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Design and preparation of captopril sustained-release dosage forms and their biopharmaceutical properties

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Summary

To obtain a prolonged-action dosage form of captopril, 7 types of formulations were prepared and administered to beagle dogs. They were coated slow-release (CSR) granules, 4 kinds of modified release tablets, enteric coated granules and oily semisolid matrix (OSSM). Each formulation was evaluated by the area under the curve (AUC) and time course of plasma captopril concentration after oral administration. The CSR granules and the modified release tablets showed them to be markedly inefficient under fasting conditions. The AUCs of these products were 0.64–1.69 ($\mu g \cdot h/ml$), which is about 20–40% of the AUC obtained by conventional tablets under fasting conditions. Under non-fasting conditions, the CSR granules and enteric coated granules suffered additional decreases in AUC. The AUC of the enteric coated granules under non-fasting conditions was only 20% of the AUC with the uncoated granules under fasting conditions. The OSSM maintained higher plasma captopril level for a long time as compared with the CSR granules under the same non-fasting conditions. Although the AUC (0.83 $\mu g \cdot h/ml$) of OSSM was only half of the conventional tablets (non-fasting condition), this formulation is expected to offer an effective prolonged-action dosage form of captopril.

Introduction

Captopril (1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline), an orally active inhibitor of angiotensin-converting enzyme (ACE) (Ondetti et al., 1977), has manifested excellent clinical effectiveness in the treatment of essential hypertension. It is widely used these days as a first choice drug in antihypertensive therapy. It has been reported, however, that the duration of antihypertensive action after single oral dosing of captopril is only 6–8 h, so clinical use requires the daily dose of 37.5–75 mg to be taken at 3 times (Miyazaki et al., 1982). Development of a prolonged-action dosage form for captopril will bring many benefits to patients, for the following reasons.

(1) Decrease in the frequency of administration can lead to an improvement in patient compliance; as a result of it, clinical efficiency is improved (Malahy, 1966; Cllnite and Kabat, 1976). This is particularly true in long-term therapy.
(2) It can be expected that minimization of fluctuations in blood concentration of the drug decreases the risk of side-effects.

In this paper, 3 types of well-known prolonged-

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action dosage forms and a recently reported approach, an oily semisolid matrix (OSSM) formulation, are evaluated.

Materials and Methods

Physicochemical properties

Solubility, partition coefficient and stability of captopril were measured at 37 °C. In the measurement of partition coefficient, the initial concentration of captopril in the aqueous buffer layer was 3 mg/ml. The aqueous solution was added to the same volume of *n*-octanol. After 2 h incubation, the partition coefficient was calculated from the determination of captopril in the aqueous layer. Stability was determined in the Japanese Pharmcopoeia (JP) 1st fluid (JP X, pH 1.2), JP 2nd fluid (JP X, pH 6.8), 1/15 M acetate buffer and 1/15 M phosphate buffer, where the initial concentration was 0.1 mg/ml. The concentration of captopril was determined by HPLC (LC-5A system, Shimadzu, Kyoto, Japan), an octadecylsilane reverse-phase column (A-312: Yamamura Chem. Lab. Co., Kyoto, Japan) was employed and the mobile phase was a mixture of methanol–water–phosphoric acid (500 : 500 : 0.5 v/v/v). The eluate was monitored at 220 nm by a UV detector (SPD-2A, Shimadzu), and samples were quantitated using methylparaben as an internal standard.

Materials

Captopril was obtained from E.R. Squibb and Sons, (Princeton, NJ, U.S.A.) and ground to a powder fine enough to pass through a 150 mesh sieve. Other materials were JP or NF grade. The conventional tablet, immediate release tablet, was Captoril (25 mg/T, Sankyo Co., Tokyo, Japan).

Coated slow-release (CSR) granules

Captopril (200 g), microcrystalline cellulose (500 g) and lactose (260 g) were mixed. Granules were prepared by the wet granulation method using an aqueous solution of hydroxypropylcellulose (conc. 5% w/w) as a binder. Fraction of 12/24 mesh size granules were collected and were coated to obtain captopril CSR granules. The coating solution was a chloroform–methanol (8 : 2 w/w) solution of hydrogenated castor oil (5% w/w), stearyl alcohol (4.5% w/w), and sorbitan monostearate (0.5% w/w).

Modified release tablets

The modified release tablets were essentially composed of two parts, a core tablet containing captopril and a water-soluble polymer, and an outer insoluble layer covering the bottom and the side wall of the core tablet. A preformed core tablet was compressed together with the powder for the outer layer, forming a kind of press-coated tablet (Sankyo, 1986). Cross-sections of the tablets are illustrated in Fig. 1. Table 1 shows the com-

TABLE 1

Composition of captopril modified release tablet

		mg/tablet					
		A	B	C		D	
				1st layer	2nd layer	1st layer	2nd layer
Core tablet	Captopril	25	25	5	20	7	18
	Lactose	71	106	43	28	60.2	40.8
	Hydroxypropyl-cellulose	100	65	50	50	70	–
	Magnesium stearate	4	4	2	2	2.8	1.2
	sum of core tablet	200	200	200		200	
Insoluble layer	Ethyl cellulose	270	270	270		270	
	Carnauba wax	30	30	30		30	
	Total	500	500	500		500	

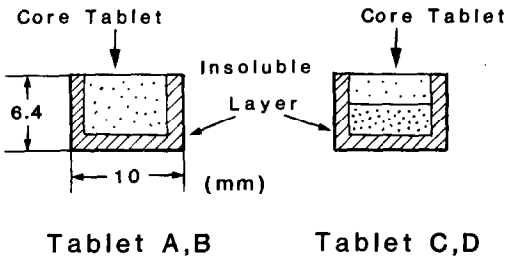

Fig. 1. Cross-sections of modified release captopril tablets.

position of 4 types of prepared modified release tablets; A and B had a uniform core tablet, whereas C and D core tablets were two-layered.

Enteric coated granules

A mixture of captopril (200 g), lactose (455 g), microcrystalline cellulose (100 g), and carboxymethylcellulose calcium (200 g) was granulated with an aqueous solution of hydroxypropylcellulose (conc. 7%, w/w) as a binder. The granules thus obtained were sieved to collect the 12/24 mesh size fraction. The sieved granules were coated with hydroxypropylmethylcellulose phthalate (HP-55, 10% w/w, Shin-Etsu Chem. Co., Tokyo, Japan) solution in acetone–ethyl alcohol (1 : 1 w/w).

Oily semisolid matrix (OSSM)

A mixture of soybean oil (45 g) and glyceryl monostearate (25 g; Sunsoft 1030, Taiyo Kagaku Co., Yokkaichi, Japan) was heated to 70 °C, at which temperature the glyceryl monostearate dissolved in the soybean oil. The solution was then cooled to room temperature and captopril (5 g) was added. Kneading of the mixture gave an oily semisolid suspension of captopril. The suspension obtained was heated to about 70 °C again in order to fill hard gelatin capsules (No. 3) using a syringe. The prepared OSSM capsules contained 250 mg OSSM; the captopril content of the capsules being 50 mg per 3 capsules.

In vitro release studies

The release of captopril from each dosage form was measured according to the procedure of the paddle method (JP X) or the rotating bottle method (NF XIV).

Paddle method. In the modified release tablet dissolution test, the dissolution medium was 500 ml of JP 2nd fluid (JP X) at 37 ± 0.5 °C and the stirring speed was 100 rpm. The dissolution test of enteric coated granules was carried out in JP 1st fluid (JP X, pH 1.2) during the first 2 h, after which the test medium was changed to JP 2nd fluid (JP X, pH 6.8). Other test conditions were the same as with the modified release tablet dissolution test.

Rotating bottle method. The bottle was rotated at 20 rpm in a waterbath maintained at 37 ± 0.5 °C. In the dissolution test of the CSR granules, pH of dissolution media was changed according to the procedure of NF XIV. The dissolution media were JP 1st fluid (JP IX, pH 1.2), JP 2nd fluid (JP IX, pH 7.5) and mixtures of the two fluids (pH 2.5, 4.5, 7.0).

Assay

Determination of captopril concentration in the dissolution media was carried out by using 2,2′-dithiodipyridine (2-PDS, Sigma Chem. Co., St. Louis, MO, U.S.A.). 2-PDS reacts completely with the sulfhydryl (SH) group in the captopril molecule and, as a result of the reaction, 2-thiopyridone (2-TP) is formed quantitatively (Grassetti and Murray, 1967). The sample solution was filtered through Ekicrodisc 13 (0.45 μm; Gelman Sci. Jap., Tokyo, Japan) and the filtrate was reacted with 2-PDS in phosphate buffer solution (pH 8.0). The resulting 2-TP concentration was determined by measuring the absorbance at 340 nm (Hitachi 156), which in turn was an indication of the captopril concentration in the medium.

Dog studies

Each dosage form was administered to groups of male beagle dogs (5 or 6 dogs, weighing between 9.3 kg and 12.4 kg) under fasting or non-fasting conditions. Under fasting conditions, the dogs were fasted for 18 h prior to administration. Under non-fasting conditions, 100 g of dog food (Oriental Yeast Co., Tokyo, Japan) was given to each dog 30 min before administration. Under both conditions, the preparations were orally given to the beagles together with 20 ml of water. During the experimental period, access to food was

not allowed but water was available ad libitum. At the designated time intervals, blood specimens were withdrawn into heparinized syringes from the forefoot vein and immediately afterwards the sampling plasma portion was obtained by centrifugation at 4°C.

Captopril determination in plasma

Unchanged captopril (free form) concentrations in plasma were determined chromatographically by using *p*-bromophenacyl bromide (p-BPB) or 6,7-methylenedioxy-4-methylcoumarinyl-3-maleimide (MDCM). Procedure details of the p-BPB method were reported previously (Kawahara et al., 1981). MDCM is a fluorescent derivatizing reagent for the SH group in captopril. MDCM was synthesized according to a previously reported method (Kawahara et al., 1983). As internal standard, 6,7-methylenedioxy-4-methylcoumarin was used, which was synthesized according to Fukui and Nakayama (1963). Freshly withdrawn plasma (0.5 ml) was added to an equal volume of 10% trichloroacetic acid aqueous solution, containing 200 ng of internal standard, and was centrifuged under refrigeration at 1200 *g* for 2 min. Then, phosphate buffer (100 μl, 0.5 M, pH 7.0) and MDCM solution (50 μl, 250 μg/ml in acetonitrile) were added successively to the collected 50 μl of the supernatant. The resulting mixture was applied onto an HPLC column. Analysis was performed on a Hitachi model 655 liquid chromatograph and a Hitachi model 650-10S fluorescence spectrophotometer. An octadecylsilane reverse-phase column (A-312) was employed and the eluent was a mixture of acetonitrile–water–acetic acid (400 : 600 : 15 v/v/v). The fluorescence intensity of the eluate was monitored at excitation and at emission wavelengths of 355 nm and 435 nm, respectively.

Absorption from gastrointestinal (GI) tract

The absorption of captopril was studied essentially according to the procedure reported by Levine et al. (1955). In this study 3 parts of the GI tract – stomach, upper small intestine (15 cm length) and lower small intestine (15 cm length) – were used. Eight mongrel dogs, weighing between 8.0 and 13.0 kg, were fasted for 18 h prior to the experiment and were anesthetized with sodium pentobarbital (25 mg/kg, i.v.). After abdominal incision, both ends of the chosen GI parts were ligated to make loops. Immediately after the operation, 2.5 ml of aqueous solution of captopril (10 mg/ml) was introduced into each loop and the opening was stitched. Then, venous blood specimens were taken at adequate time intervals to determine the plasma captopril concentration, which was absorbed from each GI loop.

Results and Discussion

Physicochemical properties of captopril are listed in Table 2. Captopril has a very high solubility in water, and its partition coefficient is small, particularly in the pH range around 7. It has been suggested that the transport process of captopril through the lipid layer of the cell membrane limits absorption. However, the rapid and sufficient absorption of captopril after oral administration

TABLE 2

Physicochemical characteristics of captopril

pK_a [a]	3.64 (−COOH)	
Solubility at 37°C	118 mg/ml (JP 1st fluid) 125 mg/ml (Water, pH 1.9)	
	pH	K [b]
Partition coefficient (K)	2.0	0.19
(at 37°C; *n*-octanol/water)	3.0	0.17
	4.0	0.03
	7.4	0.01
	pH	k [c] (h^{-1})
Stability at 37°C	1.2	–
(initial conc. 0.1 mg/ml)	2.0	7.0×10^{-5}
	3.0	9.3×10^{-5}
	4.0	4.1×10^{-4}
	5.0	4.5×10^{-4}
	6.0	1.5×10^{-3}
	6.8	3.1×10^{-3}
	7.0	4.2×10^{-3}
	8.0	4.9×10^{-3}

[a] Potentiometric titration method (0.01 M, at 25°C).

[b] $K = C_{n\text{-octanol}}/C_{water}$

[c] Pseudo-first-order rate constant for captopril degradation.

TABLE 3

Pharmacokinetic parameters of captopril (mean ± S.E.)

	Dose 100 mg/body: fasting condition						
	K_a (h^{-1})	K_e (h^{-1})	$T_{1/2}$ (h)	C_{max} ($\mu g/ml$)	T_{max} (h)	Absorption lag (h)	AUC_0^6 ($\mu g \cdot h/ml$)
Human	5.3 ± 0.7	1.4 ± 0.1	0.53 ± 0.04	0.933 ± 0.156	0.70 ± 0.12	0.34 ± 0.10	1.083 ± 0.093
Dog	3.7 ± 0.4	1.5 ± 0.1	0.47 ± 0.04	6.94 ± 0.085	0.72 ± 0.08	0.24 ± 0.02	8.40 ± 0.70

K_a = absorption rate constant; K_e = elimination rate constant; $T_{1/2}$ = biological half-life; C_{max} = maximum plasma concentration; T_{max} = time to reach maximum concentration.

(Duchin et al., 1982; Kripalani et al., 1980) suggests that the low partitioning ratio of captopril to the lipid layer is not a problem for the absorption process. As the degradation rate of captopril in aqueous solution increases with pH, it can be presumed that captopril is less stable in the intestine than in the stomach.

The pharmacokinetic parameters of captopril in man and dog are summarized in Table 3. They were calculated on the basis of a one-compartment open model using the data of plasma concentration after administration of Captoril tablets (25 mg × 4/body). In both species, biological half-life ($T_{1/2}$) and time to reach maximum concentration (T_{max}) of captopril in plasma were short, i.e. 30 and 40 min, respectively. This implies that captopril is rapidly transported into the blood circulation and also quickly eliminated from the central compartment. The difference in the parameters between man and dog was small, except for the maximum plasma concentration (C_{max}) and area under the curve (AUC). Consequently, the authors concluded that dogs are an acceptable animal model for developing captopril sustained-release dosage forms.

Fig. 2 shows the results of absorption site studies by the loop method in dogs. The time course of plasma concentration of captopril was measured respectively using the 3 chosen parts of the GI tract. It was confirmed that the optimum absorption site of captopril was the upper small intestine, as in the case of many other drugs. It was also ascertained that captopril can be absorbed from the lower small intestine, but that the absorption ability was inferior. Captopril was also absorbed from the stomach with a delayed time course of plasma concentration. From the above, it is suggested that captopril does not exhibit the so-called "window effect" which is seen in some drugs such as riboflavin and cephalexin (Levy and Jusko, 1966; Maekawa et al., 1977).

It has been reported that food intake significantly decreases the bioavailability of captopril in man (Singhvi et al., 1982; Mäntylä et al., 1984). Also in dogs, the AUC of captopril administered after meals decreased to about 40% of the AUC

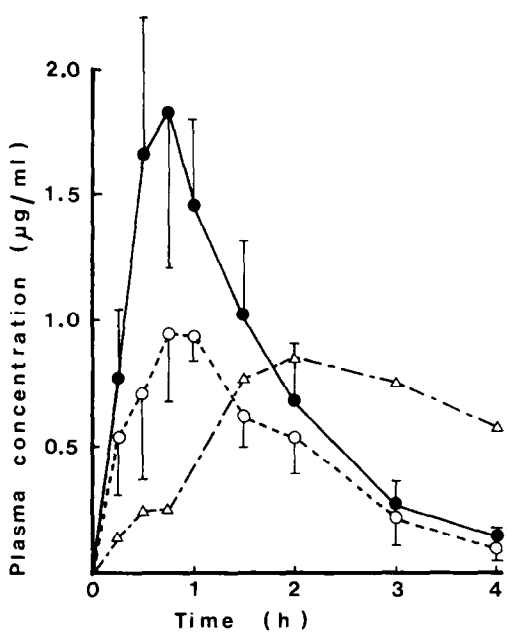

Fig. 2. Absorption of captopril from three parts of gastrointestinal tract in dog; mean plasma concentration ($\bar{x} \pm$ S.E.), by loop method. Key: ●———●, upper small intestine, $n = 3$; ○------○, lower small intestine, $n = 3$; △·-·-·△, whole stomach, $n = 2$.

TABLE 4

Influence of food intake on bioavailability of captopril

Dose (mg/body)	Condition	AUC ($\mu g \cdot h/ml$) (mean ± S.E.)	Ratio $AUC_{n.f.}/AUC_{f.}$
100 [a]	Non-fasting	3.57 ± 0.27	0.42
	Fasting	8.43 ± 0.59	
25 [b]	Non-fasting	0.71 ± 0.05	0.39
	Fasting	1.81 ± 0.16	

[a] $n = 6$, cross-over; [b] $n = 8$, cross-over: beagles, $AUC_{n.f.} = AUC$ of non-fasting condition (0–6 h); $AUC_{f.} = AUC$ of fasting condition (0–6 h).

under fasting conditions at two dose levels (Table 4; 25 mg/body, 100 mg/body). The extent of the decrease in the bioavailability resulting from food intake is very large, which makes the effect of food on the bioavailability an important point to consider in the development of captopril sustained-release products.

Based on the physicochemical and biopharmaceutical properties of captopril described in the preceding section, 3 types of well-known prolonged-action methods were chosen as test formulations. These were CSR granules, modified release tablets and enteric coated granules. The time course of captopril plasma concentration after oral administration was measured to evaluate these prolonged-action products. In this paper, doses were 50 mg/body and AUC values are expressed as mean ± S.E., if not otherwise stated.

At first CSR granules, a well-known approach to attain sustained-release dosage form, were tried. The dissolution of captopril from CSR granules is shown in Fig. 3. In spite of the pH change in the dissolution medium, the release rate from CSR granules was almost constant. Consequently, the release was taken as a zero-order process and not less than 90% of the captopril was released by the 7th hour of the dissolution test. Fig. 4 shows the time course of captopril plasma concentration following oral administration of CSR granules in comparison with that of conventional tablets. The two trials (CSR granules and conventional tablets) were not a cross-over study but the dog group and administration conditions (fasting condition) were the same. The $AUC_{0\text{-}6h}$, calculated using the

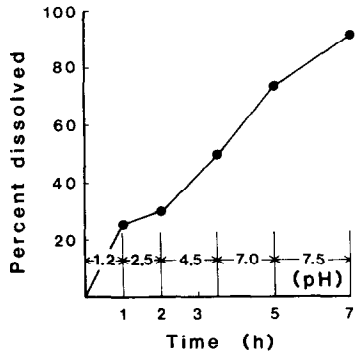

Fig. 3. In vitro dissolution of captopril from coated slow-release granules by the rotating bottle method.

trapezoidal method, was 1.23 ± 0.22 $\mu g \cdot h/ml$ with the CSR granules and 3.76 ± 0.50 $\mu g \cdot h/ml$ with the conventional tablets. This means that the AUC of CSR granules decreased to approx. one-third of the rapid-release formulation (conventional tablets). Although the C_{max} was low and the peak shape was flat in the concentration profile obtained from CSR granules, the concentration after 3 h was at practically the same low level as that of conventional tablets. The reasons for the low plasma concentration of CSR granules are

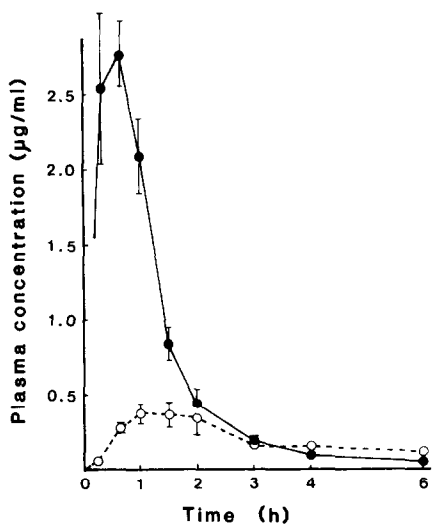

Fig. 4. Captopril plasma concentration after oral administration of coated slow-release granules (○------○) and conventional tablets (●———●); mean of 6 beagles ($\bar{x} \pm$ S.E.), dose 50 mg, under fasting conditions.

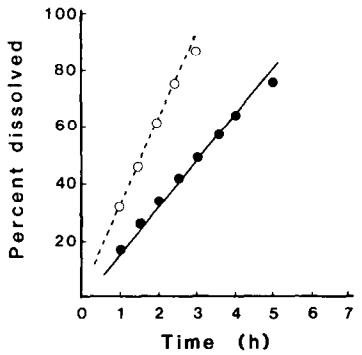

Fig. 5. In vitro dissolution of captopril from modified release tablet A (●———●) and B (○------○), by the paddle method.

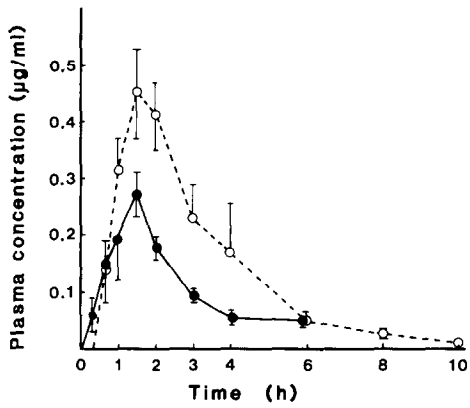

Fig. 6. Captopril plasma concentration after oral administration of modified release tablet A (●———●) and B (○------○); mean of 6 beagles ($\bar{x} \pm$ S.E.), dose 50 mg, under fasting conditions.

presumed to be: (1) imperfections in drug release of the CSR granules in the GI tract; (2) in spite of the results of absorption site study shown in Fig. 2, the in vivo absorbability of captopril from the lower part of the small intestine was not so effective as to maintain the plasma concentration of captopril; and (3) the transition rate of CSR granules in the GI tract was faster than expected, so they passed through the absorbable region too quickly (Morimoto et al., 1986).

In order to understand the relation between absorbability and dissolution behavior of sustained-release products in more detail, tablets having a variety of dissolution rates and patterns were prepared and administered to dogs. At first, two modified release tablets, having different zero-order dissolution rates, were prepared to clarify the relation between dissolution rate and bioavailability. Dissolution profiles of tablets A and B are shown in Fig. 5. Both tablets had zero-order dissolution rates; the rate being 16%/h in tablet A, and 30%/h in tablet B. Fig. 6 shows the time courses of captopril plasma concentration after administration of two kinds of tablets (50 mg/body) to the two beagle groups ($n = 6$ each) under fasting conditions. In both trials, plasma concentration reached a maximum at 1.5 h after administration and was decreased rapidly after the peak. There was no prolongation in plasma concentration. Tablets C and D were then prepared in order to enhance the plasma concentration in the period after 3 h from administration. Tablet C showed a dissolution rate of 6%/h during the 0–3 h period and 16%/h during the 3–7 h period in the dissolution tests using the paddle method, as is shown in Fig. 7. Time courses of plasma concentration after administration of both tablets are shown in Fig. 8. In spite of the increase of captopril release rate after 3 h (Fig. 7), the plasma concentration profile of tablet C remained level from 1 h to 10 h after administration (Fig. 8). Tablet D was designed to release 80% of loaded captopril quickly after 3 h from the start of the dissolution test (Fig. 7). In the time course of average plasma concentration, there was a sharp peak at 3 h after administration of tablet D (Fig. 8). This peak proved the good correlation between the dissolu-

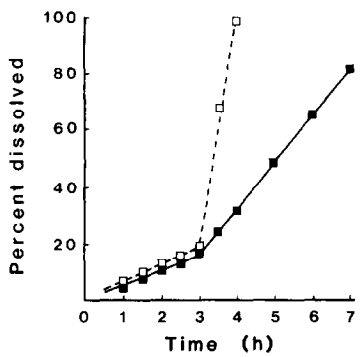

Fig. 7. In vitro dissolution of captopril from modified release tablet C (■———■) and D (□-----□) by the paddle method.

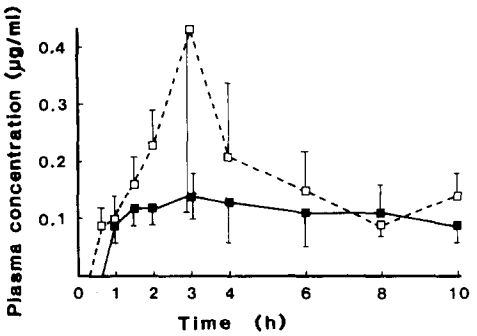

Fig. 8. Captopril plasma concentration after oral administration of modified release tablet C (■———■, $n = 6$) and D (□-----□, $n = 5$); mean of 5 or 6 beagles ($\bar{x} \pm$S.E.), dose 50 mg, under fasting conditions.

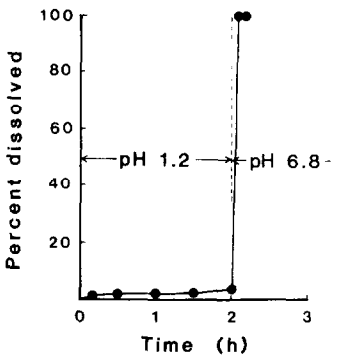

Fig. 9. In vitro dissolution of captopril from enteric coated granules, in JP 1st fluid during first 2 h then in JP 2nd fluid by the paddle method.

tion test and in vivo release from the tablet. This in vitro/in vivo correlation could be expected with tablet C. Consequently, low absorption ability was suggested at the location of the administered tablets after 3 h from administration. The following conclusions can be drawn from the results obtained by administration of these modified release tablets.

(1) The dissolution behavior of modified release tablets in the GI tract is considered to be practically identical to that in the dissolution test.
(2) The absorption ability of captopril from the GI tract become poor from which the tablet have transited about 3 h after administration.

All modified release tablets showed a significant decrease in *AUC* compared to that of conventional tablets. The *AUC* of tablets A through D were 0.64 ± 0.09, 1.35 ± 0.19, 1.05 ± 0.50 and 1.69 ± 0.59 $\mu g \cdot h/ml$, respectively. In contrast, the *AUC* of conventional tablets ranged between 3.36 and 4.04 $\mu g \cdot h/ml$, these results being obtained by administration to the same dog groups used in the modified release tablet tests. Such a decrease in *AUC* made it difficult to obtain an effective sustained-release dosage form from the usual time-dependent release products.

Enteric coated products are position-dependent release formulations. In general, the drug is released at the upper part of the small intestine, which is the most favorable region for absorption. As for captopril, it also is absorbed effectively from the upper site of the small intestine, with absorbability falling off gradually after the formulation units have passed through that site (Fig. 2). Thus the enteric coated formulation seemed to be suitable for a prolonged-action dosage form for captopril. The administration of captopril enteric coated granules to beagle dogs was carried out under non-fasting and fasting conditions. Fig. 9 shows the results of dissolution tests of captopril enteric coated granules. Fig. 10 shows the time courses of captopril plasma concentration after

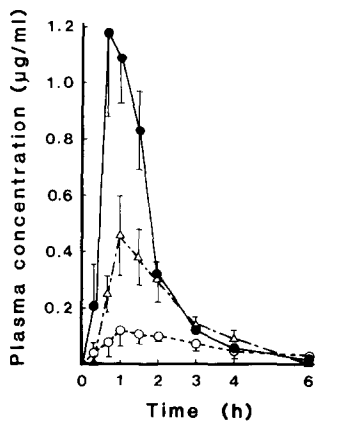

Fig. 10. Captopril plasma concentration after oral administration of enteric coated and non-coated granules; mean of 5 beagles ($\bar{x} \pm$S.E.), dose 25 mg. Key: ●———●, non-coated granules, fasting conditions; △·–·–·△, enteric coated granules, fasting conditions; ○------○, enteric coated granules, non-fasting conditions.

oral administration of non-coated granules under fasting conditions, coated granules under fasting conditions and coated granules under non-fasting conditions. These trials were conducted using a 3-way cross-over ($n = 5$) at one week intervals at doses of 25 mg/body. In enteric coated granules, the AUC was 0.99 ± 0.18 $\mu g \cdot h/ml$ when administered under fasting conditions; the value being smaller than that of non-coated granules under fasting conditions (1.72 ± 0.34 $\mu g \cdot h/ml$). Moreover, the enteric coated granules' AUC under non-fasting conditions was remarkably smaller than that in the fasted state. Although the AUC was larger in the fasted state, there was no prolongation in plasma concentration because of the rapid transit of the granules from the stomach to the small intestine. On the other hand, under non-fasting conditions enteric coated granules resulted in a steady level in the plasma concentration from T_{max} to 4 h after administration. But, the maintained concentration was insufficiently low and the AUC was small (0.37 ± 0.17 $\mu g \cdot h/ml$). The most popular technique for delaying transition is administration of enteric coated granules after meals, so that the granules transit gradually from the stomach to the small intestine with the food, then release drug. Therefore, whenever enteric coated granules are used as a prolonged-action dosage form, it is common that they be administered after meals. Consequently, in spite of the great advantage in the absorption site of this method, enteric coated granules cannot be used to attain a prolonged-action dosage form because of the large decrease in AUC resulting from food intake. In enteric coated granules administered under fasting conditions, it can be expected that rapid transition and release of captopril make the concentration of captopril high in the upper small intestine, and as there is no food in the gut, bioavailability must be equal to non-coated granules. Nevertheless, The bioavailability was lower than that of non-coated granules under fasting conditions (Fig. 10). This may be caused by in vivo instability of captopril in neutral to alkaline conditions in the gut.

Recent developments in pharmaceutical techniques for filling hard gelatin capsules with highly viscous liquid leads to utilization of hydrophobic

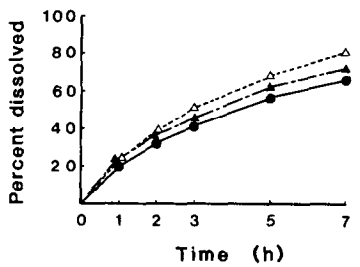

Fig. 11. In vitro dissolution of captopril from oily semisolid matrix by the rotating bottle method. Key: ▲·–·–·▲, JP (X) 1st fluid; △———△, JP (X) 2nd fluid; ●------●, purified water.

oily substances as a sustained release base (François et al., 1982). This method we tried to apply to captopril. Fig. 11 shows the in vitro release of captopril from OSSM by the rotating bottle method. Captopril OSSM capsules were administered to beagles and the plasma concentration of captopril was measured to evaluate the effectiveness of OSSM capsules. Fig. 12 shows the time course of plasma concentration after OSSM (dose 50 mg) administration under non-fasting conditions with the results of CSR granules administration as a reference. The AUC of CSR granules (dose 50 mg) under fasting conditions (1.23 ± 0.02 $\mu g \cdot h/ml$) was considerably smaller than that of conventional tablets as mentioned above, the AUC value suffering an additional big decrease in the fed state ($AUC = 0.46 \pm 0.04$ $\mu g \cdot h/ml$). Furthermore, captopril plasma concentration fell off rapidly after T_{max} (1 h), so it could not

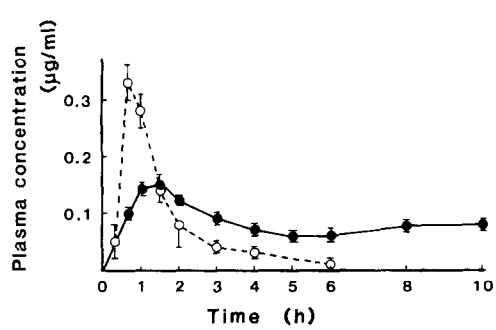

Fig. 12. Captopril plasma concentration after oral administration of oily semisolid matrix (●———●) and coated slow-release granules (○------○); mean of 6 beagles ($\bar{x} \pm$S.E.), dose 50 mg, under non-fasting conditions.

sustain the concentration level at all. On the other hand, plasma concentration of OSSM decreased very gradually from 2 h after administration, at which point the plasma concentration curve was showing a relatively flat peak. OSSM capsules could sustain the plasma concentration of captopril at a practically constant level until 10 h after administration. In spite of administration under non-fasting conditions, the AUC was comparatively high, 0.83 ± 0.08 $\mu g \cdot h/ml$. It was concluded that OSSM capsules were superior to CSR granules, a typical sustained-release product, with regard to duration of plasma concentration and AUC. The reasons for OSSM's superiority in bioavailability are speculated to be as follows: the transition rate of OSSM in the GI tract is slower than that of other sustained-release formulations, so it is able to stay longer at the effective absorbable region in the GI tract; OSSM easily adheres to the surface of the GI tract as a result of its rheological properties, so captopril can be protected from attack by food components (Seta et al., 1988) because the OSSM oily base acts as a barrier. In any case, the absorbability of OSSM is still about half that of conventional tablets under non-fasting conditions. Therefore, further improvement of captopril absorbability under non-fasting conditions is desired.

References

Cllnite, J.C. and Kabat, H.F., Improving patient compliance. *J. Am. Pharm. Assoc.*, 16 (1976) 74–76.

Duchin, K.L., Singhvi, S.M., Willard, D.A., Migdalof, B.H. and McKinstry D.N., Captopril kinetics. *Clin. Pharmacol. Ther.*, 31 (1982) 452–458.

François, D., Denmat, A., Waugh, A. and Woodage, T.,The in vitro and in vivo availability of phenylpropanolamine from oil/paste formulations in hard gelatine capsules. *Pharm. Ind.*, 44 (1982) 86–89.

Fukui, K. and Nakayama, M., Synthetic studies of seasamol derivatives II. Synthesis of 4-methylayapin. *J. Sci. Hiroshima Univ. Ser. A-II*, 26 (1963) 1313–1315.

Grassetti, D.R. and Murray Jr., J.F., Determination of sulfhydryl groups with 2,2′- or 4,4′- dithiodipyridine. *Arch. Biochem. Biophys.*, 119 (1967) 41–49.

Kawahara, Y., Hisaoka, M., Yamazaki, Y., Inage, A. and Morioka, T., Determination of captopril in blood and urine by high-performance liquid chromatography. *Chem. Pharm. Bull.*, 29 (1981) 150–157.

Kawahara, Y., Yamazaki, Y. and Naganuma, H., A sensitive derivatization reagent for the quantification of captopril by HPLC, *43rd International Congress of Pharmaceutical Science*, (1983) Montreux, Switzerland.

Kripalani, K.J., McKinstry, D.N., Singhvi, S.M., Willard, D.A., Vukovich, R.A. and Migdalof, B.H., Disposition of captopril in normal subjects. *Clin. Pharmacol. Ther.*, 27 (1980) 636–641.

Levine, R.M., Blair, M.R. and Clark, B.B., Factors influencing the intestinal absorption of certain monoquaternary anticholinergic compounds withs special reference to benzomethamine [*N*-diethylaminoethyl-*N*′-methyl-benzilamide methobromide (MC-3199)]. *J. Pharmacol. Exp. Ther.*, 114 (1955) 78–89.

Levy, G. and Jusko, W.J., Factors affecting the absorption of riboflavin in man. *J. Pharm. Sci.*, 55 (1966) 285–289.

Maekawa, H., Takagishi, Y., Iwamoto, K., Doi, Y., Ogura, T., Ito, M., Kitamura, K. and Fujimoto, H., Cephalexin preparation with prolonged activity. *Jpn. J. Antibiot.*, 30 (1977) 631–638.

Malahy, B., The effect of instruction and labeling on the number of medication errors made by patients at home. *Am. J. Hosp. Pharm.*, 23 (1966) 283–292.

Mäntylä, R., Männistö, P.T., Vuorela, A., Sundberg, S. and Ottoila, P., Impairment of captopril bioavailability by concomitant food and antacid intake. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 22 (1984) 626–629.

Miyazaki, N., Shionoiri, H., Uneda, S., Yasuda, G., Gotoh, E., Fujishima, S., Kaneko, Y., Kawahara, Y. and Yamazaki, Y., Blood concentration and urinary excretion of captopril (SQ 14,225), angiotensin converting enzyme activity and R-A-A system after administration of captopril – in patients with chronic renal failure compared with essential hypertension. *Nippon Jinzo Gakkai Shi*, 24 (1982) 421–427.

Morimoto, M., Yamashita, K., Koyama, H., Fujimoto, H., Toguchi, H. and Kitamori, N., Evaluation of sustained-release capsules of molsidomine (SIN-10) in dogs and monkeys. *Chem. Pharm. Bull.*, 34 (1986) 1257–1263.

Ondetti, M.A., Rubin, B. and Cushman, D.W., Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science*, 196 (1977) 441–444.

Sankyo Co., Ltd., Oral Sustained-Release Formulations, Jpn. Kokai Tokkio Koho JP 61-36217, 20 Feb. 1986.

Seta, Y., Higuchi, F., Otsuka, T., Kawahara, Y., Nishimura, K., Okada, R. and Koike, H., Preparation and pharmacological evaluation of captopril sustained-release dosage forms using oily semisolid matrix. *Int. J. Pharm.*, 41 (1988) 255–262.

Singhvi, S.M., McKinstry, D.N., Shaw, J.M., Willard, D.A. and Migdalof, B.H., Effect of food on the bioavailability of captopril in healthy subjects. *J. Clin. Pharmacol.*, 22 (1982) 135–140.