Pharmacokinetic Analysis of an Oral Sustained-Release Diltiazem Preparation Using Multifraction Absorption Models

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Application of multifraction absorption models to pharmacokinetic analysis of an oral sustained-release diltiazem preparation (HER-SR) was investigated. The plasma diltiazem concentrations after oral administration of the HER-SR preparation were analyzed using both the two-fraction absorption model and the two-step discontinuous absorption model. The two-fraction absorption model was suitable for the pharmacokinetic analysis of the HER-SR preparation, whereas the two-step discontinuous absorption model is often unsuitable for the analysis of sustained-release preparations which disintegrate into fractions with different release characteristics in the gastrointestinal tract. The two-step discontinuous absorption model is usually not applicable to plasma concentration data when the first peak is sharp. MFA-MULTI(V) was shown to be useful for the prediction of the bioavailability in each fraction of HER-SR. It was further demonstrated that a two-fraction absorption model is useful for the comparison of *in vitro* and *in vivo* release profiles or evaluating the influence of food on the absorption behavior of HER-SR. In addition, the application of a two-fraction absorption model to population pharmacokinetics of HER-SR was investigated.

KEY WORDS: multifraction absorption models; diltiazem; sustained-release preparation; food; *in vitro–in vivo* correlation; population pharmacokinetics.

INTRODUCTION

The gastrointestinal absorption of drugs is complex and involves several rate processes, including dissolution, absorption from different sites, and gastric emptying, that occur either simultaneously or sequentially. Despite this complexity, the rate of appearance of a drug in the systemic circulation after oral administration can usually be described by assuming simple first-order kinetics. However, irregular absorption profiles may result from dissolution characteristics of dosage forms or physiological factors in the gastrointestinal tract.

Recently, multifraction absorption models (1,2) have been proposed for the analysis of plasma concentration data of drugs that are divided in the gastrointestinal tract into several fractions, each with its own respective lag time and absorption rate constant. This new approach is suitable for comparing the absorption behavior of different sustained-release preparations (3). It can also provide useful information for the prediction of plasma drug concentrations after repeated oral administrations and for establishing dosage regimen schedules for drugs with irregular absorption profiles (2).

In this report, we describe the application of multifraction absorption models to pharmacokinetic analyses of a multiparticulate sustained-release diltiazem preparation (HER-SR) with both fast- and slow-release beads. The validity of multifraction absorption models is discussed by comparing them with results estimated using discontinuous absorption models (4). Multifraction absorption models were then applied to the evaluation of *in vitro* and *in vivo* release characteristics and influence of food on absorption behavior and to population pharmacokinetics (5) of the HER-SR preparation after single or repetitive oral administration in humans.

MATERIALS AND METHODS

Materials. Beagle dogs were purchased from Yoshikiyakko and maintained on a diet of dog chow (Oriental Yeast). The dogs were fasted for 18 hr prior to administration of drugs. Diltiazem hydrochloride (diltiazem) was synthesized by the Tanabe Seiyaku Company. Other chemicals were special-grade reagents. A multiparticulate sustained-release diltiazem capsule containing both fast (15% of total diltiazem) and slow (85%) release beads of diltiazem (HER-SR; 100 mg) was used for the study.

Animal Experiment. One capsule (100 mg as diltiazem) of HER-SR was administered orally to four dogs by compulsive swallowing with 30 mL of water (3). Blood samples were taken at 0, 1, 2, 3, 4, 6, 8, 10, 13, 15, 17, 19, 21, 24, 27, and 30 hr. Fast-release beads (15 mg as diltiazem) or slow-release beads (85 mg) were orally administered to four dogs. Blood samples were taken at 0, 0.5, 1, 2, 3, 4, 6, and 8 hr for the fast-release beads and at 0, 1, 2, 3, 4, 6, 8, 10, 13, 15, 17, 19, 21, 24, 27, and 30 hr for the slow-release beads. Plasma samples were frozen at −20°C. Slow-release beads (85 mg) were administered to two dogs, and their position in the gastrointestinal tract was examined by dissection after 6 hr. The remaining diltiazem content of the beads was determined. In addition, HER-SR was administered to two dogs and the remaining diltiazem content of the beads recovered from feces obtained by enema 10 or 24 hr after oral administration was determined.

Human Study. One capsule (100 mg as diltiazem) of HER-SR was administered to six healthy male subjects under fasting or non-fasting conditions (6). The meal composition was bread, jam, milk, and fruit. Blood samples were taken at 0, 2, 4, 6, 8, 10, 13, 15, 24, 36, and 48 hr.

Determination of Plasma Diltiazem Concentration. Plasma diltiazem concentrations were determined by high-performance liquid chromatography (Shimadzu LC-3A) with UV detector (7).

In Vitro *Dissolution Test. In vitro* dissolution of diltiazem from HER-SR was determined by the JP paddle method. The dissolution medium comprised 900 mL of water at 37°C, stirred with a paddle speed of 100 rpm. The concentration of diltiazem was assayed by the UV-HPLC method.

Pharmacokinetic Analysis. Multifraction absorption models (1) or discontinuous absorption models (4) were used

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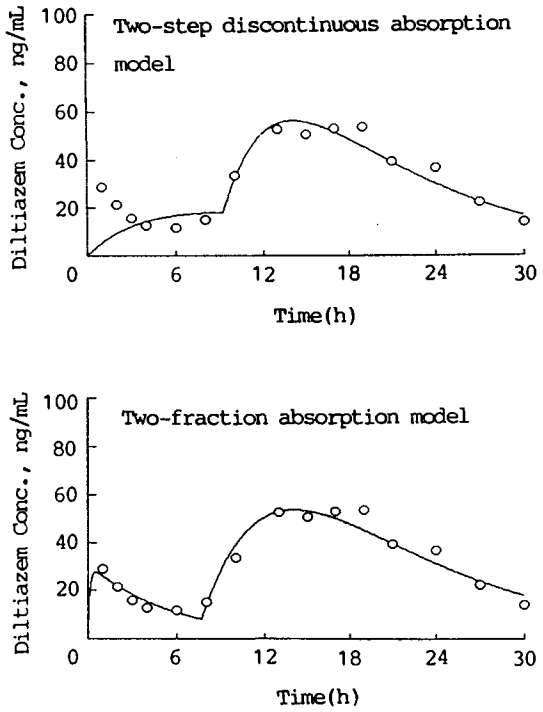


Fig. 1. Curve fit to plasma diltiazem concentration data in dogs after oral administration of HER-SR (100-mg dose) using the two-fraction absorption model and the two-step discontinuous absorption model.

to analyze plasma diltiazem concentrations in four dogs and six humans after single oral administrations of HER-SR (Appendix A). Plasma diltiazem concentrations were also analyzed by the Wagner–Nelson method (8) and *in vivo* release profiles of HER-SR were calculated. Population pharmacokinetic parameters for HER-SR were estimated from plasma diltiazem concentrations after single (6) or repetitive (3) oral administration of HER-SR to six humans. Also, single or repetitive dose data (subject 4 or subject 3) were analyzed by Bayesian estimation.

A nonlinear regression program, the microcomputer program MFA-MULTI (2) that was developed for multifraction absorption models based on a simplex method (9), was used for the analysis of plasma diltiazem concentrations. AIC (Akaike's information criterion) (10) was used as the criterion for the evaluation by multifraction absorption models. Population pharmacokinetic parameters for HER-SR were estimated using the microcomputer program MULTI(ELS) (11), which is based on the extended least-squares method (ELS) (12). Bayesian estimation was carried out on the microcomputer program MULTI(BAYES) (13), which is based on a nonlinear least-squares method incorporating the Bayesian algorithm (14). The computation was carried out on a PC-9801 microcomputer (NEC) with a N88-BASIC compiler (NEC). Estimates calculated by the method of residuals were usually used as initial values. The value $1/C$ was adopted for the weighting of data (C equals plasma drug concentration).

RESULTS AND DISCUSSION

Pharmacokinetic Analysis of a Sustained-Release Diltiazem Preparation (HER-SR) in Dogs

Plasma diltiazem concentrations with a double peak obtained in all dogs after the oral administration of HER-SR were analyzed using both the two-fraction absorption model and the two-step discontinuous absorption model. Figure 1 shows the fitted curves obtained using both models. Table I shows the pharmacokinetic parameters. In the two-fraction absorption model (MFA-MULTI), an excellent fitted curve and reasonable parameters were obtained. The HER-SR preparation was apparently divided into two fractions (14 and 86 mg) in the gastrointestinal tract. The fractions were absorbed at rate constants of 4.56 and 0.15 hr^{-1}, respectively. The lag time of absorption for the slow-release component was 8.3 hr, suggesting that the colon is the main receptive site for its release from the beads. This was confirmed experimentally by the fact that almost all of the slow-

Table I. Pharmacokinetic Parameters in Dogs for HER-SR Estimated Using the Multifraction Absorption Model and Discontinuous Absorption Model

Parameter[a]	Two-fraction absorption model		Two-step discontinuous absorption model
	MFA-MULTI	MFA-MULTI(V)	
X_a (mg)	—	—	100
X_{a1} (mg)	14 ± 2[b]	14 ± 2	—
X_{a2} (mg)	86 ± 2	86 ± 2	—
K_{a1} (hr^{-1})	4.56 ± 1.34	4.62 ± 1.40	0.031 ± 0.004
K_{a2} (hr^{-1})	0.15 ± 0.04	0.13 ± 0.02	0.17 ± 0.01
K_{el} (hr^{-1})	0.20 ± 0.02	0.23 ± 0.02	0.21 ± 0.07
T_2 (hr)	8.3 ± 0.6	8.2 ± 0.6	9.8 ± 0.8
V_d/F (L)	484 ± 57	—	651 ± 198
$V_d/F(1)$ (L)	—	496 ± 59	—
$V_d/F(2)$ (L)	—	486 ± 57	—
SS[c]	16 ± 5	16 ± 5	46 ± 13
AIC	48 ± 7	50 ± 7	64 ± 3

[a] T_1 is equal to zero.
[b] Mean ± SE (n = 4).
[c] Residual sum of squares.

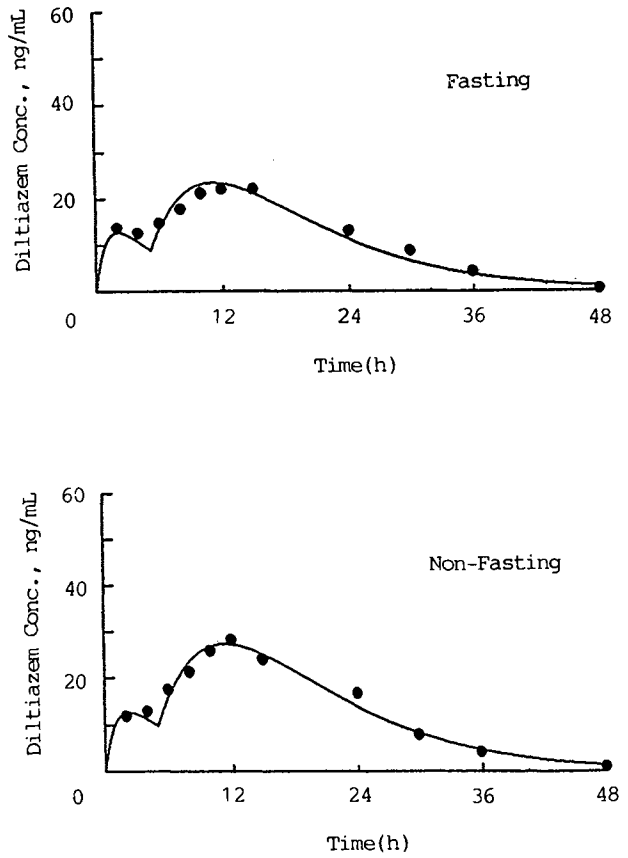


Fig. 2. Curve fit to mean plasma diltiazem concentration data after oral administration of HER-SR (100-mg dose) to six humans using the two-fraction absorption model.

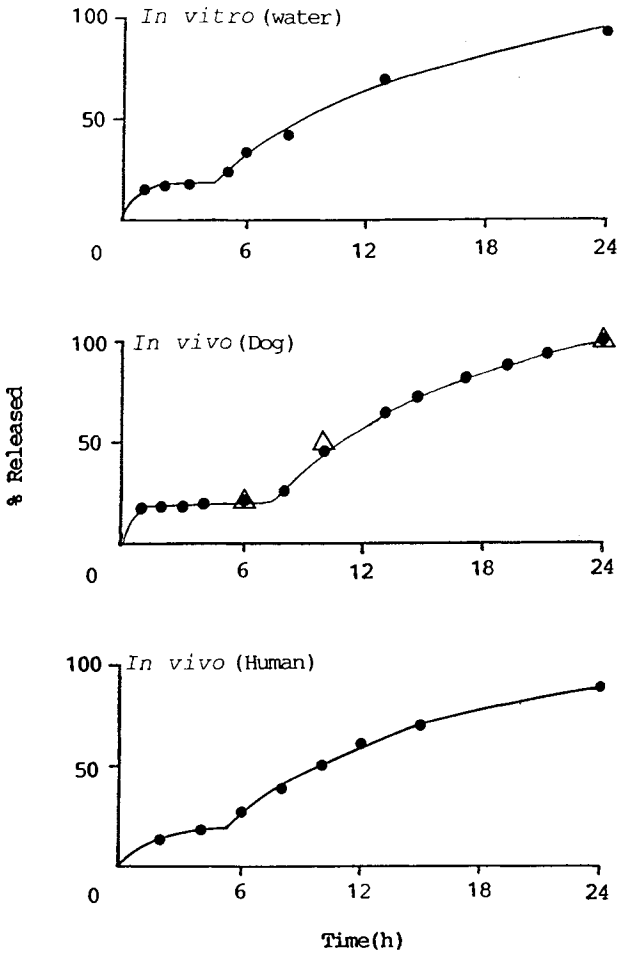


Fig. 3. *In vitro/in vivo* release profiles of HER-SR. (△) Diltiazem content released from the beads recovered from the gastrointestinal tract (n = 2).

release beads had reached the colon within 6 hr after oral administration; the remaining diltiazem content of the beads was approximately 90% (n = 2) of the initial amount. Also, it was found that the prolonged plasma diltiazem concentrations of HER-SR are due to the gradual absorption of diltiazem from the slow-release beads in the colon.

In the two-step discontinuous absorption model, the AIC (10) value was larger than that in the two-fraction absorption model, and the curve fitting was less precise. Also, K_{a1} of the fast-release component was quite small and seemed unrealistic. These results indicate that the multifraction absorption model is more suitable than the discontinuous absorption model in the pharmacokinetic analysis of HER-SR. It was found that discontinuous absorption models are usually unsuitable for the pharmacokinetic analysis of sustained-release preparations, which disintegrate into fractions with different release characteristics in the gastrointestinal tract. In addition, it was also found that the two-step discontinuous absorption model is usually unsuitable for analysis of plasma drug concentrations when the first peak is sharp, considering the characteristics of the model.

In the multifraction absorption model, we have assumed that the fraction absorbed (F) is constant when there are more than two fractions. However, it is necessary to note that the F value in each fraction may be different in some cases, although this is difficult to verify experimentally. For example, it is possible that some drugs exhibit several different F values in the gastrointestinal tract or are subject to nonlinear, first-pass metabolism during the absorption process. Further research on this matter was necessary to increase the versatility and validity of the multifraction absorption models. Therefore, we modified the MFA-MULTI (2) computer program to the MFA-MULTI(V) as shown in Appendix B, in order to evaluate the F values in each fraction.

The plasma diltiazem concentrations were analyzed using MFA-MULTI(V). Table I shows that F values ($F1/V$,

Table II. *In Vitro/in Vivo* Correlation

	In vitro	*In vivo*	
Parameter[a]	Water	Dog	Human
X_{a1} (mg)	17 ± 1[b]	16 ± 2	17 ± 2
X_{a2} (mg)	83 ± 1	84 ± 2	83 ± 2
K_{r1} (hr^{-1})	1.76 ± 0.10	1.98 ± 0.03	1.21 ± 0.22
K_{r2} (hr^{-1})	0.13 ± 0.01	0.13 ± 0.01	0.11 ± 0.01
T_2 (hr)	4.2 ± 0.1	7.4 ± 0.2	5.2 ± 0.3

[a] T_1 is equal to zero.
[b] Mean ± SE (n = 4–6).

Table III. Pharmacokinetic Parameters in Humans for HER-SR Estimated Using the Two-Fraction Absorption Model

Parameter[a]	Fasting	Nonfasting
X_{a1} (mg)	19 ± 0.4[b]	17 ± 2
X_{a2} (mg)	81 ± 0.4	83 ± 2
K_{a1} (hr^{-1})	1.03 ± 0.21	1.18 ± 0.27
K_{a2} (hr^{-1})	0.081 ± 0.01	0.098 ± 0.02
K_{el} (hr^{-1})	0.19 ± 0.01	0.17 ± 0.01
T_2 (hr)	5.3 ± 0.3	4.8 ± 0.4
V_d/F (L)	941 ± 119	962 ± 87

[a] T_1 is equal to zero.
[b] Mean ± SE (n = 6).

F2/V) obtained for both fast- and slow-release components were similar. This was further confirmed experimentally by oral administration of both beads to dogs. Fast-release beads were quickly absorbed, while slow-release beads were gradually absorbed after a lag time of about 8 hr, as predicted by the two-fraction absorption model. The AUCs for the fast-release (15 mg as diltiazem) and slow-release (85 mg) beads were 156.9 ± 36.7 and 977.0 ± 197.1 ng/mL · hr (mean ± SE; n = 4), respectively. From these results, it was shown that MFA-MULTI(V) is useful for predicting the bioavailability of each fraction in multifraction absorption models.

Comparison of *in Vitro* and *in Vivo* Release Profiles of the Sustained-Release Preparation (HER-SR)

In vivo release and *in vitro* dissolution of HER-SR were compared. The *in vivo* release profiles were calculated from plasma diltiazem concentrations in four dogs (Fig. 1) and six humans (Fig. 2, fasting) by the Wagner–Nelson method (8). Figure 3 shows the *in vitro* and *in vivo* release profiles. *In vivo* release profiles were relatively close to the *in vitro* dissolution profiles in water. The *in vitro* and *in vivo* release profiles of HER-SR were analyzed using the two-fraction release equation as shown in Appendix C. As shown in Table II, the release rate constant and lag time of the slow-release beads calculated from *in vitro* and *in vivo* release profiles were similar, although the lag time of *in vitro* and *in vivo* (dog) release profiles was slightly different. Figure 3 also shows the diltiazem content released from the beads recovered from the gastrointestinal tract in dogs by dissection or enema. The diltiazem content released from the beads agreed with the *in vivo* release profiles, and diltiazem in the beads was completely released within 24 hr after oral administration of HER-SR.

Pharmacokinetic Analysis of Absorption Behavior of the Sustained-Release Preparation (HER-SR) in Humans

Plasma diltiazem concentrations with a double peak after single oral administration of HER-SR to six humans under fasting and nonfasting conditions were analyzed using the two-fraction absorption model (Appendix A). As shown in Fig. 2, good simulation curves were obtained. Table III shows the pharmacokinetic parameters for both conditions. In the case of the fasting condition, the HER-SR preparation was apparently divided into two fractions in the gastrointestinal tract. The initial amounts of fast- and slow-release beads were 19 and 81 mg, respectively. The absorption rate constants were 1.03 hr^{-1} for the fast-release beads and 0.081 hr^{-1} for the slow-release beads. The lag time of the slow-release beads was 5.3 hr. These parameters were similar to those estimated from the plasma concentrations after oral administration of HER-SR under nonfasting conditions, indicating that food does not influence the absorption behavior of either fast- or slow-release beads of HER-SR. Also, it was shown that the two-fraction absorption model is suitable for simultaneous evaluation of the effects of food on the absorption behavior of both beads of HER-SR.

Application of Multifraction Absorption Models to Population Pharmacokinetics of HER-SR

We further investigated the pharmacokinetics of HER-SR using a two-fraction absorption model based on population pharmacokinetics. Plasma diltiazem concentrations after single (Fig. 2, fasting) or repetitive (3) oral administration of HER-SR to six humans were analyzed using the two-fraction absorption model. Table IV shows the population parameters estimated using MULTI(ElS). Figure 4 shows

Table IV. Pharmacokinetic Parameters for HER-SR Estimated Using MULTI(ELS) and MULTI(BAYES)

			MULTI(BAYES)			
	MULTI(ELS)		Single-dose data		Multiple-dose data	
Parameter[a]	Single-dose data	Multiple-dose data[b]	(A)[c]	(B)[d]	(A)	(B)
X_{a1} (mg)	20 (3)[e]	16 (4)	20	16	20	16
K_{a1} (hr^{-1})	0.80 (0.01)	0.58 (0.01)	0.80	0.58	0.79	0.58
K_{a2} (hr^{-1})	0.089 (0.002)	0.066 (0.001)	0.069	0.062	0.064	0.064
K_{el} (hr^{-1})	0.16 (0.00)	0.13 (0.00)	0.16	0.13	0.16	0.13
T_2 (hr)	5.4 (0.0)	6.4 (0.3)	5.4	6.4	5.4	6.4
V_d/F (L)	1134 (41)	1052 (135)	1203	1125	1401	1515

[a] T_1 is equal to zero; X_{a2} is equal to (dose − X_{a1}).
[b] From Ref. 3.
[c] Bayesian estimation was performed using the population parameters for single-dose data as shown in Table IV.
[d] Bayesian estimation was performed using the population parameters for multiple-dose data as shown in Table IV.
[e] Variance.

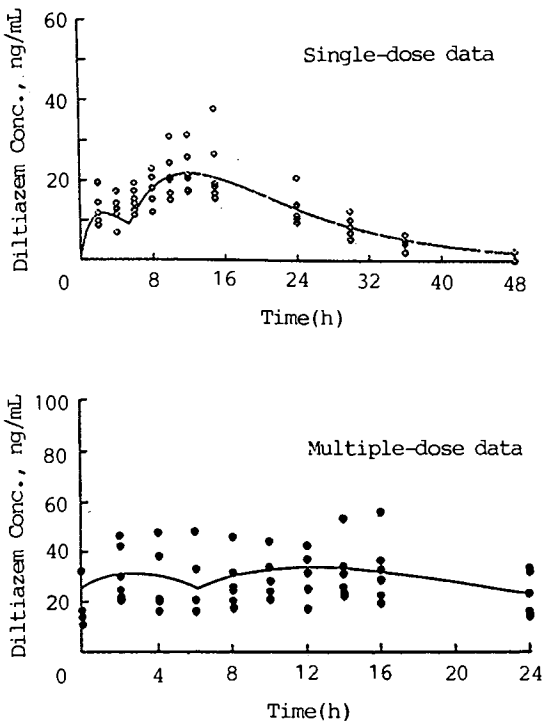


Fig. 4. Plasma diltiazem concentrations after single or repetitive oral administration of HER-SR to six healthy subjects (100-mg dose/day).

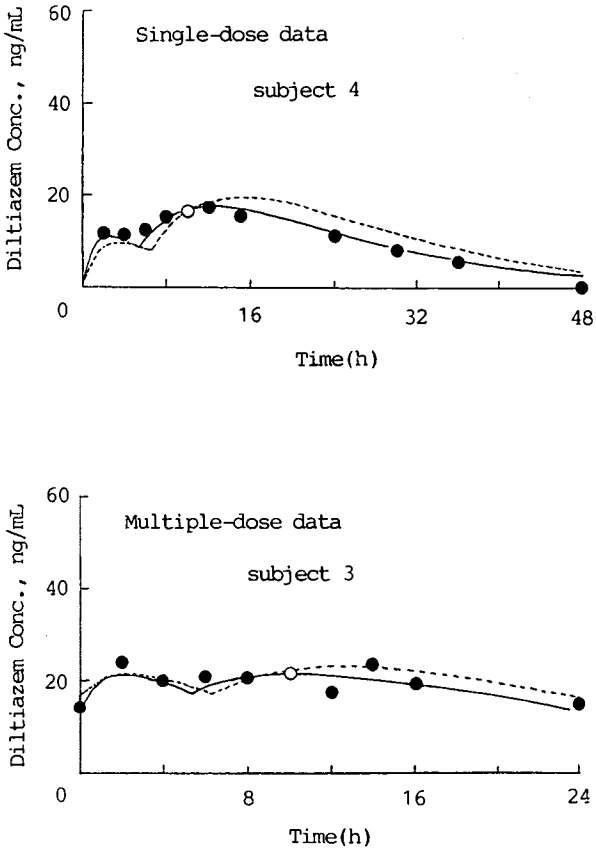


Fig. 5. Bayesian estimation of plasma diltiazem concentration data in humans after single or repetitive oral administration of HER-SR using MULTI (BAYES). (——) Plasma diltiazem concentration calculated using population parameters for single-dose data and one data point at 10 hr (○). (— — —) Plasma diltiazem concentration calculated using population parameters for multiple-dose data and one data point at 10 hr (○). (●) Observed data.

observed data points and simulation curves based on population parameters.

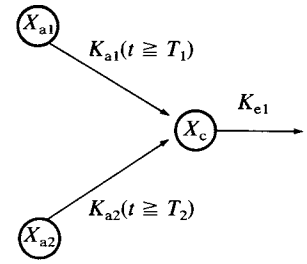
Bayesian estimation was performed using one data point obtained at 10 hr after administration and two population parameters as shown in Table IV. Figure 5 shows an example of the results of Bayesian estimation for plasma diltiazem concentration data after single or repetitive oral administration of HER-SR. As shown in Fig. 5 and Table IV, prediction of the overall plasma diltiazem concentration pattern is possible from one data point. Also, the results estimated using both single- and multiple-dose population parameters were similar to each other. Accordingly, Bayesian estimation was independent of both of the population parameters used in this study.

In conclusion, it was found that multifraction absorption models were valid and suitable for pharmacokinetic analyses of the HER-SR preparation. The approach was applicable to both the comparison of *in vitro* and *in vivo* release profiles and the evaluation of the influence of food on absorption behavior. In addition, it was demonstrated that a two-fraction absorption model is applicable to HER-SR population pharmacokinetic studies in humans.

APPENDIX A

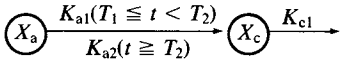
Multifraction Absorption Model

The one-compartment model with two first-order absorption processes from two fractions and one first-order elimination process (Model A) is as follows.



Discontinuous Absorption Model

The one-compartment model with a two-step first-order discontinuous absorption process and one first-order elimination process (Model B) is as follows.



where

X_a = amount of drug in the gastrointestinal tract
X_{ai} = amount of drug in the gastrointestinal tract of the ith fraction
X_c = amount of drug in the central compartment
K_{ai} = absorption rate constant of the ith fraction or the ith step

K_{el} = elimination rate constant
V_d = volume of distribution
F = fraction of absorption
T_i = lag time for absorption of the ith fraction or the ith step

APPENDIX B: SUBPROGRAM LIST FOR MFA-MULTI(V)

```
1000 = = = = = = = = = = = = = = = = = Equations Defined by User = = = = = =
1010 *FUNCTION
1015 CP=0
1020 DEF FNZREN(A,B,C)=(1-EXP(-A*B*C))/(1-EXP(-B*C))
1030 FOR ZLOOP=1 TO ZN
1040   ZTX=T : ZNN=ZN1(J)
1045   ZF=P(2+4*(ZLOOP-1))
1050   ZKA =P(3+4*(ZLOOP-1)) :ZLAG=P(4+4*(ZLOOP-1))
1055   ZD=P(5+4*(ZLOOP-1))
1060   IF ZTX-ZLAG <0 THEN ZNN=ZN1(J)-1:ZTX=T+ZTAU
1080   ZTX=ZTX-ZLAG
1090   IF ZLOOP<ZN THEN GOTO 1120
1100   ZD=DOSE
1110   FOR ZFF=1 TO ZN-1:ZD =ZD-P(6+4*(ZFF-1)):NEXT ZFF
1120   IF ZD<0 THEN ZD=0
1130   ZY1=FNZREN(ZNN,P(1),ZTAU)
1140   ZY2=FNZREN(ZNN,ZKA ,ZTAU)
1150   ZY=ZY1*EXP(-P(1)*ZTX)-ZY2*EXP(-ZKA*ZTX)
1160   ZY=ZY*ZF*ZD*ZKA/(ZKA-P(1))
1170   IF ZY<0 THEN 1190
1180   CP=CP+ZY
1190 NEXT ZLOOP
1200 RETURN
```

Subprogram list written for multifraction absorption model, where ZN is the number of the fraction, ZN1 is the number of the administration, ZLAG is the lag time, ZKA is the absorption rate constant, T is the time after administration, ZTAU is the interval of administration, DOSE is the dose, ZD is the subdose in each fraction, CP is the plasma concentration, and ZTX is the time-lag time.

APPENDIX C

The two-fraction release equation is

$$X = \Sigma X_i = \sum_{i=1}^{n} X_{ai}(1 - e^{-K_{ri}(t-T_i)}) \quad \text{——} \qquad (1)$$

$$X = X_1 \quad \text{for} \quad T_1 \leqq t < T_2$$

$$X = X_1 + X_2 \quad t \geqq T_2$$

where X is the drug amount; X_{ai}, the amount of drug in the ith fraction; K_{ri}, the release rate constant of the ith fraction; and T_i, the lag time for release of the ith fraction.

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