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Dosage form design and *in vitro*/*in vivo* evaluation of cevimeline extended-release tablet formulations

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ABSTRACT

The objective of the present work is to develop an extended-release dosage form of cevimeline. Two types of extended-release tablets (simple matrix tablets and press-coated tablets) were prepared and their potential as extended-release dosage forms were assessed. Simple matrix tablets have a large amount of hydroxypropylcellulose as a rate-controlling polymer and the matrix is homogeneous throughout the tablet. The press-coated tablets consisted of a matrix core tablet, which was completely surrounded by an outer shell containing a large amount of hydroxypropylcellulose. The simple matrix tablets could not sustain the release of cevimeline effectively. In contrast, the press-coated tablets showed a slower dissolution rate compared with simple matrix tablets and the release curve was nearly linear. The dissolution of cevimeline from the press-coated tablets was not markedly affected by the pH of the dissolution medium or by a paddle rotating speed over the range of 50–200 rpm. Furthermore, cevimeline was constantly released from the press-coated tablets in the gastrointestinal tract and the steady-state plasma drug levels were maintained in beagle dogs. These results suggested that the designed PC tablets have a potential for extended-release dosage forms.

1. Introduction

Cevimeline ((±)-*cis*-2-methylspiro [1,3-oxathiolane-5,3′-quinuclidine] monohydrochloride hemihydrate, CE) is a novel muscarinic acetylcholine receptor agonist presently being developed as a therapeutic agent for Sjögren's syndrome. Sjögren's syndrome is a serious and chronic autoimmune disorder characterized by inflammation in the exocrinal glands, such as the salivary and lacrimal glands (Bloch et al., 1992), leading to xerostomia (dry mouth) and xerophthalmia (dry eyes). CE is rapidly and completely absorbed from the gastrointestinal (GI) tract after oral administration in humans (Washio et al., 2003a). However, its plasma half-life in humans is short ($T_{1/2}$ = 4.1 h) and clinically the drug must be administered three times daily. Therefore, it is important and desirable to prolong the effective plasma level in order to maintain the clinical efficacy of the drug. Controlled-release delivery systems provide greater safety and efficacy than the conventional formulations (Yang and Fassihi, 2003; Nakamura et al., 2006). Their purpose is to achieve a desirable and predictable pharmacodynamic response and pharmacokinetics, as well as to minimize side effects, and maximize the efficacy of the drug (Gusler et al., 2001; Wang et al., 2004).

The objectives of the present work are to develop an extended-release dosage form of CE. When an extended-release dosage form of CE is being developed, its extremely high solubility must be taken into account. The solubility of CE is 766 mg/mL in water and over 600 mg/mL in various buffer solutions (pH 2–12).

Hydrophilic matrices continue to be popular as the drug delivery system for oral administration. Hydroxypropylcellulose (HPC) has been frequently utilized as a pharmaceutical additive for various purposes, as a binder in tablets or granule formulations, a film-coating material or as a thickener for syrup (Alderman, 1984). Also, controlled-release dosage forms have been prepared utilizing its swelling properties in aqueous medium (Nakano et al., 1983; Fukui et al., 2000).

On the other hand, some researches about controlled-release delivery systems involve designing a system with zero-order drug release; that is, one which produces steady-state plasma drug levels (Conte et al., 1993). In general, the drug release from a simple matrix tablet rarely shows zero-order releases unless an additional controlling mechanism is added into the matrix tablet. Some of researches in the area of hydrophilic matrices are to modify the geometry or the composition in order to obtain linear drug release profiles (pseudo zero-order release). For example, Kim and Fassihi (1997) demonstrated that zero-order release is achievable using a binary polymeric matrix consisting of pectin and hydroxypropyl methylcellulose. The press-coated (PC) technique also shows greater flexibility in obtaining different drug release profiles, such as bimodal, pulsatile and delayed release profiles

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Table 1
Compositions of HPC tablets used in this study.

Components	Formulations (mg)			
	HPC tablet-1	HPC tablet-2	HPC tablet-3	HPC tablet-4
Cevimeline hydrochloride $1/2H_2O$ (cevimeline hydrochloride)	93.5 (90.0)	93.5 (90.0)	93.5 (90.0)	93.5 (90.0)
Hydroxypropylcellulose	230.0	230.0	230.0	230.0
Stearic acid	40.0	–	–	–
Stearyl alcohol	–	40.0	–	–
Glycerol esters of fatty acids	–	–	40.0	–
Polyethylene glycol 6000	–	–	–	40.0
Magnesium stearate	3.0	3.0	3.0	3.0
Total	366.5	366.5	366.5	366.5
Diameter (mm)	10.0	10.0	10.0	10.0

(Pozzi et al., 1994; Fukui et al., 2001). It seems that the PC technique is useful in achieving a linear release profile (pseudo zero-order release).

In this paper, two types of extended-release tablets of CE (simple matrix tablets and PC tablets) were prepared using HPC as a rate-controlling polymer and their *in vitro* release profiles and *in vivo* absorption following oral administration of these tablets to beagle dogs were investigated.

2. Materials and methods

2.1. Materials

Cevimeline (CE), a water-soluble drug, was obtained from Ishihara Sangyo Kaisha Ltd. (Japan). Hydroxypropylcellulose (HPC-H; fine particle grade, 1000–4000 mPa s) was purchased from Nippon Soda Co. Ltd. (Japan). As core materials with low melting points, stearic acid (m.p. 65–69 °C, NAA-180, NOF Co. Ltd., Japan), stearyl alcohol (m.p. approximately 55 °C, Kao Co. Ltd., Japan), glycerol esters of fatty acids (m.p. 65–67 °C, Riken Vitamin, Ltd., Japan) and polyethylene glycol 6000 (m.p. 56–61 °C, NOF Co. Ltd., Japan) were used. Magnesium stearate as a lubricant was purchased from Nitto Kasei Co. Ltd. (Japan). Polystyrene beads were purchased from AS ONE Co. Ltd. (Japan). All other chemicals and solvents were of reagent grade.

2.2. Tablets formulations

Two types of extended-release tablets containing 90 mg of CE were used for this study. The formulations of these tablets are shown in Tables 1 and 2.

2.3. Preparation of simple matrix tablets

Simple matrix tablets (HPC tablets) have a large amount of HPC-H and the matrix is homogeneous throughout the tablet. Granules for tabletting were prepared using a fluidized hot-melt granulation method (Kojima and Nakagami, 2001). In the granulation method, at first, CE, HPC and core materials with low melting points such as stearic acid, stearyl alcohol, glycerol esters of fatty acids or polyethylene glycol 6000, were blended in a V-type blender (S-3-S, Tokujyu Co. Ltd., Japan) for 10 min. Then the powder mixture was transferred into a fluidized-bed granulator (MP-01, Powlex Co. Ltd., Japan) and gradually heated by blowing hot inlet air at 80 °C. After the bed temperature reached at least 5° higher than the melting point of each core material, the inlet air heater was turned off and the mass was cooled to 40 °C. After cooling, the granules were removed from the granulator and passed through an 18-mesh sieve. With magnesium stearate as the lubricant, the obtained granules were mixed using a V-type blender (S-3-S, Tokujyu Co. Ltd., Japan) for 5 min. The granules thus obtained were continuously compressed into tablets on a single-punch tabletting machine (Type N-30E, Okada Seiko Co. Ltd., Japan). The tabletting machine was equipped with a die of 10.0 mm diameter and operated at a compression force of 800 kgf.

2.4. Preparation of press-coated tablets

Press-coated tablets (PC tablets) have a core tablet and an outer shell, which each have a different composition matrix. The total amount of the drug was divided between the core and the outer shell. The granules for the core tablet and outer shell were also prepared as described in HPC tablet and two compositions of granules were obtained. After the granules for the core tablet were blended with lubricant using a V-type blender (S-3-S, Tokujyu Co. Ltd., Japan) for 5 min, the core tablet was compressed manually under a compression force of 400 kgf using the single-punch tabletting machine (Type N-30E, Okada Seiko Co. Ltd., Japan). After then the granules for the outer shell were blended with lubricant using a V-type blender (S-3-S, Tokujyu Co. Ltd., Japan) for 5 min, the outer shell was compressed under a compression force of 800 kgf with the core tablet in its center. The diameter of the PC tablet including the 6.7 mm or 6.0 mm-diameter core tablet was 9.5 mm or 8.5 mm.

Table 2
Compositions of PC tablets used in this study.

Components	Formulations (mg)		
	PC tablet-1	PC tablet-2	PC tablet-3
Cevimeline hydrochloride·$1/2H_2O$ (Cevimeline hydrochloride)			
Core	62.3 (60.0)	72.7 (70.0)	62.3 (60.0)
Outer	31.2 (30.0)	20.8 (20.0)	31.2 (30.0)
Total	93.5 (90.0)	93.5 (90.0)	93.5 (90.0)
Hydroxypropylcellulose			
Core	20.0	10.0	5.0
Outer	150.0	160.0	120.0
Total	170.0	170.0	125.0
Stearic acid			
Core	10.0	10.0	5.0
Outer	20.0	20.0	17.5
Total	30.0	30.0	22.5
Magnesium stearate			
Core	1.0	1.0	1.0
Outer	2.0	2.0	2.0
Total	3.0	3.0	3.0
Total			
Core	93.3	93.7	73.3
Outer	203.2	202.8	170.7
Total	296.5	296.5	244.0
Diameter (mm)			
Core	6.7	6.7	6.0
Outer	9.5	9.5	8.5

2.5. In vitro dissolution testing

In vitro dissolution studies were carried out using USP dissolution apparatus type 2 (paddle method) in 900 mL of dissolution medium. The drug release was evaluated with water, the first fluid for the JP disintegration test (pH 1.2), 0.1 M phosphate buffer (pH 4.5) and the second fluid for the JP disintegration test (pH 6.8) at 37 ± 0.5 °C. The dissolved amount of CE was determined using an automatic dissolution test apparatus (NTR-6100, Toyama Sangyo Co. Ltd., Japan), equipped with a UV spectrophotometer (UV-1600, Shimadzu Co. Ltd., Japan) at 210 nm. The rotation speeds of the paddle were 50, 100 and 200 rotations per minutes (rpm). At appropriate intervals, each sample was withdrawn from the dissolution vessel and sent to the spectrophotometer automatically. The sample solution was filtered automatically. Samples were sent back to each vessel after measuring. The dissolution tests were continued until 12 h.

2.6. Kinetics of drug release

The kinetics of the drug release was analyzed by applying the empirical exponential equation shown below, which is often used for identifying release mechanisms. In this equation, the drug fraction released is related to time according to the expression:

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t/M_∞ = fraction of drug released, k = a kinetic constant, t = release time and n = the diffusional exponent for drug release. Ritger and Peppas (1987) claimed that Eq. (1) could adequately describe the release of solutes from slabs, spheres, cylinders and discs (tablets), regardless of the release mechanism. The value of n gives an indication of the release mechanism. Ritger and Peppas (1987) stated that n is 0.5 for Fickian diffusion, $0.5 < n < 1.0$ for non-Fickian transport and 1.0 for case II transport.

2.7. Mechanical properties of tablets

The paddle-beads method reported by Machida et al. (1992) was applied to evaluate the resistance of tablets to the mechanical impact force in the dissolution process. In the paddle-beads method, polystyrene beads (diameter, 6.3 mm; specific gravity, 1.05 g/cm^3) were used. The dissolution test for each tablet was conducted using USP dissolution apparatus type 2 (paddle method) in 800 mL of water at 50 rpm with 800 beads per vessel. As a control, each tablet was also examined in 800 mL of water at 50 rpm without beads. The dissolved amount of CE was determined using an automatic dissolution test apparatus (NTR-6100, Toyama Sangyo Co. Ltd., Japan), equipped with a UV spectrophotometer (UV-1600, Shimadzu Co. Ltd., Japan) at 210 nm. An amount of the dissolved drug was measured in the same way as in the ".2.5. *in vitro* dissolution testing".

2.8. In vivo pharmacokinetic study

All the studies were performed according to the institutional rules governing animal experiments and the study design was approved by the ethics review board of DAIICHI SANKYO Co. Ltd. (Japan). An *in vivo* pharmacokinetic study was carried out for each tablet in five male beagle dogs weighing 10–12 kg. There was at least a 6-day washout period between each dosing. The dogs were fasted for at least 14 h prior to the study, with free access to water. Dry dog food (TC-2, Toyota Tsusho Co. Ltd., Japan) was given 30 min prior to dosing. Each tablet containing 90 mg of CE was administered to the dogs with around 30 mL of water. Blood samples were recovered at several time points (0.5, 1, 2, 4, 6, 8, 10, 12 and 14 h after administration) and the plasma samples were kept frozen at −20° until being assayed. Because CE absorbed from the GI tract is largely metabolized and its N-oxide is the main metabolite in dogs (Washio et al., 2003b), CE and the N-oxide were measured by LC/MS/MS (LC; Alliance 2695, Waters, USA, MS/MS; TSQ 7000, HITACHI, Ltd., Japan). Then each sample was assayed by the previously reported method (Washio et al., 2003b).

2.9. Pharmacokinetic analysis

The maximum plasma level (C_{max}) and time to maximum plasma level (T_{max}) were determined from the individual plasma concentration–time profiles. The area under the plasma level–time curves (AUC) was calculated by the linear trapezoidal method to the last blood collection point. The rates of CE absorption in dogs were calculated by the deconvolution method using WinNonlin Ver.5.2, in which the oral aqueous solution data were used for the weight function. The elimination rate constant of CE after the administration of the aqueous solution to dogs was determined by applying a two-compartment model using WinNonlin Ver.5.2.

2.10. Statistical analysis

The differences in each parameter were statistically evaluated by a paired t-test.

3. Results and discussion

3.1. In vitro dissolution profiles

At first, HPC tablets were examined. It is important to improve a poor flowability of hydrophilic polymers such as HPC by a granulation for continuous tabletting. However, it is difficult to granulate a formulation containing a large amount of polymers which have high viscosity by wet granulation with water because of the strong cohesive property of the polymers under wet conditions. Kojima and Nakagami (2001) reported that a fluidized hot-melt granulation method, which is for dry granulation, was useful for the granulation of extended-release formulations which contain a lot of polymers. In this method, melted core materials with low melting points work as binders. In this study, a couple of formulations containing a large amount of HPC were prepared with several kinds of core materials using the fluidized hot-melt granulation method. The dissolution profiles of CE from HPC tablets in water are shown in Fig. 1. None of the HPC tablets could effectively sustain the release of CE regardless of the kind of core material. In the case of these tablets, the initial release rate is rapid and half of the dose was

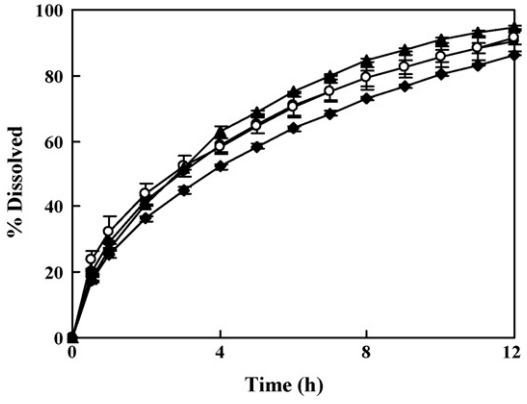

Fig. 1. Dissolution profiles of CE from HPC tablets in water. Paddle method, 50 rpm, 900 mL, mean ± S.D., n = 4–6.

Table 3
Fitting of release data to Eq. (1) (mean ± S.D., $n = 4–6$).

Formulations	Diffusional exponent (n)
HPC tablet-1	0.48 ± 0.02
HPC tablet-2	0.43 ± 0.03
HPC tablet-3	0.50 ± 0.02
HPC tablet-4	0.53 ± 0.01

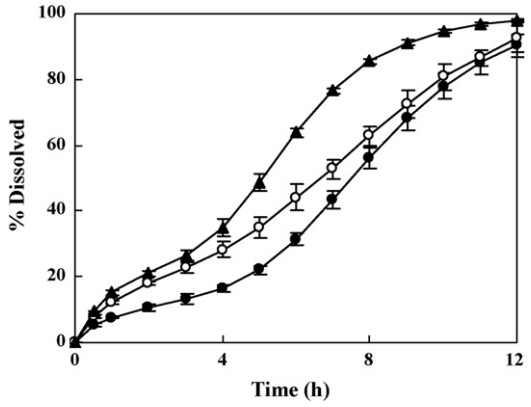

Fig. 2. Dissolution profiles of CE from PC tablets in water. Paddle method, 50 rpm, 900 mL, mean ± S.D., $n = 4–6$.

released at 3 h. The drug release from the granules prior to compression was very rapid and more than 90% of the dose was released within 30 min (data not shown). The kinetic parameters of the HPC tablets were determined and are tabulated in Table 3. The exponent values from HPC tablets indicated that the matrices mainly exhibited diffusional release mechanisms. These results might be due to the higher solubility of CE in aqueous solution. Some previous reports have showed that a water-soluble drug was released by diffusing out of the gelatinous layer whereas the release rate of low or sparingly water-soluble drugs was controlled by the rate of the tablet erosion (Alderman, 1984; Tahara et al., 1995; Kim and Fassihi, 1997). It seems difficult technologically to slow the initial dissolution rate of highly water-soluble drugs, such as CE, from simple matrix tables because the drugs are easily dissolved by seeped medium in the matrices.

On the other hand, the dissolution profiles of CE from PC tablets in water are shown in Fig. 2. The dissolution rates from PC tablets were less than 30% at 3 h and these tablets showed a slower dissolution rate until 5 h compared with those of HPC tablets ($p < 0.01$). The PC tablets consisted of a matrix core tablet, containing CE and HPC, which was completely surrounded by an outer shell containing CE and HPC. When the outer shell is almost hydrated, the fluid penetration into the core tablet starts and the drug is released from the core tablet. As shown in Table 2, in the PC tablets, CE makes up more than half of the formulation components in the core tablet and the outer shell has a large amount of HPC. Depending on their structure, PC tablets showed slower dissolution profiles, as shown in Fig. 2. Additionally, the release rate was influenced by the load ratio of CE in the core tablet and outer shell. In this system, it might be possible to achieve linear drug release by the combination of formulation components in the core tablet and the outer shell. However, the initial rise of the drug release until 30 min was not suppressed by this system because the drugs which resided in the surface of the outer shell were released rapidly. In fact, the release curve for PC tablet-1 was nearly linear with time after a short time from the beginning of the release.

3.2. Effects of dissolution medium pH

Tablets undergo transit from the stomach to the colon after oral administration. The physical pH in the GI tract is highly variable among individual and the oral dosage forms are exposed to this variable environmental pH (Evans et al., 1988). Therefore, determination of the dissolution behavior in various dissolution media is necessary. The dissolution profiles of CE from HPC tablet-1 and PC tablet-1 are shown in Fig. 3. The drug release rates of these tablets were controlled using nonionic polymer HPC. As shown in Fig. 3, the dissolution rates of CE from both tablets were not markedly affected by the pH of the dissolution medium ($p > 0.05$). Thus, the dissolution of CE from each tablet appeared not to be affected by the GI pH.

3.3. Mechanical property of tablets

GI motility is characterized by a four-phase, cyclically recurring complex known as the interdigestive migratory myoelectric complex (IMMC: Code and Marlett, 1975). Phase III activity propels the residual stomach contents into the small intestine (Itoh et al., 1986; Mojaverian et al., 1991). Therefore, the effect of mechanical destruction or of frictional force should be examined in an *in vitro* dissolution test. Sako et al. (1996) examined the effect of the paddle rotating speed on the drug dissolution rate to assess the resistance of tablets to the mechanical impact force in the dissolution process. The effects of the paddle rotating speed on drug dissolution from HPC tablet-1 and PC tablet-1 were investigated. Fig. 4 shows the effects of the rotation speed of the paddle on the dissolution behavior of the tablets. The CE dissolution rates from the two tablets were not affected by a paddle rotating speed over the range of 50–100 rpm. In the case of a paddle speed of 200 rpm, the drug dissolution rate from PC tablet-1 increased

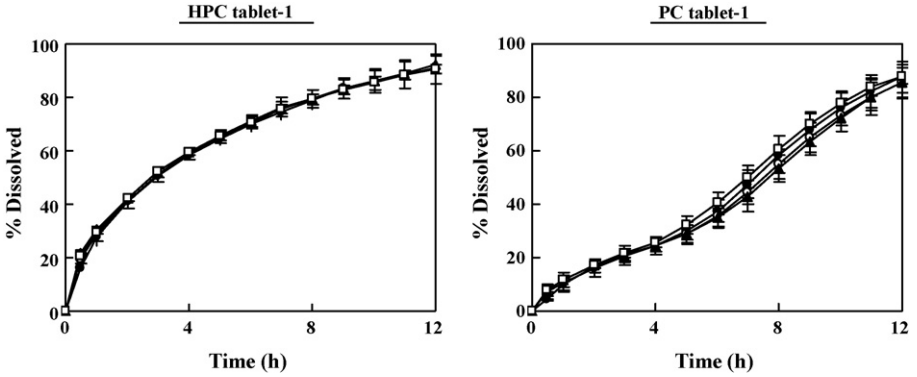

Fig. 3. Effects of pH of dissolution medium on the dissolution rates of CE from extended-release tablets. (●) Water; (○) JP 1st solution; (▲) pH 4.5 phosphate buffer; (□) JP 2nd solution. Paddle method, 50 rpm, 900 mL, mean ± S.D., $n = 5$.

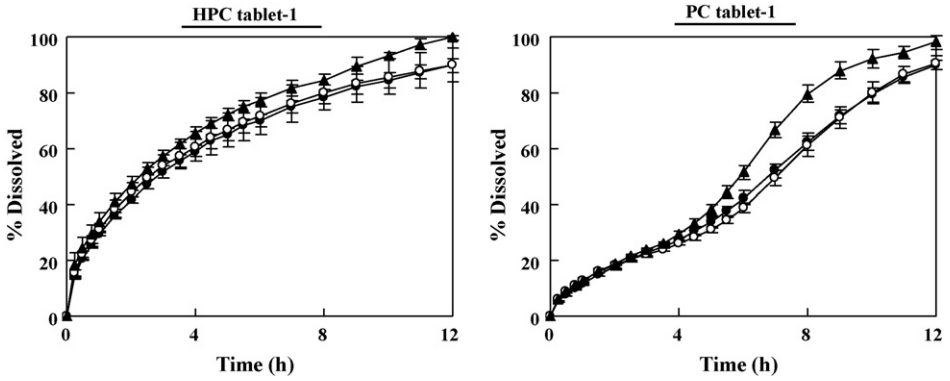

Fig. 4. Effects of paddle rotation speeds on the dissolution rates of CE from extended-release tablets in water. (●) 50 rpm; (○) 100 rpm; (▲) 200 rpm. Paddle method, 900 mL, mean ± S.D., $n = 4–6$.

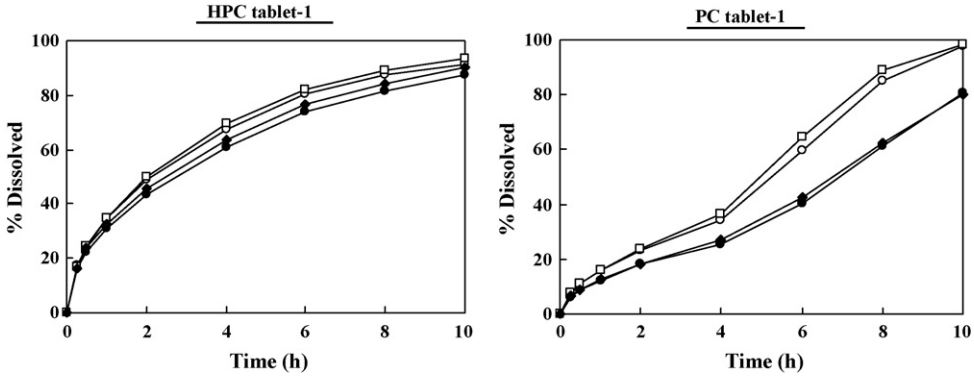

Fig. 5. Effects of beads on the dissolution rates of CE from extended-release tablets in water. (●) Without beads (vessel-1); (♦) without beads (vessel-2); (○) with beads (vessel-3, 800 beads per vessel); (□) with beads (vessel-4, 800 beads per vessel). Paddle method, 50 rpm, 800 mL, individual data.

slightly. Moreover, a paddle method in which the medium contains beads seemed useful in order to evaluate the drug release from the tablet and to predict the mechanical strength of the tablet in the GI tract. This method has been reported by Machida et al. (1992). The mechanical strength of each tablet was assessed using the paddle-beads method. The release characteristics of CE from each tablet using the paddle-beads method are shown in Fig. 5. Although the drug dissolution rate with beads increased slightly, the differences of the dissolution rate between with beads and without beads were less than about 10% until 4 h. These results suggest that the dissolution profiles of each preparation were not greatly affected by mechanical stress like the peristaltic motion of the GI tract. The solubility of CE is extremely high. Its solubility is 766 mg/mL in water and over 600 mg/mL in buffer solutions with pH values from 2 to 12. Therefore, each tablet had a large amount of HPC to control the CE release rate. It seemed that the dissolution profiles of each tablet were not greatly affected under the various test conditions because each tablet had a large amount of polymer, which was sufficient to bear the mechanical impact force. Moreover, the granules were prepared using the fluidized hot-melt granulation method, which is dry granulating, because this formulation involves a large amount of HPC which has high viscosity under wet conditions. Stearic acid is used as a binder in the granulation method and the material has hydrophobic property. Stearic acid also may play a role in robustness of the tablets.

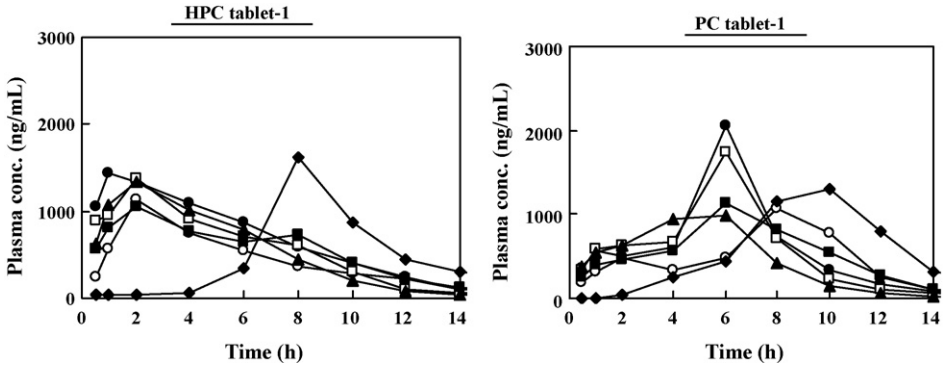

Fig. 6. Plasma concentration profiles of CE and N-oxide (CE metabolite) after single oral administration of HPC tablet-1 and PC tablet-1 to fed dogs. (●) Dog 1; (○) Dog 2; (♦) Dog 3; (□) Dog 4; (▲) Dog 5; (■) mean ($n = 5$).

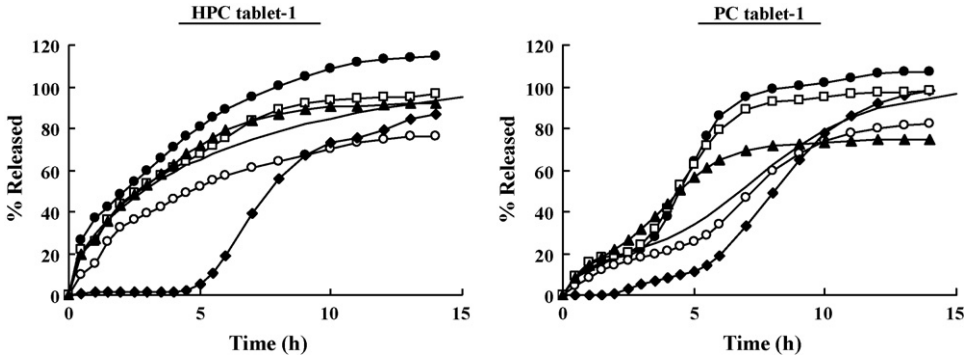

Fig. 7. *In vivo* and *in vitro* release of CE from HPC tablet-1 and PC tablet-1. The *in vivo* release profile was estimated from the plasma CE and N-oxide (CE metabolite) concentration profiles after oral administration to fed dogs. The *in vitro* release profile was determined by a dissolution test in water (paddle method, 900 mL, 50 rpm, $n = 6$). (●) Dog 1; (○) Dog 2; (♦) Dog 3; (□) Dog 4; (▲) Dog 5; solid line, *in vitro* release.

3.4. In vivo pharmacokinetic study

In a preliminary study, it was clear that the absorptions of CE from prototype extended-release matrix tablets were slower than that from the existing immediate release capsules (Evoxac®, DAI-ICHI SANKYO Co. Ltd., Japan) in fasted dogs (data not shown). On the other hand, the drugs are clinically administered after meals. Therefore, in this paper the difference in the absorption behavior between HPC tablet-1 and PC tablet-1 was assessed using dogs in a fed condition. The individual and mean plasma concentrations of CE and N-oxide (CE metabolite) after oral administration of both tablets to dogs are shown in Fig. 6. Because CE absorbed from the GI tract is metabolized rapidly and its N-oxide is the main metabolite in dogs (Washio et al., 2003b), CE and its N-oxide were assayed as absorption markers. The pharmacokinetic parameters of CE and its N-oxide are summarized in Table 4. As shown in Fig. 6 and Table 4, the drug plasma concentration after oral administration of HPC tablet-1 increased rapidly and reached C_{max} at about 2 h except for Dog 3. In the case of Dog 3, the drugs were hardly observed in plasma until 4 h and increased after 4 h. This tablet might be buried in meals in the stomach until 4 h. In contrast, the absorption of the drug from PC tablet-1 was slower than that from HPC tablet-1 and the plasma concentration of CE and N-oxide was prolonged. The T_{max} value for PC tablet-1 was 7.2 h, which was longer than that after the administration of HPC tablet-1 ($p < 0.01$). This result suggested that PC tablet-1 had potential as an extended-release dosage form.

The amount of the released drug from each tablet *in vivo* was calculated by deconvolution and the *in vitro* release profiles are plotted in Fig. 7. The *in vivo* individual release profile of CE from HPC tablet-1, except for Dog 3, was similar to the *in vitro* dissolution pattern and about 50% of drug was released at 3 h post-dosing in the GI tract. The *in vivo* release of PC tablet-1 also had the same pattern as *in vitro* dissolution profile and this tablet had a tendency to suppress the initial drug release. As shown in Figs. 3–5, the *in vitro* dissolution of CE from each tablet was not affected by the pH of the dissolution medium and mechanical stress. Thus, CE might be released similarly to the *in vitro* release profiles even in the GI tract, which has a complex structure. However, in Dog 5 of the PC tablet-1 group, CE was hardly released after 6 h post-dosing. Beagle dogs are commonly used as a convenient species for testing oral dosage forms because of their ability to ingest human scale dosage forms. In general, however, the GI retention time of dogs is recognized to be shorter than that of humans (Dressman, 1986; Kararli, 1995; Sutton, 2004). For example, the small intestinal transit time is 2.8 h in dogs (Sagara et al., 1992), but is 4.5 h in humans (Staniforth et al., 1987). Therefore, PC tablet-1, whose dissolution time is relatively longer, might pass the GI of Dog 5 without the complete release of the drug. The low plasma drug concentration after 6 h post-dosing may be lower than the expected values due to the short GI retention time in this dog.

The $T_{1/2}$ value of CE in humans is 4.1 h and is longer than that of dogs ($T_{1/2}$ value in dogs is 1.7 h, Washio et al., 2003a,b). Gruber et al. (1987) reported that the total GI transit time in humans was around 20–30 h, while beagle dogs had a substantially shorter transit time of 6–8 h. In the case of PC tablets, the drug dissolution rate can also be adjusted by the combination of formulation components in the core tablet and the outer shell. Therefore, optimized PC tablets might offer steady-state plasma drug levels for a prolonged period if the PC tablet is administered clinically to humans.

Table 4
Pharmacokinetic parameters of CE and N-oxide (CE metabolite) after single oral administration of HPC tablet-1 and PC tablet-1 to fed dogs (mean ± S.E., $n = 5$).

Formulations	$AUC_{0-14\,h}$ (ng/mL)	C_{max} (ng/mL)	T_{max} (h)
HPC tablet-1	8156 ± 603	1380 ± 80	3.0 ± 1.3
PC tablet-1	7934 ± 409	1430 ± 203	7.2 ± 0.8[a]

[a] $p < 0.01$ vs. HPC tablet-1.

4. Conclusions

PC tablets showed a slower dissolution rate compared with simple matrix tablets and the release curve was nearly linear. Furthermore, CE was constantly released from PC tablets in the GI tract and the steady-state plasma drug levels were maintained in dogs. These results suggested that the designed PC tablets have a potential for extended-release dosage forms.

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