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Studies on Sustained-Release Dosage Forms. II.[1] Pharmacokinetics after Rectal Administration of Indomethacin Suppositories in Rabbits[2]

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The plasma concentration of indomethacin (IM) after administration of sustained-release suppositories containing microencapsulated IM was analyzed by means of the compartment model method and the statistical moment method. The plasma concentration–time course after rectal administration of conventional suppositories followed a two-compartment model with first-order absorption for all doses examined, 6.25, 12.5 and 25 mg. The pharmacokinetic constants did not show dose-dependency.

It was presumed that the plasma concentration–time course after rectal administration of sustained-release suppositories could be accounted for by a two-compartment model with two consecutive first-order input steps. The release rate constants (k_1) of these dosage forms were very small compared with the absorption rate (k_a). Consequently, the release process from sustained-release suppositories was the rate-determining step. This conclusion was confirmed by statistical moment analysis.

Keywords——indomethacin; microcapsule; sustained-release suppository; two-compartment model; statistical moment analysis

In the previous paper,[1] we reported the preparation and bioavailability of sustained-release suppositories of indomethacin (IM), and found that the plasma concentration after rectal administration of this dosage form reached a plateau level without an excessive peak.

The purpose of the present study was to clarify the release rate of IM and its absorption kinetics for sustained-release suppositories containing microencapsulated IM. The evaluations of pharmacokinetic parameters were carried out by means of the compartment model method and the statistical moment analysis method.

Experimental

Materials——The suppositories used were similar to those described in the previous paper.[1] The conventional suppositories were prepared by the fusion method using intact IM and macrogol 4000 as a base. The sustained-release suppositories were prepared by using microencapsulated IM. The content of IM in one suppository was 6.25, 12.5 or 25 mg.

Animal Experiments——For intravenous administration, white male rabbits weighing 3.28 ± 0.26 kg were used. Twenty-five mg of IM was dissolved in 0.5 ml of 1% monoethanolamine (Wako Pure Chemical Industries) and the solution was diluted to 2 ml with 0.1 M phosphate buffer (pH 7.2). The solution was injected intravenously into a rabbit in one minute, and blood samples were taken at the appropriate times. The concentrations of IM in plasma were measured by the same method as described in the previous paper.[1] The plasma concentrations following administration of the conventional and the sustained-release suppositories were those reported previously.[1]

Data Analysis——The computer simulations of plasma concentration were carried out using the SALS program[3] on a NEAC system 900 computer in Kobe University Data Processing Center through a TSS terminal and

with the MULTI program[4] on a NEC N-4700 mini-computer system at Kobe University School of Medicine.

Results and Discussion

Plasma Concentrations after Intravenous Administration

Figure 1 shows the time course of the plasma concentration of IM after intravenous

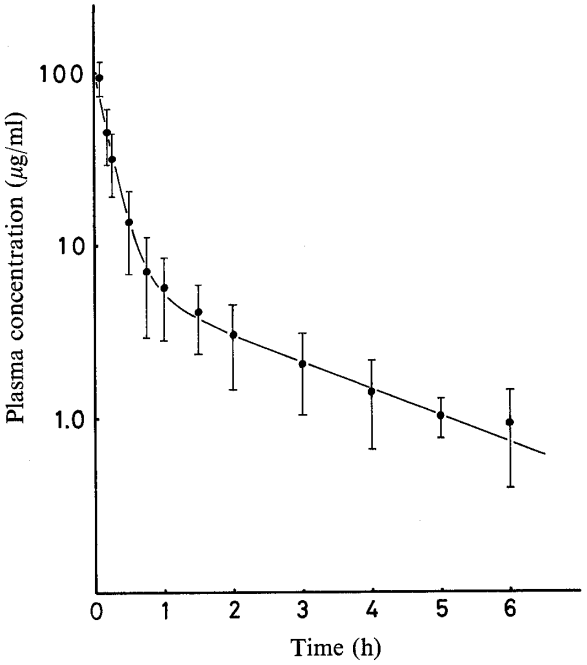


Fig. 1. Plasma Concentrations of Indomethacin Following Intravenous Administration (25 mg dose)

Each point represents the average ± S.D.

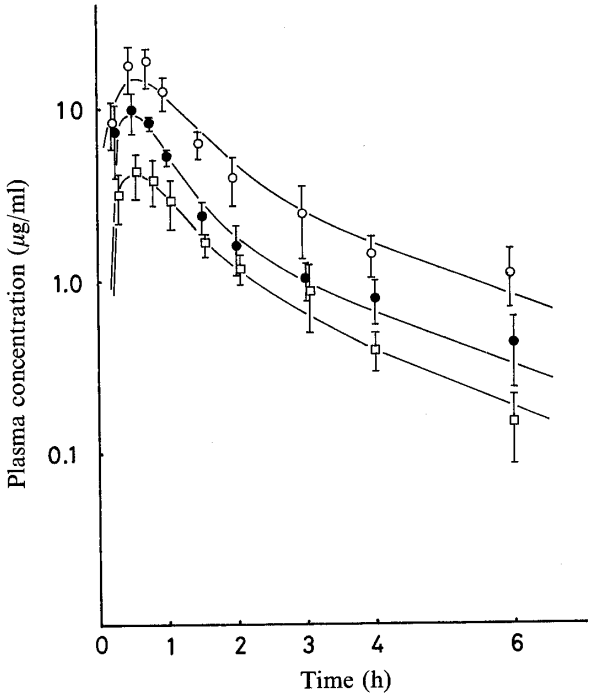


Fig. 2. Plasma Concentrations after Rectal Administration of Conventional Suppositories

—□—, 6.25 mg; —●—, 12.5 mg; —○—, 25 mg. Each point represents the average ± S.D.

TABLE I. Pharmacokinetic Parameters[a] Calculated by the Compartment Model Method

		Intravenous administration[b]	Conventional suppositories[c]		
Dose	(mg)	25	25	12.5	6.25
n[d]		6	6	6	6
B.W.	(kg)	3.28±0.26	2.97±0.20	3.15±0.58	3.34±0.33
A or H	(μg/ml)	118.07±2.111	−34.29±12.35	−25.39±11.91	−8.551±2.962
B or I	(μg/ml)	6.549±0.883	4.309±1.268	2.274±0.569	1.562±0.401
J	(μg/ml)		29.95±10.03	23.13±5.256	6.992±1.862
α	(h^{-1})	5.483±0.444	4.479±1.318	5.550±0.600	5.983±0.591
β	(h^{-1})	0.366±0.032	0.284±0.048	0.326±0.034	0.361±0.349
k_a	(h^{-1})		1.377±0.296	1.938±0.211	1.508±0.328
E_1[e]	(h^{-1})	5.297	4.411	5.378	5.748
E_2	(h^{-1})	0.552	0.352	0.498	0.596
Lag time	(h)		0.136	0.108	0.126

a) Each value is the average±S.D. *b*) $C_p=Ae^{-\alpha t}+Be^{-\beta t}$.
c) $C_p=He^{-\alpha t}+Ie^{-\beta t}+Je^{-k_a t}$. *d*) n is the number of experimental animals.
e) $\alpha+\beta=E_1+E_2$, $E_2=\alpha\beta(AUC)V_1/D$ for *i.v.* and $E_2=\alpha\beta(AUC)V_1/D\cdot F$ for supp.

administration to rabbits. Several studies relating to the pharmacokinetics of IM have been reported, and they suggested that the plasma concentration–time course after intravenous administration followed the two-compartment model.[5] The plasma concentration declined in a biphasic manner as shown in Fig. 1. This profile was, therefore, consistent with a two-compartment model, as shown in Chart 1, model A. The calculated concentration curve fitted the observed plasma data well, as shown in Fig. 1. The parameters obtained are given in Table I.

Plasma Concentrations after Administration of Conventional Suppositories

The plasma levels after administration of conventional suppositories which contained 6.25, 12.5 and 25 mg of IM are shown in Fig. 2. The curve fitting of the time course data was done by applying a two-compartment model with first-order absorption as shown in Chart 1, model B.

The computer analysis of the results obtained after rectal administration of conventional suppositories was carried out by simultaneous fitting of the equation for both the intravenous injection and the suppositories. The pharmacokinetic parameters estimated from these data are listed in Table I. Dose-dependency was not observed in estimating the pharmacokinetic constants. It was found that the maximal plasma concentration was achieved rapidly after rectal administration, *i.e.* T_{max} was 30—45 min.

Plasma Concentrations after Administration of Sustained-Release Suppositories

Figure 3 shows the plasma concentration–time course after rectal administration of sustained-release suppositories. It was found that these dosage forms produced a more gradual rise and a more sustained plateau in plasma concentration of IM than did the conventional suppositories. It seemed that these phenomena were predominantly influenced by the release rate of IM from the sustained-release suppositories. Thus, curve fitting was carried out according to the two-compartment model with two consecutive first-order steps of release and absorption as shown in Chart 1, model C.

In complicated experiments, when a great number of data from many compartments are fitted to a model, it is difficult to obtain reasonable converged values.[6] In this study, therefore, the computer analyses were carried out as follows; the initial values were calculated by

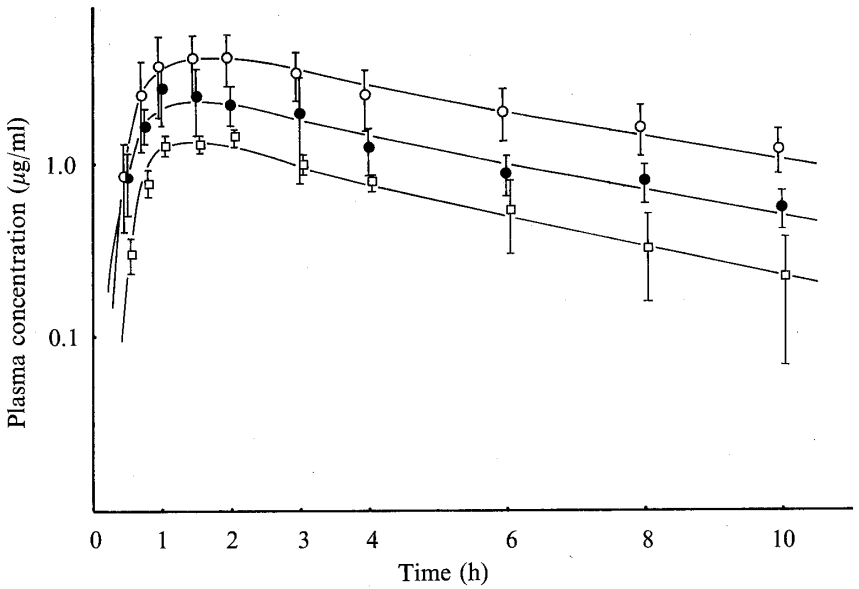


Fig. 3. Plasma Concentration after Rectal Administration of Sustained-Release Suppositories

—□—, 6.25 mg; —●—, 12.5 mg; —○—, 25 mg. Each point represents the average ± S.D.

TABLE II. Pharmacokinetic Parameters Calculated by the Compartment Model Method after Administration of Sustained-Release Suppositories[a)]

Dose (mg)		25	12.5	6.25
n[b)]		9	6	6
B.W.	(kg)	3.43±0.40	2.90±0.27	3.30±0.23
P	(μg/ml)	−1.612±0.79	−1.740±0.262	−1.243±0.225
Q	(μg/ml)	2.588±0.274	1.490±0.856	1.251±0.218
R	(μg/ml)	−4.473±0.840	−1.474±0.218	−0.657±0.082
S	(μg/ml)	3.498±1.412	1.724±0.233	0.650±0.317
α	(h^{-1})	5.292±0.461	5.015±0.464	4.864±0.560
β	(h^{-1})	0.376±0.035	0.343±0.032	0.348±0.049
k_a	(h^{-1})	1.776±0.211	1.656±0.377	1.634±0.498
k_1	(h^{-1})	0.130±0.077	0.138±0.101	0.132±0.015
E_1[c)]	(h^{-1})	5.117	4.882	4.745
E_2	(h^{-1})	0.551	0.476	0.467
Lag time (h)		0.442	0.405	0.452

a) Each value is the average ± S.D., $C_p = Pe^{-\alpha t} + Qe^{-\beta t} + Re^{-k_a t} + Se^{-k_1 t}$.
b) n is the number of experimental animals.
c) $\alpha + \beta = E_1 + E_2$, $E_2 = \alpha\beta(AUC)V_1/D \cdot F$.

simultaneous fitting of the equation for both the conventional and the sustained-release suppositories by the simplex method using the MULTI program, and the final converged values were further analyzed by means of the SALS program using these initial values in order to estimate the parameters exactly. It is known that the simplex method shows good convergency even when the initial values for parameters greatly deviate from the final converged values.[7)] Although the method used in this study was time-consuming, the final parameters obtained were consistent. Each calculated concentration curve was successfully fitted to the observed plasma data, and the derived pharmacokinetic parameters for sustained-release suppositories are presented in Table II. From these results, it appears that the plasma

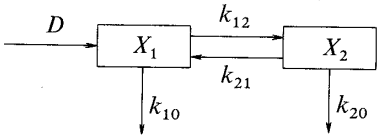
concentration–time course after rectal administration of sustained-release suppositories of IM was satisfactorily accounted for by a two-compartment model with first-order release and absorption steps.

It was found that the release rate constant (k_1) is smaller than the absorption rate constant (k_a), and therefore the release process of IM from the sustained-release suppository was rate-determined. The lag time was increased approximately 4 times compared to conventional suppositories.

model A bolus intravenous administration

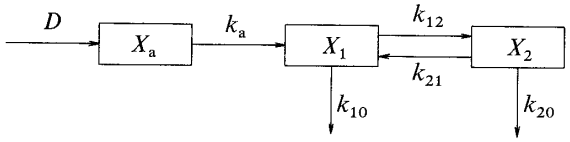
$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (\alpha > \beta)$

$E_1 = k_{12} + k_{10}, \quad E_2 = k_{21} + k_{20}$



model B two-compartment model with first-order absorption

$C_p = He^{-\alpha t} + Ie^{-\beta t} + Je^{-k_a t} \quad (\alpha > \beta)$



model C two-compartment model with two consecutive first-order input steps

$C_p = Pe^{-\alpha t} + Qe^{-\beta t} + Re^{-k_a t} + Se^{-k_1 t}$

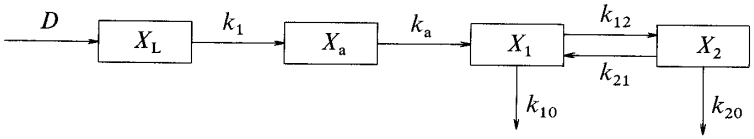


Chart 1. Pharmacokinetic Compartment Models used for Indomethacin

D, dose administered; X_L, amount of drug in dissolution site; X_a, amount of drug in absorption site; X_1, X_2, amounts of drug in central and peripheral compartments; k_1, dissolution rate constant; k_a, absorption rate constant; k_{12}, k_{21}, distribution rate constants; k_{10}, k_{20}, elimination rate constants.

Statistical Moment Analysis

The release and the absorption of IM from each dosage form were compared by means of moment analysis. Table III lists the values of area under the blood concentration curve (*AUC*), mean residence time (*MRT*), mean absorption time (*MAT*), mean dissolution time (*MDT*) and extent of bioavailability (*EBA*) for each dosage form. The *MDT* value was greater than the *MAT* value. This result suggested that the release process of IM in sustained-release suppositories was rate-determining, as in the compartment model analysis. *AUC* values of conventional suppositories were nearly equal to those of sustained-release suppositories. No difference in bioavailability could be seen betwen sustained-release suppositories and conventional suppositories ($p < 0.05$).

Wiegand *et al.*[8] showed that the percentages of released drug per unit time given in the literature for many sustained-release preparations followed apparent first-order rate proc-

TABLE III. Pharmacokinetic Parameters Calculated by the Moment Method

	Intravenous administration	Conventional suppositories			Sustained-release suppositories		
Dose (mg)	25	25	12.5	6.25	25	12.5	6.25
AUC (μg·h/ml)[a]	34.409	31.484	14.474	7.773	31.518	15.420	7.605
	±0.444	±3.360	±1.483	±0.451	±1.882	±1.390	±0.484
MRT (h)	1.204	2.881	2.216	2.088	7.744	6.382	5.270
MAT		1.607	1.012	0.884	9.540	5.178	4.066
MDT (h)[c]					4.933	4.166	3.182
EBA (%)[d]	100	91.50	84.33	90.36	91.60	89.61	88.41

a) Each value is the average ± S.D.
b) $MAT = MRT_{supp.} - MRT_{i.v.}$
c) $MDT = MAT_{sus.supp.} - MAT_{con.supp.}$
d) $EBA\ (\%) = D_{i.v.} \cdot AUC_{supp.} / D_{supp.} \cdot AUC_{i.v.} \times 100.$

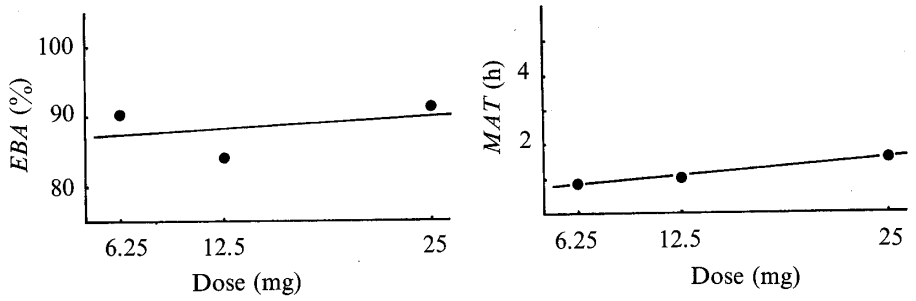


Fig. 4. Dependencies of *EBA* and *MAT* on the Dose for Conventional Suppositories

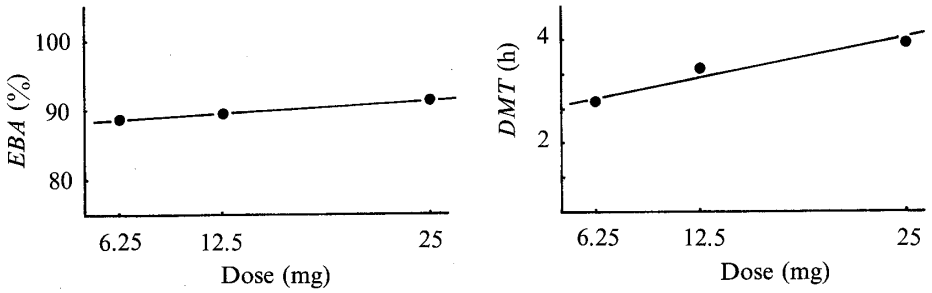


Fig. 5. Dependencies of *EBA* and *MDT* on the Dose for Sustained-Release Suppositories

esses. In other cases, some sustained-release preparations released drugs by apparent zero-order rate processes.[9]

In order to differentiate first-order release and zero-order release, the relationship between *EBA* and *MAT* or *MDT* was examined. Figure 4 shows the dependencies of *EBA* and *MAT* on the dose in the conventional suppositories. The straight lines are the regression lines obtained by the least-squares method.

$$EBA\ (\%) = 86.68 + 0.136 \cdot D \qquad (r = 0.328)$$

$$MAT\ (\text{h}) = 0.587 + 0.040 \cdot D \qquad (r = 0.986,\ p < 0.05)$$

Where D is the dose (mg), and r is the correlation coefficient. It was found that both *EBA* and *MAT* remain almost constant with respect to dose. Therefore, the absorption rate can be

regarded as first-order.[10]

Figure 5 shows the dependencies of *EBA* and *MDT* on the dose in the sustained-release suppositories,

$$EBA\ (\%) = 87.43 + 0.168 \cdot D \qquad (r = 0.998,\ p < 0.01)$$

$$MDT\ (\mathrm{h}) = 2.799 + 0.089 \cdot D \qquad (r = 0.966,\ p < 0.05)$$

EBA values remained constant with respect to dose. The regression line of *MDT vs.* dose had a slope of nearly zero ($p < 0.05$). Therefore, these results indicated that the release of IM from the sustained-release suppositories prepared in this study is an apparent first-order process. From these results, it was concluded that the compartment model represented above is reasonable.

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References and Notes

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