro dissolution test in JP 2nd fluid. Also, the results seemed to be in accordance with the time at which the tablets reached the colon after gastric emptying. Therefore, ETP tablets seemed to be an effective tool for oral site-specific delivery including targeting of the colon.

Keywords: Oral drug delivery; Hydroxypropylcellulose; Enteric coated; Press-coated tablet; Colon targeting

1. Introduction

Oral site-specific drug delivery systems, especially colon-specific drug delivery systems, have attracted a great deal of interest recently for the local treatment of a variety of bowel diseases and also for improving systemic absorption of drugs susceptible to enzymatic digestion in the upper gastrointestinal tract such as peptides and proteins. Various approaches have been reported during the last decade to develop new methodologies for site-specific drug release, including pH-

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sensing release (Stolk et al., 1990; Ashford et al., 1993), time-controlled release (Stolk et al., 1990) and microbially controlled release (Kopecek et al., 1992).

Methods based on pH-sensitive delivery systems such as enteric coated dosage forms could be a simple and practical means for colon-specific drug delivery. However, such methods do not have sufficient site specificity because, with this type of dosage form, most of the drug is released in the upper small intestine after gastric emptying even though drug release is effectively prevented in the stomach.

Time-controlled release systems, such as sustained or delayed-release dosage forms, are also very promising. However, due to the potentially large variation of gastric emptying time of dosage forms in humans (Davis et al., 1986; Adkin et al., 1993), in this approach the colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability.

In the previous study, we clarified that press-coated tablets with an outer shell composed of hydroxypropylcellulose (HPC) functioned as a good timed-release system (Fukui et al., 2000). This press-coating technique is advantageous because the tablets can be prepared with the various characteristics suitable for a number of uses (Maggi et al., 1993; Pozzi et al., 1994; Otsuka and Matsuda, 1994). Our system is also applicable as colon-targeting dosage forms by prolonging the lag time to more than 6 h. However, this system has the following disadvantages affecting its suitability for use as a colon delivery system.

1. The gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
2. Gastrointestinal movement, especially vigorous peristalsis or contraction in the stomach, would result in a wide erosion rate of HPC in the outer shell.

Based on the physiological characteristics of the human gastrointestinal tract and the movement of dosage forms therein (Davis et al., 1986; Adkin et al., 1993), appropriate integration of pH-sensitive and timed-release functions into a single dosage form may improve the site-specificity of drug delivery to the colon. That is, since the transit time of dosage forms in the small intestine is less variable, i.e. about 3 ± 1 h, the timed-release function (or 'timer function') should work more effectively in the small intestine as compared with the stomach. In the small intestine, the drug carrier will be delivered to the target site and drug release will begin at a predetermined time point after gastric emptying. On the other hand, in the stomach, the drug release should be suppressed by a pH-sensing function (acid resistance) in the dosage form, which would reduce the variation in gastric residence time.

Therefore, we have studied on new colon delivery systems that may have the advantages of timed-release press-coated tablets and overcome the disadvantages described above. The first objective was to design enteric coated timed-release press-coated tablets (ETP tablets), and the second was to evaluate their effects both in vivo and in vitro. The ETP tablets designed in this study and their expected drug release behavior are shown schematically in Fig. 1A. The tablets were composed of three components; a drug-containing core tablet (rapid release function), the press-coated HPC layer (timed-release function) and an enteric coating layer (acid resistance function).

The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves, and the intestinal fluid begins to slowly erode the press-coated HPC layer, and when the erosion front reaches the core tablet, rapid drug release occurs. Since the erosion process takes a long time, there is no drug release period (lag phase or lag time) after gastric emptying. The duration of lag phase can be controlled either by the weight or composition of the HPC layer (Fukui et al., 2000). Therefore, as the intestinal transit time of dosage forms after gastric emptying is rather constant, such systems can deliver drugs to the desired site in the intestine. Furthermore, colon-targeting of drugs can be achieved by controlling the in vivo lag time to 3 ± 1 h.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride (DIL; Tanabe Seiyaku Co. Ltd. Osaka, Japan) and phenylpropanolamine hydrochloride (PPA; Alps Pharmaceutical Ind., Gifu, Japan) were used as a model drug and a marker of gastric emptying, respectively. Cornstarch (Nihon Shokuhin Kako Co. Ltd., Tokyo, Japan), calcium citrate (Satsuma Kako Co. Ltd., Japan), polyvinylpirrolydone (BASF, Germany), carboxymethyl-cellulose-calcium (Gotoku Chemical Co. Ltd., Tokyo, Japan) and magnesium stearate (Sakai Chemical Industry Co. Ltd., Osaka, Japan) were used for preparation of the core tablets. Hydroxypropylcellulose (HPC-L; 8.5mPa·sec, Nihonsoda Tokyo, Japan) was used for the hydrophilic outer shell of timed-release press-coated tablets. Hydroxypropylmethylcellulose acetate succinate-MF (AQORT® AS-MF; Shin-etsu Chemical, Tokyo, Japan) was used for enteric coating of timed-release tablets. All other chemicals and solvents were of reagent grade.

2.2. Preparation of enteric coated timed-release press-coated tablets

The compositions of the core tablets, enteric coated timed-release press-coated tablets (ETP tablets) and ETP tablets with PPA (ETP-PPA tablets) are shown in Table 1.

2.2.1. Preparation of core tablets

A wet granulation method was applied to prepare the granules for the core tablets. The powder mixture of DIL and cornstarch was kneaded with 33% (w/v) polyvinylpirrolydone ethanolic solution

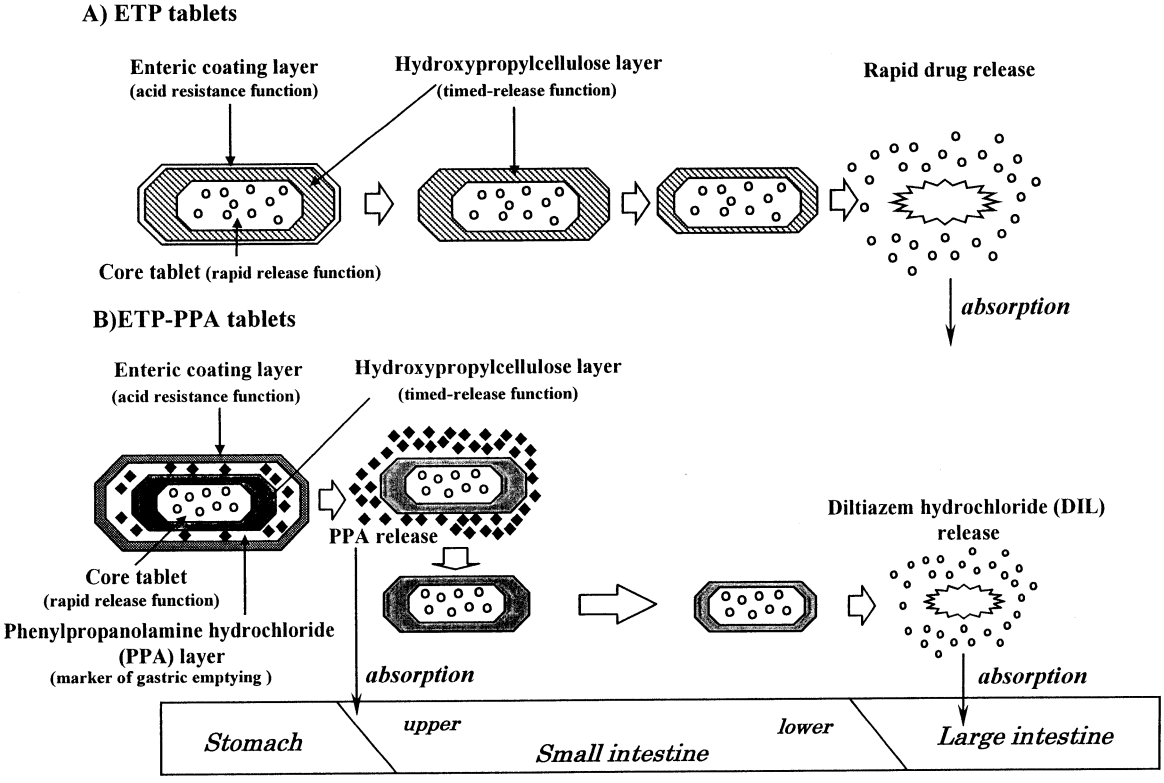

Fig. 1. Design of enteric coated timed-release press-coated tablets (ETP tablets) (A) and ETP tablets with phenylpropanolamine hydrochloride (PPA) (ETP-PPA tablets) (B), and expected drug release behavior. Drug: (○) DIL (diltiazem hydrochloride); (◆) PPA (phenylpropanolamine hydrochloride).

Table 1
Compositions of core, ETP and ETP-PPA tablets[a]

	Composition	ETP tablets	ETP-PPA tablets
Core tablet	Diltiazem hydrochloride (DIL)	30.0	30.0
	Cornstarch	20.0	20.0
	Polyvinylpirrolydone	3.0	3.0
	Calcium citrate	12.0	12.0
	Carboxymethylcellulose-calcium	4.0	4.0
	Magnesium stearate	1.0	1.0
Timed-release layer (Outer shell)	HPC-L	200.0	200.0
Enteric coating layer with PPA	HPMCAS-MF	–	7.3
	Triethyl citrate	–	0.7
	Phenylpropanolamine hydrochloride (PPA)	–	16.0
Enteric coating layer	HPMCAS-MF	27.3	27.3
	Triethyl citrate	2.7	2.7
Total (mg)		300.0	324.0

[a] Each value represents weight (mg) per a tablet.

as the binder. The wet mass was forced through a 1000 μm screen. The granules were dried and then sized by passing through a 710 μm screen. Calcium citrate, carboxymethylcelluose-calcium and magnesium stearate were mixed with the granules for 10 min. Tabletting was performed under a compression force of 1190–1530 kg/cm^2 using a rotary tabletting machine (CLEANPRESS Correct 12HUK, Kikusui Seisakusho Ltd., Kyoto, Japan). Concave punches 6 mm in diameter (curvature radius = 8 mm) were used for the preparation of the core tablets. The thickness of the core tablets was about 2.5 mm.

2.2.2. Press-coating of core tablets

HPC-L was passed through a 500 μm screen and used for the timed-release outer shells. The press-coating of tablets was performed using a tabletting machine (Type RT-F-9-2, Kikusui Seisakusho Ltd., Kyoto, Japan). HPC powder (100 mg) was filled in the die to make a powder bed on the center of which was placed the core tablet. The remaining equivalent powder was filled in the die, and the contents were compressed under a compression force of 990–1140 kg/cm^2, using a concave punch 9 mm in diameter (double radius, 4.5/12.5 mm).

2.2.3. Enteric coating

2.2.3.1. ETP tablets. The enteric coating solution was prepared by dissolving 8% (w/w) HPMCAS-MF and 0.8% (w/w) triethyl citrate in an 80% (w/w) aqueous ethanolic solution. Coating of the press-coated tablets was performed using a coating machine (Type HCT-48EX, Freund Industrial Co. Ltd., Shizuoka, Japan) under the following conditions: spray air pressure, 3 kg/cm^2; spray solution feed, 20 ml/min; inlet temperature, 60°C; outlet temperature, 35–40°C; rotating speed of pan, 15 rpm. The coated tablets were dried for 16 h at 45°C. The amount of coating was 30 mg per a tablet.

2.2.3.2. ETP-PPA tablets. For loading of PPA as a marker of gastric emptying between the press-coated tablet and the enteric coating layer, the coating solution was prepared by dissolving 14.9 g of PPA in 100 g of the above enteric coating solution. The press-coated tablets were first coated with the coating solution containing PPA, and after drying in the coating pan at 45°C for 10 min the tablets were coated with the enteric coating solution by the same procedure as described for the ETP tablets. The design of ETP-PPA

tablets and the expected drug release behavior in the gastrointestinal tract are shown schematically in Fig. 1B. The tablets were composed of four components; core tablet containing DIL, HPC layer, PPA loaded layer, and an enteric coating layer (acid resistance).

After oral administration, the behavior of the ETP-PPA tablets in the gastrointestinal tract will be as follows. The tablets will not release PPA and DIL in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer and PPA layer will rapidly dissolve in the upper small intestine and PPA will be absorbed and appear rapidly in the systemic circulation. Then, the HPC timed-release layer will begin to erode slowly in the intestinal fluid and when the erosion front finally reaches the core tablet, DIL will be released and appear in the systemic circulation.

The gastric emptying time and intestinal transit time of the tablets could be estimated by determination of PPA and DIL levels in the blood following oral administration of ETP-PPA tablets. The former and the latter correspond to the time at which PPA first appears in the blood (TFA_{PPA}) and the time subtracted TFA_{PPA} from that at which DIL first appear in the blood (TFA_{DIL}), (i.e. $TFA_{DIL}-TFA_{PPA}$), respectively.

2.3. In vitro dissolution tests

The dissolution study was performed according to the paddle method described in the 13th edition of Pharmacopoeia of Japan (JPXIII) with 900 ml of dissolution fluid at 37°C. JP 1st fluid (pH 1.2) and JP 2nd fluid (pH 6.8) from the disintegration test in JPXIII were used as the dissolution media. Aliquots of dissolution fluid were removed at specified time intervals and assayed for the amount of DIL released by a spectrophotometer (UV-160, Shimadzu Co., Kyoto, Japan) at a wavelength of 265 nm.

The paddle-beads method reported by Aoki et al. (1992) was applied to evaluate the resistance of tablets to mechanical stress in the dissolution process. In this experiment, 1500 polystyrene beads (diameter; 6.35 mm, specific gravity; 1.05 g cm^3) were applied to 250 ml of the 1st fluid. The rotation speed applied was 100 rpm for all dissolution studies.

2.4. In vivo study

Three male beagle dogs (weighing 10–12 kg) were fasted overnight for at least 12 h in each experiment, although free access to water was allowed. During the course of the experiment, water was not given until 6 h after administration of the test preparation. A control blood sample (6 ml) was obtained at 30 min before drug administration. After oral administration of the test preparation with 50 ml distilled water, 5 ml blood samples were collected at predetermined time intervals. Plasma was immediately separated by centrifugation of the blood samples at 12,000 rpm for 5 min. All the plasma samples were immediately frozen at -20°C until analysis. Also, 10 μg/ml of tetragstrin was given via the left jugular vein at 0.5 and 1.5 h before and after administration to control the gastric pH of the animals.

2.5. Analytical procedure to determine plasma concentration

The analytical method reported by Kainuma et al. (1989) was used to determine DIL concentration in the plasma with some modifications. Samples of 1 ml of plasma, 0.5 ml of distilled water, 0.5 ml of internal standard (1-phenyl-1-dimethylaminomethylpropyl - 3,4,5 - trimethoxy - benzoate, 400 ng/ml) and 0.5 ml of 1 M phosphate buffer were vortexed briefly, and 6 ml of diethylether/cyclohexane (volume ratio = 1/1) was added. This mixture was shaken for 10 min and centrifuged. The diethylether/cyclohexane layer (5 ml) was withdrawn and vortexed with 0.3 ml of 0.01 N HCl. Then, 200 μl of the resulting aqueous layer was injected into an HPLC apparatus (Shimadzu Co., Kyoto, Japan) with 1% triethylamine (pH 3)/acetonitrile (7/3) as the mobile phase at a flow rate of 1.0 ml/min. The column was a reverse-phase column (Hypersil 5-ODS, 4.0×300 mm, Chemco, Osaka, Japan), and UV detection was performed at 254 nm.

For analysis of PPA, 0.5 ml of plasma, 0.3 g of sodium chloride, 0.5 ml of 1 N NaOH and internal

standard (fenethylamine hydrochloride, 5 μg/ml) were vortexed briefly, and 5 ml of dichrolmethane/diethylether (volume ratio = 3/7) was added. This mixture was shaken for 10 min and centrifuged at 2,000 rpm for 5 min. The diethylether/cyclohexane layer (4 ml) was withdrawn, to which was then added 0.4 ml of 0.5% phosphate solution. This mixture was shaken for 10 min and centrifuged at 2,000 rpm for 5 min, then 100 μl of the resulting water layer was injected into an HPLC apparatus (Shimadzu Co.) with 0.2% phosphate solution/acetonitrile (8/2) including 0.01 M sodium 1-octanesulfonate as a mobile phase at a flow rate of 0.8 ml/min. The column was a reverse-phase column (TSK-gel ODS-80Tm, 4.0 × 250 mm, TOSOH, Tokyo, Japan), and UV detection was performed at 210 nm.

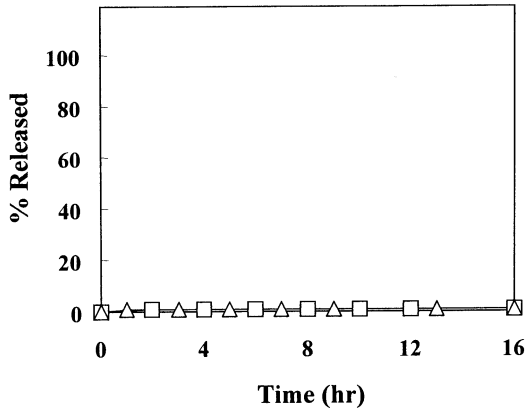

Fig. 2. Dissolution profiles of DIL from ETP tablets in JP 1st fluid (pH 1.2). Method: (△) paddle-beads method; (□) conventional paddle method. Each point represents the mean ± S.D.

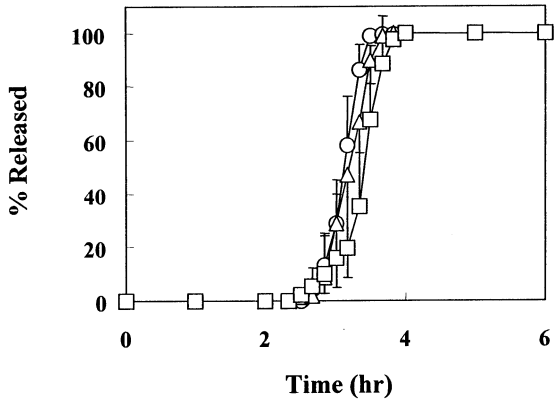

Fig. 3. Dissolution profiles of DIL from ETP tablets in JP 2nd fluid (pH 6.8) after pretreatment with JP 1st fluid (pH 1.2). Pretreatment method: (○) non-treatment; (□) pretreatment with conventional paddle method for 16 h; (△) pretreatment with paddle-beads method for 16 h. Each point represents the mean ± S.D.

3. Results and discussion

3.1. In vitro dissolution profiles of drugs from ETP tablets

After oral administration, ETP tablets undergo transit from the stomach to the cecum or colon. Physiological pH in the gastrointestinal tract is highly variable among human subjects (Evans et al., 1988) and dosage forms are exposed to this variable environmental pH. As the gastric emptying time differs with individual dosage form (Davis et al., 1986) or physiological conditions, the dissolution pattern after gastric emptying time may be altered due to the time of exposure to gastric pH.

In addition, gastrointestinal motility will cause mechanical disruption of administered tablets. Aoki et al. (1992) reported that the dissolution profile determined in vitro using the paddle-beads method resembled the in vivo release profiles in fasted dogs. Thus, the resistance of ETP tablets to mechanical impact was evaluated by this method. Fig. 2 shows the dissolution profiles of DIL from ETP tablets by conventional paddle and paddle-beads methods in JP 1st fluid (pH 1.2). DIL was not released under either condition for 16 h, and this result showed that ETP tablets have sufficient resistance against the low pH and impact or frictional force in the stomach.

The in vitro dissolution test was then performed in JP 2nd fluid (pH 6.8) for the tablets after the dissolution test shown in Fig. 2. The results are shown in Fig. 3.

The dissolution profiles were not markedly different among non-treated tablets and those pre-

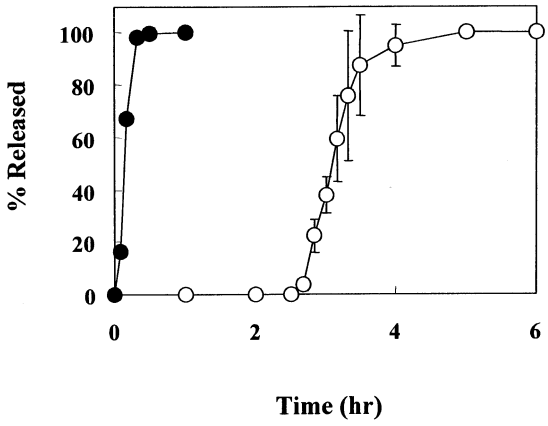

Fig. 4. Dissolution profiles of DIL and PPA from ETP-PPA tablets in JP 2nd fluid (pH 6.8). Drug: (○) DIL; (●) PPA. Each point represents the mean ± S.D.

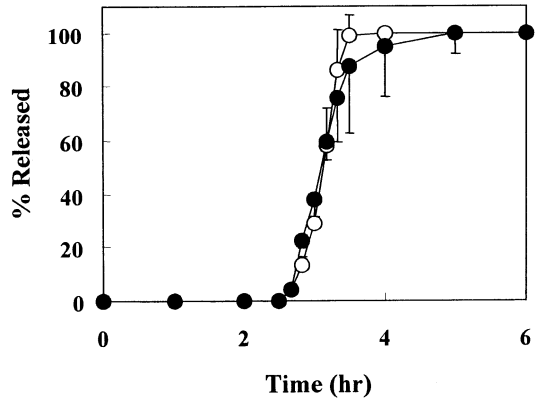

Fig. 5. Comparison of DIL dissolution profiles from ETP and ETP-PPA tablets in JP 2nd fluid (pH 6.8). Preparations: (●) ETP tablets; (○) ETP-PPA tablets. Each point represents the mean ± S.D.

treated with conventional paddle and paddle-beads methods in JP 1st fluid (pH 1.2). This result showed that exposure time in the stomach would not affect the dissolution performance during transit in the intestine. Therefore, ETP tablets were expected to be protected in the stomach, and would be delivered to the intended target site (lower small intestine or colon) after a predetermined lag time.

3.2. In vitro dissolution profiles of drugs from ETP-PPA tablets

Evaluation of in vivo performance could provide more important information for the development of ETP tablets. However, it is difficult to accurately determine the gastric emptying time after oral administration and the position at which the drug is released from ETP tablets in the gastrointestinal tract in vivo. To resolve this difficulty, we prepared ETP-PPA tablets as described in Fig. 1B and first evaluated their dissolution performance.

Fig. 4 shows the dissolution profiles of PPA and DIL from the ETP-PPA tablets in the JP 2nd fluid (pH 6.8). PPA was rapidly released in the JP 2nd fluid, suggesting that the enteric coating layer dissolved rapidly. The rapid release of DIL was also observed in the JP 2nd fluid after a lag time of approximately 3 h. In connection with the dissolution profiles of PPA and DIL from ETP-PPA tablets in the JP 1st fluid, neither drug was released for 6 h (data not shown), suggesting the ETP-PPA tablets showed satisfactory acid resistance similarly to ETP tablets.

The dissolution profile of DIL from ETP-PPA tablets in the JP 2nd fluid was compared with that of ETP tablets (not containing PPA) and the results are shown in Fig. 5. The dissolution profiles of DIL from ETP and ETP-PPA tablets agreed well, suggesting that the DIL release was not affected by the PPA layer. Therefore, the in vivo performance using ETP-PPA tablets was considered to be equivalent to that of ETP tablets.

3.3. In vivo evaluation of ETP-PPA tablets

ETP-PPA tablets were administered to three beagle dogs to examine acid resistance and timed-release functions in the gastrointestinal tract. Fig. 6 shows the plasma concentration-time curves of PPA and DIL after oral administration of ETP-PPA tablets. Also, Table 2 shows the time point at which PPA and DIL first appeared (TFA_{PPA} and TFA_{DIL}, respectively), as well as value obtained by subtracting TFA_{PPA} from TFA_{DIL} ($TFA_{DIL} - TFA_{PPA}$). PPA, an indicator of the gastric emptying time of the tablets, started to

appear in the systemic circulation at 4 hr after administration (i.e. TFA_{PPA} = mean 4.0 h), and C_{max} of about 350 ng/ml was achieved at 1 h after TFA_{PPA}. Since PPA is known to be quickly absorbed via the intestinal wall, this result implied that the gastric residence time of ETP-PPA tablets was about 4 h. DIL first appeared in the systemic circulation at 7–8 h after administration (i.e. TFA_{DIL} = mean 7.3 h). $TFA_{DIL} - TFA_{PPA}$ was about 3 h, corresponding to the in vitro lag time, suggesting that DIL was released at 3 h after gastric emptying as expected. Also, because C_{max} of DIL was about 120 ng/ml and nearly equal to the C_{max} (about 135 ng/ml) of the core tablets (Fukui et al., 2000), it seems that the releases of DIL from timed-release press-coated tablets were not affected by the environment of low moisture in colon. However, it will be also necessary to study on drugs of low solubility except for DIL of high solubility.

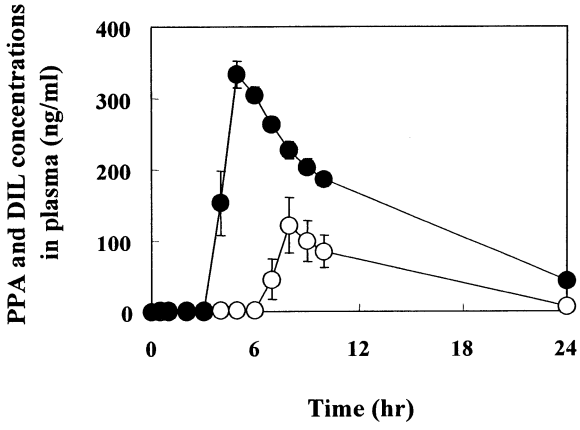

Fig. 6. Plasma concentration-time curves of DL and PPA following oral administration of ETP-PPA tablets to beagle dogs. Drug: (○) DIL; (●) PPA. Each point represents the mean ± S.D.

Table 2
Drug first appearance times (TFAs) and subtraction of TFAs in systemic circulation after oral administration of ETP-PPA tablets

Drug	Dog No. 1	Dog No. 2	Dog No. 3	Mean ± S.D.
TFA (h)				
PPA	4.0	4.0	4.0	4.0 ± 0.0
DIL	8.0	7.0	7.0	7.3 ± 0.3
Subtracted time (h)				
	4.0	3.0	3.0	3.3 ± 0.3

These results suggested that the timed-release function of ETP-PPA tablets after gastric emptying was similar to that of ETP tablets. Therefore, the acid resistance protected the ETP tablets during the gastric residence time, and then the timed-release function of the HPC press-coated layer resulted in release of the drug at the target site. Also, the tablets reached the colon within 3 h after gastric emptying, where it was suggested that DIL was released rapidly since T_{max} after TFA_{DIL} were nearly equal to the T_{max} (1 h) detected after the administration of the core tablets (Fukui et al., 2000). Thus, ETP tablets showed acid resistance as well as timed-released and would provide excellent means for delivery of drugs to the colon.

4. Conclusions

Our results indicated that enteric coated timed-release press-coated tablet (ETP tablets), comprised of a core tablet containing drug, an outer shell of HPC and an enteric coating layer, showed acid resistance and time-released functions on in vitro dissolution tests and applicability in the field of chronopharmacotherapy. By the administration of the ETP tablets with PPA layer between the enteric coating layer and the outer shell (ETP-PPA tablets), the gastric emptying time and the in vivo lag time after gastric emptying could be evaluated in dogs. The time at which DIL first appeared in the blood agreed well with the lag time estimated by the in vitro dissolution tests.

Thus, ETP tablets are potentially useful for oral site-specific drug delivery including colon targeting.

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