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Design of captopril sustained-release preparation with oily semisolid matrix intended for use in human subjects

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Summary

A captopril sustained-release dosage form using oily semisolid matrix (OSSM) has been studied to develop a formulation useful in human treatment. Four OSSMs which had different in vitro dissolution rates were administered to human subjects. The resulting bioavailabilities revealed that the best OSSM suitable for humans had a faster in vitro dissolution rate than that for dogs. Another series of administrations of OSSM also showed that formulated ascorbic acid improved the bioavailability of OSSM, and that the bioavailability was sufficient for a sustained-release dosage form so long as the amount of ascorbic acid in the OSSM was more than 5 times that of the captopril by weight. Pharmacokinetic analysis was performed based on plasma concentrations of captopril in humans ($n = 8$) after a single oral administration of conventional tablets or OSSM reformulated for humans. Calculated areas under the curve (AUCs, 0–∞ h) of plasma captopril concentration were 250.5 for conventional tablets and 283.5 (ng · h/ml) for OSSM. The mean residence times (MRTs) obtained by both formulations were 1.75 h and 3.59 h, respectively. The duration time in which plasma captopril concentration stayed above 50% inhibitory concentration of angiotensin converting enzyme activity was calculated. Total duration time (TDT) per day of conventional tablets (12.5 mg) taken 3 times daily was calculated to be 10.95 h. The TDT of OSSM was 17.00 h when the OSSM (18.75 mg of captopril) was administered twice a day at 12-h intervals. Consequently, OSSM dosed twice a day is expected to show a greater efficiency than conventional tablets taken 3 times daily.

Introduction

In our previous reports, captopril oily semisolid matrix (OSSM) dosage forms were made using oily semisolid vehicles as the base into which ascorbic acid was added (Seta et al., 1988b). It was shown to be useful due to their long-lasting effect in the biopharmaceutical and pharmacological studies using dog experiments. It is, however, difficult to extrapolate the results of animal experiments directly to studies with human subjects because of the differences in various physiological conditions (Cressman and Summer, 1971; Lui et al., 1986). This is especially true in the development of a sustained-release dosage form. Because of this, as a rule evaluations have to be made using human subjects. In the present study, therefore, OSSM administrations to human subjects

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were tried, to optimize the OSSM formulation for use in human treatment. The optimizing process is described in this paper.

Materials and Methods

Preparations

All the materials used for preparing the samples were of Japanese Pharmacopoeia (JP) grade, except captopril. Captopril was obtained from E.R. Squibb and Sons, (Princeton, NJ, U.S.A.). The preparation procedures of OSSMs were the same as mentioned in our previous work in this series (Seta et al. 1988a and b). The conventional tablet was Captoril 25 mg tablet (Sankyo Co., Tokyo, Japan).

Dissolution test

For the dissolution test, the rotating bottle method (NF XIV) was used, while determination of captopril in the medium was the same as that described in one of our previous papers of this series (Seta et al., 1988a).

Subjects and study design

Five male adult volunteers (42–48 years old, mean age 45.6 years; weight 56–69 kg, mean 62.8 kg) participated in our first bioavailability study (Formulation I in Table 1). Eight male adult volunteers (43–51 years old, mean age 47.3 years; weight 56–69 kg, mean 62.0 kg) participated in our bioavailability study of Formulation II in Table 1. The volunteers who participated in the present study were confirmed in advance to be normal regarding blood pressure, pulse rate, electrocardiogram, profiles of hematology and serum chemistry, urinalysis, etc. Subjects were randomly divided into 2 groups, and were given conventional tablets or the OSSM preparation (each containing 25 mg of captopril) according to a cross-over design at intervals of one week. Food intake and alcoholic drinks were prohibited to the volunteers from 23.00 h of the day prior to administration. They took the same breakfast (one cup of black tea and a sandwich) 30 min before administration of each dosage form.

Blood and urine samples were collected from the subjects at the designated time intervals. Unchanged (free form) captopril and total (free and oxidized form) captopril in both the plasma and urine specimens were determined.

TABLE 1

Composition of captopril oily semisolid matrix

	mg/single dose	
	I	II
Captopril	25	25
Ascorbic acid	125	125
Soybean oil	175	142.9
Glyceryl monostearate	50	7.1
Total	375	300
(capsule size)	(No. 2)	(No. 3)

Analysis of captopril

The methods of quantitative assay for unchanged captopril in plasma (MDCM method; Seta et al., 1988a) and unchanged captopril in urine (p-BPB method; Kawahara et al., 1981) have been published earlier. The total captopril amount was determined by treating plasma and urine with tributyl phosphine to reduce the oxidized form of captopril (Ivashkiv, 1984), which was then analysed according to the methods for the free form of captopril.

Kinetic procedures

After oral administration of both formulations, plasma unchanged captopril concentration–time curves showed a monoexponential decay on a semilogarithmic graph. Thus, a one-compartment open model, with a lag time in its absorption phase, was adopted. Least-squares regression analysis was carried out using the computer program NONLIN 74 (Metzler et al., 1974). The plasma concentration profiles of both dosage forms, conventional tablets and OSSM, with various dosage regimens were simulated using these pharmacokinetic parameters. Then the total duration time (TDT) was calculated with the drug concentration producing 50% inhibition of enzyme activity (IC_{50}) of captopril reported by Cushman et al. (1977).

Results and Discussion

The concentration of captopril in plasma and its urinary excretion rate were determined after a single oral administration to human subjects of the OSSM which had the same in vitro dissolution behavior as the OSSM given to dogs. That is, about 40% of captopril was released within 3 h. This OSSM was used as it had already been confirmed to show a long-lasting plasma captopril level in dogs and also because it exhibited 80% bioavailability against that of conventional tablets in administration to non-fasted dogs. Our first bioavailability trial was carried out using a cross-over with healthy male adults ($n = 5$), who received the OSSM or conventional tablet formulations, each containing 25 mg captopril, 30 min after the standard breakfast. The composition of the OSSM is shown in Table 1; formulation I in Table 1 being the OSSM used in this experiment.

The results with conventional tablets showed that the maximum plasma concentration (C_{max}) was observed at 1.5 h after administration and the maximum urinary excretion rate was observed at 0–2 h post-administration. On the other hand, the results with the OSSM revealed that the time required to reach the maximum plasma concentration (T_{max}) was 4 h and the time (period) of maximum urinary excretion rate ($T_{max\text{-}U}$) was 2–4 h, showing the tendency towards a long-lasting absorption phase. However, the relative bioavailability of the OSSM to conventional tablets was only 35%, 50% and 48%, based on area under the curve ($AUC_{0\text{-}10h}$) of free plasma captopril, $AUC_{0\text{-}10h}$ of total plasma captopril and cumulative urinary excretion percentage of total captopril until 10 h after administration, respectively. Therefore, it was confirmed that improvement in bioavailability of the OSSM was desired for human treatment.

Possible reasons for the remarkable differences in bioavailability of the OSSM between dogs and human subjects were factors such as, dose, composition of food taken, movement of gastrointestinal (GI) tract, gastric emptying rate and secretions in the GI tract. Using griseofulvin tablets, Aoyagi et al. (1984) reported that in a comparative study of bioavailability between dogs and human beings, the tablet disintegration ability in the GI tract was stronger in dogs than in human beings, judging from the plasma concentration measured. Therefore, the motility of the GI tract should be considered as one of the factors for such differences between animal species. Consequently, the relationship between the bioavailability and the in vitro dissolution rate of the OSSM was studied using the cumulative urinary excretion percentage and its time courses, because the in vitro dissolution rate is one of the most important properties of sustained-release dosage forms in the design of long-acting formulation by the pharmaceutical approach.

TABLE 2

Composition of captopril oily semisolid matrix

	mg/single dose			
	A	B	C	D
Captopril	25	25	25	25
Ascorbic acid	500	500	500	500
Soybean oil	525	510	500	375
Glyceryl monostearate	–	15	25	150
Total	1050 (3 cap.)	1050 (3 cap.)	1050 (3 cap.)	1050 (3 cap.)

Table 2 shows the composition of 4 kinds of OSSMs having different dissolution rates, and Fig. 1 illustrates the in vitro dissolution profiles of the OSSMs used for the present experiments. The amount of ascorbic acid formulated in the OSSMs was fixed at 20 times of captopril by weight, and the bioavailabilities of the resulting formulations

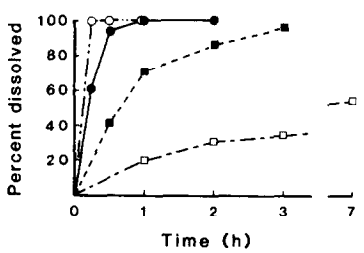

Fig. 1. In vitro dissolution of captopril from oily semisolid matrices by the rotating bottle method; 60 ml of purified water, 20 rpm. Key: ○·–·–·○, A; ●———●, B; ■- - - - -■, C; □- · -□, D.

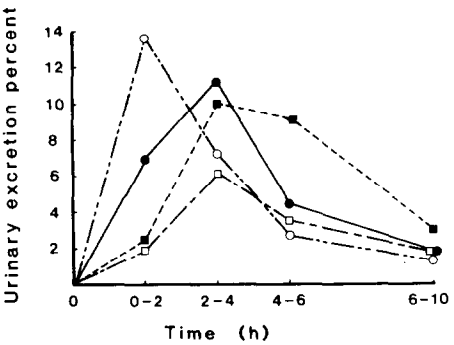

Fig. 2. Captopril urinary excretion recovery per 2 h or 4 h after oral administration of the oily semisolid matrices to human subjects, mean of 3 male healthy volunteers under non-fasting conditions, dose 25 mg. Key: ○·–·–·○, A; ●———●, B; ■- - - - -■, C; □·–·–·□, D.

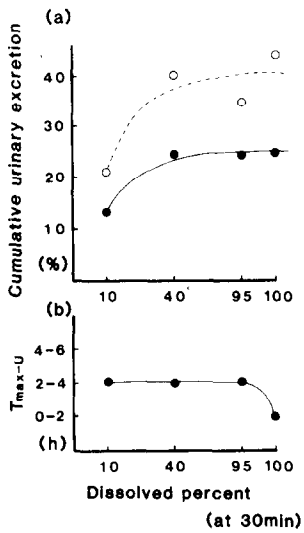

Fig. 3. a: relationship between mean urinary excretion recovery (0–10 h) of free (●———●) and total(○- - - - -○) captopril and dissolution rate (D_{30}) of the oily semisolid matrices. b: relationship between time required to reach the maximum urinary excretion rate ($T_{max\text{-}U}$) and dissolution rate of the oily semisolid matrices.

were compared in human subjects. Formulation D was designed to have almost the same dissolution pattern as that of the formulation used in our first administration trial in human subjects. The preparations were orally administered to 3 healthy male adults 30 min after a meal, and the amount of captopril excreted into the urine was determined. As shown in Fig. 2, the T_{max-U} of formulation A, which had the fastest dissolution rate, was 0–2 h, but the rest of 3 OSSMs had the same $T_{max\text{-}U}$ in spite of their dissolution rate difference. The cumulative urinary excretion percentages up to 10 h with formulations A, B, C and D were 25%, 24%, 25% and 13% based on captopril free form, respectively, and 44%, 35%, 40% and 21% based on total captopril, respectively. These results are summarized in Fig. 3, in relation to in vitro dissolution rates. Fig. 3a illustrates the relationship between the dissolution rates D_{30} (dissolved amount in the first 30 min, %) and the cumulative urinary excretion percentages based on free and total captopril; Fig. 3b shows D_{30} and $T_{max\text{-}U}$.

It can be considered that the percent urinary recovery indicates the absorbability of the drug and $T_{max\text{-}U}$ indicates the persistence of blood level. The most favorable long-acting dosage form would be one having an absorbability equal to the immediate-release dosage form and a long $T_{max\text{-}U}$. Based on these requirements, the most desirable preparation was formulation C having a D_{30} of 40%; formulation B was also considered satisfactory. Formulation A, having the fastest dissolution rate, showed almost equal cumulative urinary excreted percentage to formulation B and C, but its urinary excretion rate profile was inferior to B and C because of its short $T_{max\text{-}U}$. Formulation D, having the slowest dissolution rate, had the long $T_{max\text{-}U}$, but its absorbability was inferior to the other 3 formulations. It was confirmed that the dissolution pattern like in formulation A or D is unacceptable for a captopril OSSM.

The addition of ascorbic acid to captopril OSSM was previously reported to be useful for improvement of its bioavailability in administrations to dogs (Seta et al., 1988b). In order to confirm whether the same effect can be observed with human subjects, the cumulative urinary excretion percentages of 5 OSSM preparations were determined without and with 4 different amounts of ascorbic acid. Their dissolution profiles were similar to that of formulation C mentioned above. It means that their dissolution percentages were 40–55% at 30 min and not less than 90% of captopril was released by 3 h of dissolution test.

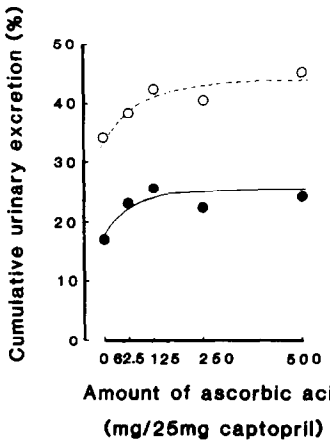

Fig. 4. Relationship between cumulative urinary excretion recovery and amount of ascorbic acid to the 25 mg of captopril in the oily semisolid matrices, mean of 3 male healthy volunteers under non-fasting conditions. Key: (●———●) free captopril; (○- - - - -○) total captopril.

The relationship between the amount of ascorbic acid in the OSSM and the percent urinary recovery for 10 h is shown in Fig. 4. The curves illustrated in Fig. 4 indicate that cumulative urinary excretion percentage tended to be enhanced by an increase in the amount of ascorbic acid formulated in the OSSM. But, addition of ascorbic acid over 125 mg/capsule (per 25 mg of captopril) gave progressively less additional enhancement in urinary recovery ratio. The addition of ascorbic acid proved to be as effective in human subjects as in dogs. Therefore, it was concluded that ascorbic acid is a useful agent in improving the absorption of captopril in OSSM formulations.

The influence of dissolution rate and ascorbic acid content on bioavailability of OSSM have been reported in this paper. According to the results of these studies in human beings and that of dog experiments reported in previous papers in this series, the composition shown in Table 1 as formulation II was selected as the formulation most suitable for human subjects. Dissolution profiles of formulation II are shown in Fig. 5.

Fig. 6 shows the plasma concentrations of captopril following OSSM (formulation II in Table 1) or conventional tablet administration. The trial was carried out using a cross-over and 8

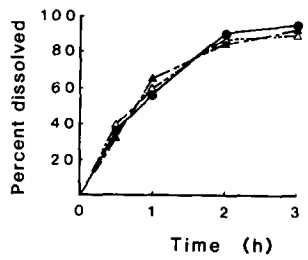

Fig. 5. In vitro dissolution of captopril from oily semisolid matrix (formulation II) by the rotating bottle method, fluid volume 60 ml, 20 rpm. Key: ▲·–·–·▲, JP (X) 1st fluid; △·–·–·△, JP (X) 2nd fluid; ●———●, purified water.

healthy male adults who were given each dosage form 30 min after the standard breakfast. The experimentally determined data points and the regression curves calculated by using a one-compartment open model are shown in Fig. 6. In the OSSM of formulation II, plasma concentration of captopril was lower than that obtained with conventional tablets at the initial stage following administration, but it was obviously higher than that of conventional tablets after 4 h post-administration. Moreover, free captopril could be detected even at 6 and 8 h after the administration.

The pharmacokinetic parameters of both dosage forms are summarized in Table 3. The *AUC*s of the OSSM and control formulation were almost equal to each other, and the biological half-life ($T_{1/2}$), mean residence time of the drug in the

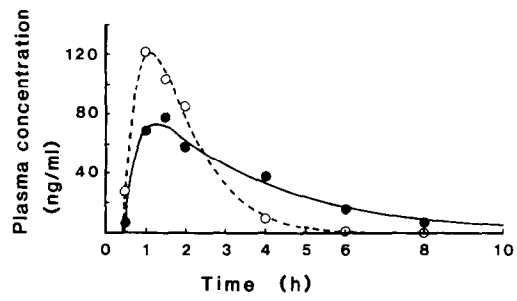

Fig. 6. Captopril plasma concentration after oral administration of oily semisolid matrix and conventional tablets; mean of 8 male healthy volunteers under non-fasting conditions, dose 25 mg. The solid and dotted lines represent the fitted curve calculated from the experimental data; ●, oily semisolid matrix; ○, conventional tablets.

TABLE 3

Summary of pharmacokinetic parameters of captopril for conventional tablet and oily semisolid matrix (based on plasma free captopril concentration)

Parameters		Formulation	
		Conventional tablet	Oily semisolid matrix
C_{max}	(ng/ml)	121.0	73.7
T_{max}	(h)	1.13	1.25
$T_{1/2}$	(h)	0.62	2.13
AUC	(ng·h/ml)	250.5	283.5
Xu_f	(% of Dose)	25.1	25.7
Xu_t	(% of Dose)	41.3	42.5
MRT	(h)	1.75	3.59
VRT	(h^2)	0.805	7.79

MRT = mean residence time; VRT = variance of residence time; Xu_f = urinary excretion of free captopril; Xu_t = urinary excretion of total captopril.

body (MRT) and variance of residence time of the drug in the body (VRT) obtained with the OSSM are obviously larger than respective values obtained with conventional tablets. The value of these 3 parameters reflect the degree of duration tendency in blood concentration of the drug (Yamaoka et al., 1978).

Examples of plasma concentration profiles of captopril simulated for multiple administrations of both dosage forms are shown in Fig. 7. The simulation was carried out using the pharmacokinetic parameters listed in Table 3 and under the assumption of linearity. The horizontal solid line in Fig. 7 represents the IC_{50} of ACE activity reported by Cushman et al. (1977).

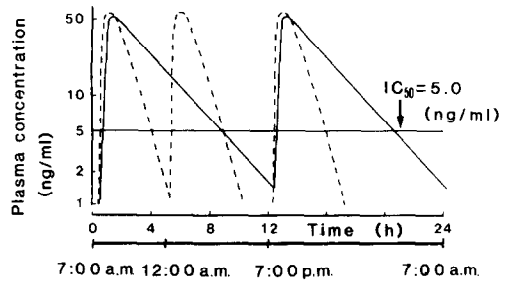

Fig. 7. Simulated time courses of captopril plasma concentration. Key: ------, conventional tablets (12.5 mg×3)/day; ———, oily semisolid matrix (18.75 mg×2)/day.

The duration of the concentration over the IC_{50} value and AUC was calculated with varying dosage regimens and doses for both dosage forms and the duration time was expressed as TDT per day. The TDT following OSSM administration was found to be longer than that for conventional tablets in all of the dosage regimens shown in Table 4.

In this way, we obtained an OSSM sustained-release dosage form suitable for human administration. It is suggested that dosing OSSM twice a day has comparable antihypertensive action to that of the presently used dosage regimen of 3 times a day for the same daily dose. At the same time, the OSSM sustained release dosage

TABLE 4

Comparison of total duration time between conventional tablet and oily semisolid matrix

Dosage form	Dosage regimens			Total duration time [a] (h)	$AUC_{0\text{-}24h}$ (ng·h/ml)
	Dose (mg)	Times/day	Time interval (h)		
Conventional tablet	12.5	3	5–5–14	10.95	351.5
	12.5	3	5–7–12	10.95	351.5
Oily semisolid matrix	25.0	2	10–14	18.85	577.8
	18.75	2	10–14	17.05	433.3
	12.5	2	10–14	14.55	288.9
	25.0	2	12–12	18.80	577.8
	18.75	2	12–12	17.00	433.3
	12.5	2	12–12	14.45	288.9

[a] Total time during which plasma free captopril concentration is maintained above the 50% inhibitory level of ACE activity (IC_{50} = 5.0 ng/ml).

form can be expected to minimize the risk of side-effects.

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