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Biopharmaceutical Evaluation of Sustained-Release Ethylcellulose Microcapsules Containing Cefadroxil and Cephradine Using Beagle Dogs[1)]

TAKAHIRO UCHIDA and SHIGERU GOTO*

Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan

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Two cephem antibiotics, cefadroxil and cephradine, were microencapsulated with ethyl cellulose using a solvent evaporation process in liquid paraffin containing sorbitan tristearate as a dispersing agent. These products were administered to beagle dogs and biopharmaceutical evaluations were made of the sustained-release effect. First, Vallner's method was employed for the assessment of the sustained-release ethylcellulose microcapsules. The controlled release effectiveness was close to 0.8 for ethylcellulose microcapsules containing 70% cefadroxil and 60% cephradine. Second, assessments were made using pharmacokinetic parameters based on a model allowing for the gastric-emptying and intestinal transit rates of the drug itself and the solid state drug contained in the microcapsules using nonlinear least-squares regression. The results obtained showed that transfer of the rate-limiting step to the release process from the absorption process could be observed in microcapsules containing 70% cefadroxil but not in the case of microcapsules containing 60% cephradine. The release rates calculated on the basis of the above model correlated well with the release rate in dissolution tests at pH 6.8. Finally, a new nomogram was introduced for the design of sustained-release formulations in the future.

Keywords——microencapsulation; ethylcellulose; cefadroxil; cephradine; sustained release; pharmacokinetic model; dissolution; beagle dog

Sustained-release preparations have frequently been prepared by dispersing a drug in polymer matrices where the polymer is to act as a rate-controlling barrier. Use of such preparations may result in a number of benefits such as reduction of the frequency of dosing, lowered adverse reactions and improved patient compliance. Applications of ethylcellulose microcapsules as drug carriers have been studied to an increasing extent recently. However, *in vivo* evaluations of ethylcellulose microcapsules containing drugs for oral use have rarely been reported in the literature. Current methods for ethylcellulose microcapsule preparation involve either a solvent evaporation process in water or one in liquid paraffin at elevated temperature.[1,2)] Small amounts of surfactants are needed to disperse such microcapsules in water or liquid paraffin. In the present study, two cephem antibiotics were chosen as model drugs from a consideration of their short biological half-lives. Better antimicrobial activities by maintaining more constant plasma levels have been cited as advantages which may result from repeated oral administration of sustained-release preparations at long intervals instead of that of standard regular-release preparations at short intervals.

The purpose of the present study was to assess the feasibility of formulating sustained-release microcapsules of a dispersing type using ethylcellulose as a rate-controlling barrier from plasma concentration–time curves of the antibiotics released. Two methods, Vallner's method[3)] and calculation of pharmacokinetic parameters based on a proposed model, were applied.

Experimental

Materials——Cefadroxil and cephradine were kindly provided by Towa Pharmaceutical Co., Osaka, Japan, and were sieved through a 270 mesh (58 μm). Ethylcellulose from Tokyo Kasei Co., Tokyo, Japan, viscosity of 90—110 cps grade, was used. Other reagents were all of special reagent grade.

Preparation of Ethylcellulose Microcapsules——A solvent evaporation method in liquid paraffin using sorbitan tristearate as a dispersing agent was employed as described previously.[1]

Dissolution Experiments——The procedures and apparatus were the same as described in the previous paper.[1]

Measurement of Plasma Levels of Cefadroxil and Cephradine——The concentration of cefadroxil or cephradine was determined by the high performance liquid chromatography (HPLC) method. To 1 ml of plasma, 20 μl of the internal standard (cephalexin solution, 1 mg/ml) and 1 ml of 10% trichloroacetic acid were added, and mixed by shaking for 15 min. After centrifugation at 3000 rpm for 15 min, 1 ml of the upper layer was taken. To this, 5 ml of diethyl ether was added and mixed by shaking for 20 min. Then, 100 μl of water layer was injected into a high-performance-liquid chromatograph (Shimadzu LC-3A, Kyoto, Japan) equipped with a ultraviolet (UV) detector (Shimadzu SPD-3A), an integrator (Shimadzu C-R1A) and a reversed-phase octadecyl column (4.6 × 150 mm, Shim-pack CLC-ODS). The mobile phase employed was acetonitrile : tetrahydrofuran : 0.5 mM KH_2PO_4 solution : acetic acid = 7 : 3 : 150 : 6 (cefadroxil) or 7 : 3 : 100 : 4 (cephradine) with a flow rate of 1.5 ml/min. Wavelengths of 263 nm for cefadroxil and 260 nm for cephradine were selected. The temperature of the column was maintained at 40 °C.

Animals——Male beagle dogs weighing 12.5—15.1 kg were fasted overnight and used for the experiments. They were allowed free access to water, and no food was given until the last blood sample had been taken.

Single Intravenous Administration——Each of the cephem antibiotics (125 mg) was dissolved in 0.3 ml of 1 N HCl and 5 ml of isotonic NaCl solution and administered intravenously *via* the cephalic vein. Blood samples were withdrawn from the caphalic vein with a heparinized syringe up to 8 h after the administration, and the collected blood was centrifuged at 3000 rpm for 15 min to obtain plasma.

Oral Administration——Four beagle dogs were fasted overnight and the formulations were administered. A drug solution containing 125 mg in 10 ml of isotonic NaCl solution was orally administered with 20 ml of purified water. Special hard gelatin capsules (inner radius, 1.4 cm; length, 3.9 cm) were filled with powder or microcapsules of the two cephem antibiotics. Double oral administration of the powder (125 mg × 2) at 0 and 6 h and single oral administration of the microcapsules corresponding to 250 mg of the antibiotics at 0 h, were made with 30 ml of water. Blood samples were withdrawn from the cephalic vein of the front leg up to 12 h after the administration. These procedures have been described in detail the previously.[4]

Calculation of Pharmacokinetic Parameters——Pharmacokinetic parameters were calculated by nonlinear least-squares regression employing the pharmacokinetic analysis program "MULTI" for microcomputers.[5]

Results and Discussion

Plasma Concentration Curves of Cephem Antibiotics Following Double Oral Administration of Powder and Single Oral Administration of Ethylcellulose Microcapsules

The plasma cefadroxil and cephradine levels after oral dosing of the standard regular-release preparation (powder) at an antibiotic dose of 125 mg/body at 0 and 6 h were compared with those of the sustained-release preparation (ethylcellulose microcapsule) administered in a single dose of 250 mg/body at 0 h. The results are shown in Figs. 1 and 2. In the case of ethylcellulose microcapsules containing 70% cefadroxil, the maximum plasma antibiotic concentration (C'_{max}) after microcapsule dosing was comparable to that (C_{max}) after the first dose of the regular-release preparation. If C_{max} is the desired maximum concentration of a drug in the body following a single dosing of the regular-release preparation based on many years' experience, the same maximum concentration may be required for the sustained-release preparation, $C_{max} = C'_{max}$. The above experimental fact is thus very favorable as one of the desirable sustained-release properties.[6]

Assessment by Vallner's Method[3]

A method for testing whether a newly developed sustained-release preparation is functioning has been proposed by Vallner *et al.*[3] Two important parameters are suggested for evaluating sustained-release preparations: (1) the length of time for which a sustained-release preparation maintains a desirable plasma level, and (2) the rate at which the sustained-release preparation reaches that desirable plasma level. In accordance with Vallner's report,[3] certain

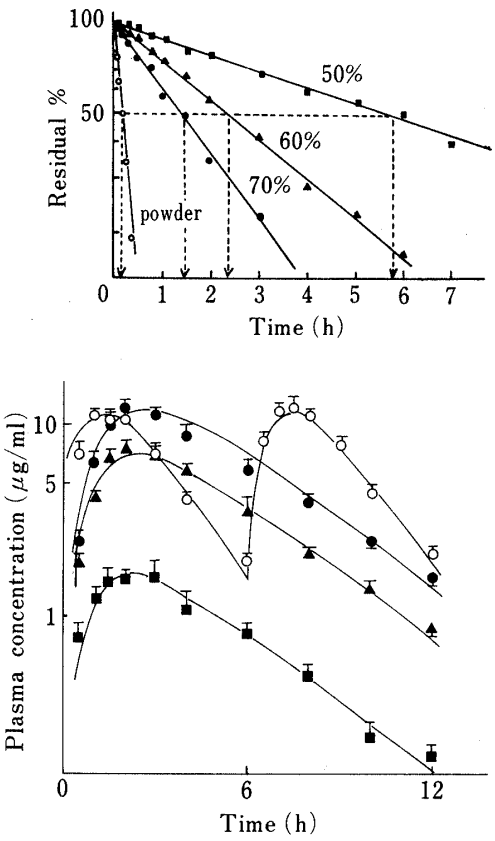


Fig. 1. Plasma Cefadroxil Levels after Single Oral Administration of Ethyl Cellulose Microcapsules Containing 70% (●, 250 mg/body; $n=4$), 60% (▲, 250 mg/body; $n=4$) and 50% (■, 250 mg/body; $n=4$) Cefadroxil and Double Doses of Cefadroxil Powder (○, 125 mg/body × 2; $n=4$) in Beagle Dogs

The plasma concentration–time curves are computer fitted lines. Each point represents a mean and the vertical line indicates the standard deviation. The upper figure shows the corresponding dissolution patterns of microcapsules at pH 6.8, 50 rpm and 37 °C. The dotted lines and arrows represent T_{50} (h) for the *in vitro* dissolution patterns.

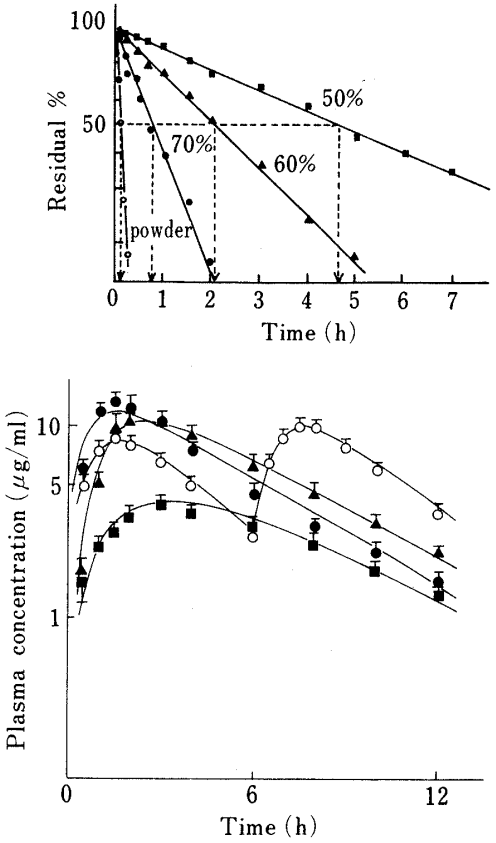


Fig. 2. Plasma Cephradine Levels after Single Oral Administration of Ethyl Cellulose Microcapsules Containing 70% (●, 250 mg/body; $n=4$), 60% (▲, 250 mg/body; $n=4$) and 50% (■, 250 mg/body; $n=4$) Cephradine and Double Doses of Cephradine Powder (○, 125 mg/body × 2; $n=4$) in Beagle Dogs

The plasma concentration–time curves are computer fitted lines. Each point represents a mean and the vertical line indicates the standard deviation. The upper figure shows the corresponding dissolution patterns of microcapsules at pH 6.8, 50 rpm and 37 °C. The dotted lines and arrows represent T_{50} (h) for the *in vitro* dissolution patterns.

assumptions are made in relation to the above-mentioned evaluation parameters, as follows. (a) The desirable plasma level is defined as the concentration range varying from the trough level, which is reached just prior to the time when the second dose of the standard regular-release preparation in normally given, to the maximum plasma concentration observed, generally following the second dose of the regular-release preparation. (b) The apparent absorption rate is defined as the time needed to reach the trough plasma concentration as stated in (a) following administration of the first dose of the regular-release or sustained-release preparation.

Figure 3 illustrates the parameters employed in this study. C_{min} is the initial plasma concentration in the sequential administration of a regular-release dosing regimen, C_{max} is the maximum plasma concentration for a sequentially administered regular-release preparation, and R_{SR} is the apparent absorption rate on the basis of which the time necessary for a given dose of drug to first reach a plasma concentration of C_{min} can be measured. AUC is the area under the plasma concentration–time curve within the desirable plasma concentration range

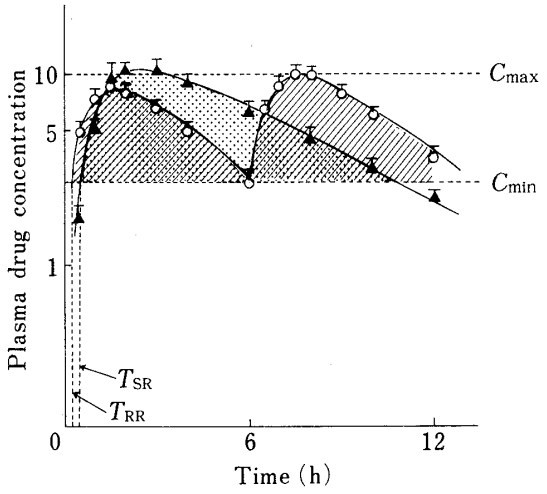


Fig. 3. Illustration of Parameters in Vallner's Method

▨, AUC_{RR}; ▩, AUC_{SR}.
See text for explanation of T_{SR}, T_{RR}, RR and SR.

TABLE I. Parameters Calculated on the Basis of Vallner's Method

Formulation[a]	*ARE*	*CRE*
CDX-70	0.366±0.039	0.787±0.064
CDX-60	0.257±0.032	0.348±0.031
CDX-50	0	0
CED-70	1.17 ±0.18	0.673±0.061
CED-60	0.418±0.034	0.790±0.082
CED-50	0.197±0.035	0.075±0.017

a) CDX, cefadroxil; CED, cephradine. The numbers represent the percentages of cephem antibiotics contained in the ethyl cellulose microcapsules.

between the C_{min} and C_{max} levels. The subscripts, SR and RR, refer to the sustained-release and regular-release preparations, respectively. The area above C_{max} in the sustained-release preparation can be used to evaluate the "dose dumping" of a preparation. The area below C_{min} is assumed to be therapeutically ineffective. However, an important estimate of the preparation effectiveness is given by *CRE* (the controlled release effectiveness) defined as in Eq. 1.

$$CRE = AUC_{SR}/AUC_{RR} \tag{1}$$

If the value of *CRE* is close to 1, a single dose of the sustained-release preparation is equivalent to multiple doses of the regular-release preparation. *CRE* can be useful as a parameter for assessing the sustained-release preparation efficiency.

Another valuable parameter for comparing the sustained-release preparation and the regular-release one is the ratio of the time to reach C_{min} for the sustained-release preparation (T_{SR}) to that for the regular-release preparation (T_{RR}). The term R is calculated for the sustained-release (SR) and regular-release (RR) preparations, as follows:

$$R_{SR} = C_{min}/T_{SR} \text{ and } R_{RR} = C_{min}/T_{RR} \tag{2}$$

The absorption rate effectiveness (*ARE*) may be determined from Eq. 3.

$$ARE = T_{RR}/T_{SR} \tag{3}$$

Furthermore, values close to 1 indicate that a single dose of the sustained-release preparation reaches an effective concentration in the plasma at the same rate as the first dose of a sequential regimen of the regular-release preparation.

Application of the above method in the present study on ethylcellulose microcapsules containing cefadroxil or cephradine (sustained-release preparations) and powders of cefadroxil or cephradine (regular-release preparations), suggested that the data obtained provided a good assessment of the plasma concentration as shown in Table I.

The *CRE* was close to 0.8 for ethylcellulose microcapsules containing 70% cefadroxil and 60% cephradine. It seems reasonable to consider therefore that the above microcapsules may be better than others as a sustained-release preparation. Ethylcellulose microcapsules containing 70% cephradine and 60% cefadroxil gave a decreased *CRE*. Moreover, calculations for ethylcellulose microcapsules containing 50% cefadroxil gave $ARE=0$ and $CRE=0$. It can be readily seen from these data that such a preparation may be an unavailable one.

Assessment Using Pharmacokinetic Parameters

In a previous paper,[4] we introduced a relatively simple pharmacokinetic model allowing for the gastric emptying and intestinal-transit rates of a drug itself and a solid-state drug contained in microcapsules. This simplified model (shown in Chart 1) assumes a first-order release rate from the solid dosage form, a first-order absorption rate from solution, a first-order transition rate of the drug dissolved in solution, first-order transition rates of the solid-state drug itself and solid-state drug contained in microcapsules from the absorption compartment, and a linear two compartment open model disposition. Under these conditions, the representative equations for the drug concentration in the plasma at a time t after intravenous injection (C^{IV}), after oral administration of solution (C^{S}) and that of powder of the drugs (C^{M}) are given by Eqs. 4, 5 and 6, respectively.

$$C^{IV}=C\cdot\left[\frac{(\alpha-k_{21})}{(\alpha-\beta)}e^{-\alpha t}+\frac{(k_{21}-\beta)}{(\alpha-\beta)}e^{-\beta t}\right] \tag{4}$$

$$C^{S}=C'\cdot k_a\left[\frac{(k_{21}-\alpha)}{(k_a+k'_{gi}-\alpha)(\beta-\alpha)}e^{-\alpha t}+\frac{(k_{21}-\beta)}{(k_a+k'_{gi}-\beta)(\alpha-\beta)}e^{-\beta t}+\frac{(k_{21}-k_a-k'_{gi})}{(k_a+k'_{gi}-\alpha)(k_a+k'_{gi}-\beta)}e^{-(k_a+k'_{gi})t}\right] \tag{5}$$

$$C^{M}=C''\cdot k_a\cdot k_r\left[\frac{(k_{21}-k_r-k_{gi})}{(k_a+k'_{gi}-k_r-k_{gi})(\alpha-k_r-k_{gi})(\beta-k_r-k_{gi})}e^{-(k_r+k_{gi})t}+\frac{(k_{21}-k_a-k'_{gi})}{(k_r+k_{gi}-k_a-k'_{gi})(\alpha-k_a-k'_{gi})(\beta-k_a-k'_{gi})}e^{-(k_a+k'_{gi})t}+\frac{(k_{21}-\alpha)}{(k_r+k_{gi}-\alpha)(k_a+k'_{gi}-\alpha)(\beta-\alpha)}e^{-\alpha t}+\frac{(k_{21}-\beta)}{(k_r+k_{gi}-\beta)(k_a+k'_{gi}-\beta)(\alpha-\beta)}e^{-\beta t}\right] \tag{6}$$

k_r and k_a are the first-order rate constants for the drug release into the gastro-intestinal (GI) juices from cefadroxil or cephradine powder and for the absorption of cefadroxil or cephradine dissolved in the GI juices, respectively. k'_{gi} and k_{gi} are the first-order rate constants for the flux of cefadroxil or cephradine dissolved in the GI juices into the nonabsorption compartment from the absorption compartment of the GI tract and for the movement of solid state cefadroxil or cephradine itself into the nonabsorption compartment from the absorption compartment of the GI tract, respectively.[9] C, C' and C'' are constants. α and β are the first-order macro-constants describing the disposition of cefadroxil and that of cephradine, respectively. k_{21} is the first-order exit rate constant into the central compartment from the peripheral compartment for cefadroxil or cephradine.

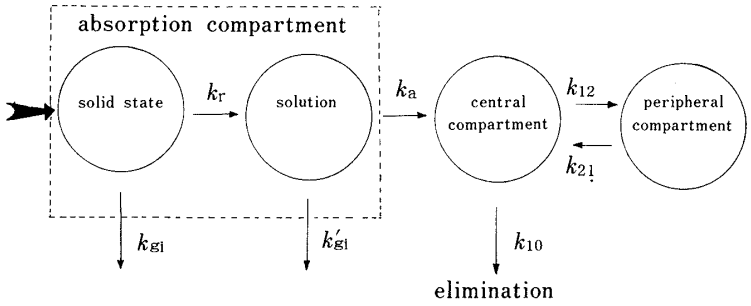


Chart 1. Pharmacokinetic Model Used in This Study

TABLE II. Pharmacokinetic Parameters for Cefadroxil Following Injection, Oral Administration of Solution and Solid State Preparations Based on the Pharmacokinetic Model as Shown in Chart 1

Parameters	Injection	Solution	Powder	Microcapsules		
				CDX-70	CDX-60	CDX-50
C (μg/ml)	50.6	51.4	47.5	46.7	47.2	48.3
	(5.2)	(4.2)	(3.5)	(4.9)	(1.5)	(2.2)
C' (μg/ml)	—	46.9	45.2	42.9	44.2	44.5
		(5.1)	(4.2)	(5.4)	(3.2)	(3.3)
C'' (μg/ml)	—	—	46.3	93.6	89.8	92.7
			(5.1)	(6.5)	(11.9)	(15.7)
α (h^{-1})	2.67	2.84	3.42	2.77	2.60	2.73
	(0.34)	(0.49)	(0.55)	(0.25)	(0.31)	(0.24)
β (h^{-1})	0.403	0.449	0.389	0.401	0.395	0.381
	(0.046)	(0.036)	(0.045)	(0.067)	(0.040)	(0.053)
k_{12} (h^{-1})	0.983	0.984	1.37	0.957	0.929	1.05
	(0.195)	(0.305)	(0.37)	(0.231)	(0.334)	(0.13)
k_{21} (h^{-1})	1.21	1.42	1.51	1.16	1.21	1.19
	(0.05)	(0.30)	(0.20)	(0.25)	(0.21)	(0.19)
k_{10} (h^{-1})	0.884	0.893	0.877	0.863	0.863	0.874
	(0.042)	(0.050)	(0.037)	(0.041)	(0.052)	(0.051)
k_a (h^{-1})	—	0.891	1.00	1.06	0.972	1.07
		(0.125)	(0.17)	(0.06)	(0.100)	(0.15)
k'_{gi} (h^{-1})	—	0.012	0.013	0.014	0.013	0.020
		(0.002)	(0.003)	(0.001)	(0.002)	(0.003)
k_r or k'_r (h^{-1})	—	—	8.14	0.398[a)]	0.242[a)]	0.101[a)]
			(2.12)	(0.041)	(0.023)	(0.012)
k_{gi} (h^{-1})	—	—	0.905	0.100	0.262	0.778
			(0.236)	(0.008)	(0.023)	(0.125)
SS[b)]	0.073	0.221	0.326	0.367	0.426	0.317
	(0.025)	(0.054)	(0.067)	(0.064)	(0.082)	(0.051)

The parameters were estimated using the pharmacokinetic analysis program "MULTI" for microcomputers.[5] The figures in parentheses represent the standard deviations. In the case of injection, oral administration of solution and solid state preparations, one-, two- and three-line fittings were performed, respectively. Significantly different from the k_a value of powder at *a*) $p<0.001$. *b*) The residual sum of squares (SS) was calculated from $SS=\sum W_i\cdot(C_i(\text{obs.})-C_i(\text{cal.}))^2$, where W_i is the weight of the points. $(C_i)^{-2}$ was adopted as the weight, where C_i is the value of the i-th point.

In general, it is difficult to interpret the plasma concentration–time profile following oral administration of drug preparations and to assess the drug absorption quantitatively. Even in the relatively simple case of first-order absorption, the situation is complicated by the "flip-flop" phenomenon[7] and the problem of "vanishing exponential terms".[8] To obtain reliable release and absorption rate information, a model-dependent approach provided by the

TABLE III. Pharmacokinetic Parameters for Cephradine Following Injection, Oral Administration of Solution and Solid State Preparations Based on the Pharmacokinetic Model as Shown in Chart 1

Parameters	Injection	Solution	Powder	Microcapsules		
				CED-70	CED-60	CED-50
C (μg/ml)	43.5	45.6	43.9	38.3	37.2	41.4
	(4.0)	(7.8)	(3.2)	(3.8)	(3.3)	(1.6)
C' (μg/ml)	—	39.5	38.1	35.2	34.2	37.5
		(5.2)	(4.2)	(4.1)	(6.2)	(2.2)
C'' (μg/ml)	—	—	37.2	72.3	69.1	78.1
			(4.1)	(16.4)	(8.2)	(11.2)
α (h^{-1})	2.77	3.41	2.93	2.64	2.31	2.61
	(0.38)	(0.42)	(0.32)	(0.31)	(0.42)	(0.25)
β (h^{-1})	0.223	0.235	0.241	0.225	0.212	0.207
	(0.034)	(0.025)	(0.014)	(0.027)	(0.024)	(0.021)
k_{12} (h^{-1})	1.28	1.68	1.32	1.34	1.02	1.17
	(0.28)	(0.35)	(0.25)	(0.24)	(0.34)	(0.23)
k_{21} (h^{-1})	1.30	1.43	1.35	1.21	1.07	1.21
	(0.07)	(0.21)	(0.17)	(0.20)	(0.21)	(0.21)
k_{10} (h^{-1})	0.509	0.520	0.493	0.458	0.432	0.447
	(0.068)	(0.054)	(0.042)	(0.031)	(0.092)	(0.043)
k_a (h^{-1})	—	0.792	0.859	0.869	0.791	0.750
		(0.124)	(0.091)	(0.073)	(0.105)	(0.112)
k'_{gi} (h^{-1})	—	0.088	0.095	0.097	0.088	0.082
		(0.011)	(0.021)	(0.017)	(0.010)	(0.012)
k_r or k'_r (h^{-1})	—	—	7.29	2.88[a]	0.586	0.192[b]
			(1.75)	(0.54)	(0.078)	(0.033)
k_{gi} (h^{-1})	—	—	1.41	0.561	0.147	0.336
			(0.34)	(0.121)	(0.025)	(0.084)
SS[c]	0.035	0.217	0.294	0.371	0.296	0.354
	(0.011)	(0.035)	(0.054)	(0.101)	(0.041)	(0.122)

The parameters were estimated using the pharmacokinetic analysis program "MULTI" for microcomputers.[5] The figures in parentheses represent the standard deviations. In the case of injection, oral administration of solution and solid state preparations, one-, two- and three-line fittings were performed, respectively. Significantly different from the k_a value of powder at *a*) $p<0.001$, *b*) $p<0.05$. *c*) The residual sum of squares (SS) was calculated from $SS=\sum W_i \cdot (C_i(\text{obs.})-C_i(\text{cal.}))^2$, where W_i is the weight of the points. $(C_i)^{-2}$ was adopted as the weight, where C_i is the value of the i-th points.

pharmacokinetic analysis program "MULTI" for microcomputers[5] using intravenous and oral reference plasma concentration–time data following administration of drug solution, powder and microcapsules containing cefadroxil or cephradine, was applied. The main pharmacokinetic parameters calculated from Eqs. 4, 5 and 6 are summarized in Tables II and III.

Rapid release was observed for the regular-release preparations (powders of cefadroxil and cephradine). However, the value of the release rate constant (k_r') after administration of sustained-release preparations (microcapsules containing cefadroxil or 60% and 50% cephradine) was smaller than that of the absorption rate constant (k_a) of cefadroxil or cephradine. These findings indicate transfer of the rate-limiting step to the release process from the absorption process in the light of the kinetic behavior of the consecutive release and absorption processes. This is favorable as one of the sustained-release properties. However, such transfer of the rate-limiting step could not be observed in the case of microcapsules containing 70% cephradine.

The literature[10] on drug absorption, gastric emptying and intestinal motility suggests that a drug leaves the GI tract within 9—12 h after administration. Based on such an effective release/absorption time, it follows that the maximum absorption half-life should be 3—4 h

(0.17—0.23 h^{-1} as the k_r value). Preparations which release a drug more slowly are likely to result in an unacceptably low bioavailability. According to Gibaldi and Patrick,[10] a preparation that releases a well-absorbed drug in a first-order fashion with a half-life of 3 h (0.23 h^{-1} as the k_r or k_a value) results in a bioavailability ranging from 88 to 94% of the dose if the absorption time is limited to 9—12 h. With these principles in mind, we judged that ethylcellulose microcapsules containing 70% cefadroxil may represent an effective and available preparation, and those containing 60% cefadroxil may be next best. Moreover, good agreement was observed between the above assessment and the previous evaluation based on Vallner's method.

Relationship between the Pharmacokinetic Properties of a Drug and Control Ratio of Drug Release from the Sustained-Release Preparation

A simple nomogram performed with model 1 in Chart 2 for the establishment and evaluation of sustained-release preparations was given in a previous paper[1]. We prepared a new nomogram (Fig. 4) based on model 2 (Chart 2) which incorporated the release process (k_r as the rate constant) into model 1.

Figure 4 was drawn on the basis of the following assumptions: (a) the sustained-release preparation (ethylcellulose microcapsules) is given at 0 h (once a day; dosing amount, D_0^m) and the standard regular-release preparation (powder) is given at 0 and 12 h (twice a day; dosing amount, $D_0 \times 2$), that is, the dose of the sustained-release preparation is generally twice that of the regular-release preparation ($D_0^m/D_0 = 2$); and (b) the maximum plasma concentration after

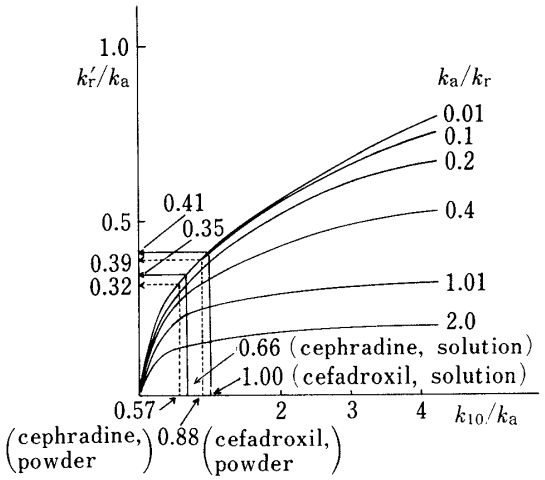
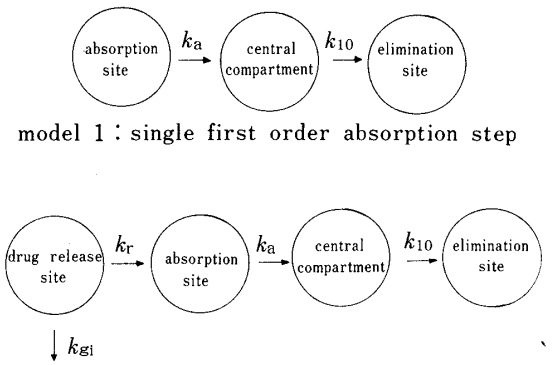


Fig. 4. Interrelationship between k_r'/k_a and k_{10}/k_a in the Case where D_0^m/D_0 is 2

The calculation was performed based on model 2 in Chart 2. See text for explanation of k_r, k_r', k_a, k_{10} and D_0^m/D_0.



model 1 : single first order absorption step

model 2 : two consecutive first-order absorption steps ($k_{gi}=0$ for preparation of Fig. 4)

Chart 2. Fundamental Pharmacokinetic Models for Construction of a Nomogram as Shown in a Previous Paper[2] and Fig. 4

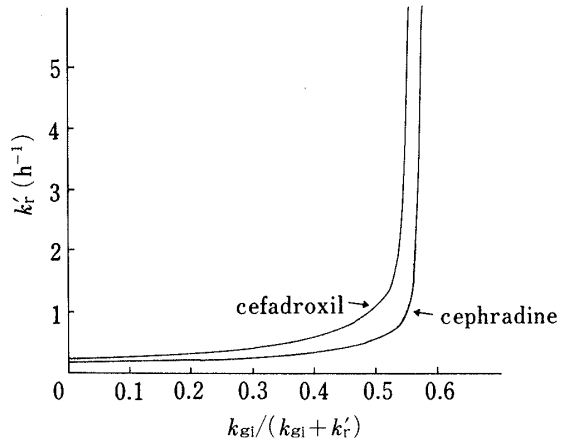


Fig. 5. Relationship between k_r' and $k_{gi}/(k_{gi}+k_r')$ for Sustained-Release Preparations of Cefadroxil and Cephradine

See text for explanation of k_r' and k_{gi}.

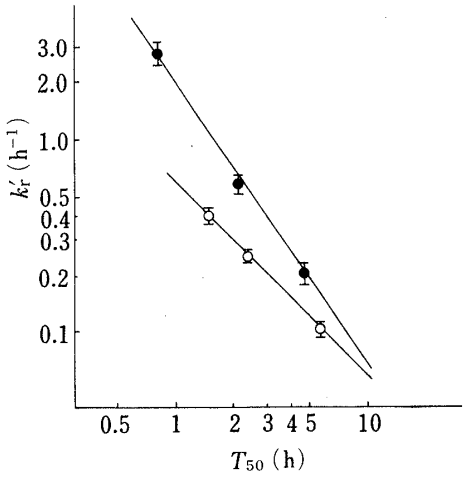


Fig. 6. log–log Plots of k_r' Calculated on the Basis of the Proposed Pharmacokinetic Model (Chart 1) against T_{50} Determined by Dissolution Tests

Refer to the dissolution patterns in Figs. 1 and 2 for the T_{50} (h) of cefadroxil (○) and cephradine (●).

administration of the sustained-release preparation is just equal to that after the first dose of the regular-release preparation.

The k_{10}/k_a value representing the pharmacokinetic properties of the drug itself, was plotted against k_r'/k_a representing the control ratio of the release rate constant of the sustained-release preparation (k_r') to the absorption rate constant of the drug itself as shown in Fig. 4. Model 2 in Chart 2 differs from the pharmacokinetic model for cefadroxil or cephradine shown in Chart 1. Unfortunately, preparation of a general nomogram based on Chart 1 is impossible, since there are many combinations of the values of the rate constants (k_{gi}, k_{gi}', k_{12}, k_{21} and k_{10}). As a second-best approach, we attempted to use the nomogram (Fig. 4) based on model 2 in Chart 2 for assessment of the sustained-release properties of ethylcellulose microcapsules containing cephem antibiotics. Moreover, the effect of an increase in k_{gi} value with respect to the k_r' value was checked. Employing pharmacokinetic parameters for cefadroxil or cephradine, the relationship between k_r' and $k_{gi}/(k_r'+k_{gi})$ was examined. If $k_{gi}/(k_r'+k_{gi})$ was restricted to values from 0 to 0.2, the k_r' value is remained almost constant (Fig. 5).

The k_{10}/k_a values become 0.88 for powder of cefadroxil and 1.0 for solution of cefadroxil by calculation using the data listed in Table II. Simultaneously, values of 0.57 and 0.66 are obtained for powder and solution of cephradine. On the other hand, the k_a/k_r values for the standard regular-release preparations (powders of cefadroxil and cephradine) are 0.123 for cefadroxil and 0.117 for cephradine. Then, taking the $k_a/k_r=0.1$ curve is for them, 0.40 for cefadroxil and 0.34 for cephradine can be obtained as the mean values of k_r'/k_a in the direction of the arrows (Fig. 4). The theoretical $k_r'=0.39\,h^{-1}$ for cefadroxil and theoretical $k_r'=0.25\,h^{-1}$ for cephradine can then be calculated. Only the theoretical k_r' value of ethylcellulose microcapsules containing 70% cefadroxil agrees well with the experimental value as shown in Table II. All other microcapsule preparations have no adequate k_r' values. Although the k_r' value for microcapsules containing 50% cephradine is a suitable one as shown in Table III, the k_{gi} and $k_{gi}/(k_r'+k_{gi})$ in this case become quite large and the k_r' value is therefore unacceptable.

It is useful for the design of future preparations to examine the relationship between *in vitro* dissolution and the *in vivo* pharmacokinetic parameters. In the study on the log–log relationship between the *in vitro* dissolution half-lives (T_{50}) shown in Figs. 1 and 2 and the

experimental k_r' values of cephem antibiotics listed in Tables II and III, a good correlation was obtained (Fig. 6). Such a log–log relationship should provide a very useful index for studies on the design of sustained-release dosage preparations.

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