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Bioavailability of Pyridoxal Phosphate from Enteric-Coated Tablets. III. Correlations between Bioavailability in Humans and Beagle Dogs and between Bioavailability in Humans and *in Vitro* Dissolution Rates

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The bioavailability of five enteric-coated tablets and one sugar-coated tablet of pyridoxal phosphate previously tested in humans was studied in beagle dogs, and the dissolution rates of the tablets were measured by various dissolution methods. The results in beagle dogs correlated significantly with those in humans, and beagle dogs can therefore be used as an animal model to predict the bioavailability in humans of enteric-coated tablets of pyridoxal phosphate.

On the other hand, dissolution tests were not as useful as the bioavailability test in beagle dogs. Only the dissolution parameter obtained by the oscillating basket method using medium of pH 5.9 correlated significantly with the initial excretion rates of pyridoxic acid found in the human study. The oscillating basket method with pretreatment in the No. 1 medium (J.P. IX) failed to reject tablets having inferior bioavailabilities in humans. Pretreatment with acidic solution in dissolution or disintegration tests was considered to make the prediction of bioavailability less reliable.

Keywords——bioavailability; human; beagle dog; pyridoxal phosphate; sugar-coated tablets; enteric-coated tablets; dissolution rate; power analysis; correlation

In a previous report,[1] we determined the apparent critical dissolution pH of forty-eight enteric-coated tablets of pyridoxal phosphate (I) commercially available in Japan, and examined the bioavailability of some of the tablets in humans.

Several reports have dealt with the correlation between bioavailabilities in humans and in beagle dogs, recently.[2–5] A good correlation between penicillin bioavailabilities in humans and in beagle dogs was obtained.[2] However, good correlations were not obtained with flufenamic acid, diazepam and griseofulvin,[3–5] which suggested that beagle dogs are not unrestrictedly applicable as an animal model for bioavailability studies. The above results were obtained with plain tablets[4,5] or capsules,[3] and little work has been done on the correlations between the bioavailabilities of enteric-coated tablets in humans and beagle dogs. We studied the bioavailability of I in beagle dogs using the same enteric-coated tablets previously examined in humans, in order to evaluate the usefulness of beagle dogs as an animal model for the bioavailability testing of enteric-coated tablets. The dissolution rates of I from the tablets were also measured by various dissolution methods and the correlations between *in vivo* results in humans and the *in vitro* dissolution rates were investigated.

Experimental

Formulations——Six lots of tablets of I (10 mg) previously employed in the human bioavailability test[1] were

used. One was a sugar-coated tablet (F) and the others (A, B, C, D and E) were enteric-coated tablets.

Bioavailability Test in Beagle Dogs——Twelve male beagle dogs, weighing 9 to 13 kg, were randomly divided into six groups, and a 6×6 latin square design was employed. A washout period of a week was allowed between treatments. After overnight fasting, the beagles were given a test tablet orally with 40 ml of water. Blood samples were taken before and at 0.5, 1, 2, 4, 6, 8 and 24 h after the administration, and the plasma samples were stored frozen until assay. The beagles were not given any food or drink until the end of a treatment.

Assay——Compound I and pyridoxal (II) in plasma of beagle dogs were determined fluorometrically.[6] After the administration of I orally, however, only II was found in beagle plasma.

Statistical Analyses——The bioavailability for each formulation was evaluated from the plasma concentrations of II at each sampling time (C_t), the peak concentrations of II (C_{max}), the time to reach C_{max} (T_{max}) and the area under the plasma concentration–time curve from 0 to 24 h (AUC_{24}) calculated by means of the trapezoidal rule. AUC_∞ (AUC from 0 to infinity) was calculated by the method of Wagner[7] and the mean residence time (MRT) was calculated by the method of Yamaoka *et al.*[8] These parameters were statistically analyzed according to the method described previously.[1] Correlation coefficients were calculated between the results in humans and in beagle dogs and between the former and the *in vitro* dissolution rates.

Power analyses were performed by using the following power functions.[9]

$$\Phi^2_{\nu_1,\nu_2} = \frac{\sum_{i=1}^{k} (X_i - \bar{X})^2}{s^2/n}$$

where ν_1, ν_2 are the first and second degrees of freedom, k is the number of formulations, s^2 is the residual mean square, n is the number of subjects per group, X_1 is the mean bioavailability of the i-th formulation and $\bar{X}$ is the mean of all formulations. The power was calculated under the conditions that X_i is equal to (1—0.2) X_k, and $X_2 - X_{k-1}$ are all equal to $\bar{X}$. With such a set of means of bioavailabilities, the power of analysis $(1-\beta)$ is estimated most strictly and the largest number of subjects per group is needed to detect a 20% difference in comparison with other sets of means.[10] When the values of Φ were less than 1, precise values of $1-\beta$ could not be read on the Dixon–Massey graph.[9] The minimum detectable difference ($\alpha=0.05$, $\beta=0.2$) and the number of subjects per group required to detect a 20% difference ($\alpha=0.05$, $\beta=0.2$) were also estimated.[10]

Pharmacokinetics——One ml of pyridoxal hydrochloride solution (8.2 mg/ml), which corresponded to 10 mg of I, was injected intravenously into three beagle dogs. The plasma concentrations of II were fitted to a two-compartment model using the NONLIN program.[11]

Dissolution Rates——The dissolution rates of I from tablets were determined at 37 °C by the oscillating basket,[4] rotating basket[4] at 120 rpm, beaker[4] at 196 rpm, paddle[4] at 196 rpm and Solubility Simulator[4] methods, using 0.1 M phosphate buffer of pH 5.9 and 6.6 and medium No. 2 for the disintegration test (J.P. IX). The dissolution rates were also determined by the oscillating basket method with pretreatment in medium No. 1 (J.P. IX, pH 1.2) for 2 h, just as in the disintegration test for enteric-coated tablets. The amount of I dissolved in the medium was determined at 390 nm in a flow cell. Dissolution rates were estimated in terms of T_{lag}, T_{20}, T_{50} and T_{70}, *i.e.*, the lag times and the time required for 20, 50 and 70% dissolution of the active ingredient, respectively.

Results and Discussion

Pharmacokinetics of II in Beagle Dogs

Compound II was eliminated in accordance with a two-compartment model in beagle dogs, and the pharmacokinetic parameters, AUC and MRT, after *i.v.* injection of II are summarized in Table I.

Bioavailability Test in Beagle Dogs

Figure 1 shows the average plasma level curves of II after oral administration of five enteric-coated and one sugar-coated tablets of I to beagle dogs. The results of ANOVA are summarized in Table II.

The rank order of bioavailability in both rate and extent in beagle dogs was very similar to that observed in the human test. In the human test, bioavailability of I was determined by measuring pyridoxic acid, one of the metabolites of I, in urine. Compound I was not absorbed from tablets A and B in five and six out of twelve beagle dogs, respectively; these tablets have an apparent critical dissolution pH of 6.6 and show long lags at pH 6.6.[1] Incomplete absorption of I from tablets A and B was also found in humans.[1] The mean bioavailabilities

TABLE I. Pharmacokinetic Parameters Based on a Two-Compartment Model after *i.v.* Injection of Pyridoxal Hydrochloride into Beagle Dogs

Parameter		Dog No.		
		3	4	5
k_{el}	(h^{-1})	0.761	0.706	0.817
k_{21}	(h^{-1})	1.950	0.701	1.425
k_{12}	(μg/ml)	3.007	0.856	2.008
V_c	(l)	1.719	2.193	1.883
V_{ss}	(l)	4.370	4.871	4.536
AUC	(μg·h/ml)	7.278	6.213	5.957
Cl	(ml/min)	18.8	22.0	23.0
MRT	(h)	3.93	4.95	3.19

MRT, mean residence time.

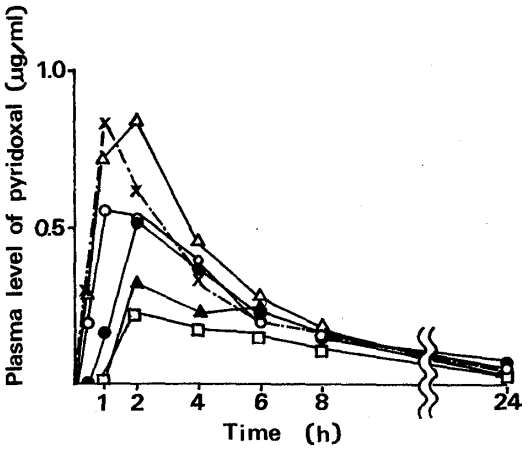

Fig. 1. Average Plasma Pyridoxal Concentration–Time Curves after Oral Administration of Pyridoxal Phosphate Tablets to Beagle Dogs

▲, tablet A; □, tablet B; △, tablet C; ●, tablet D; ○, tablet E; ×, tablet F.
Tablets A, B. C, D and E were enteric-coated tablets and tablet F was a sugar-coated tablet.

of tablets A and B were far smaller than those of the other enteric-coated tablets, and this was also the case in beagle dogs.

The plasma level of II at 0.5 h after the administration of tablet E, which showed the lowest apparent critical dissolution pH among the enteric-coated tablets tested, was nearly the same as that of the sugar-coated tablet F, while in humans the former differed significantly from the latter. T_{max} and *MRT* were also analyzed according to a randomized block design in beagle dogs among tablets C, D, E and F, as had been done in humans. No significant difference was obtained in *MRT* among tablets C, D, E and F in beagle dogs, which suggested that these enteric-coated tablets disintegrated as fast as the sugar-coated tablet in the gastrointestinal tract of beagle dogs. This was different from the observation in humans, where the disintegration of enteric-coated tablets was apparently delayed as compared with that of the sugar-coated tablet. These results show that the time lag in the absorption of I in beagle dogs is shorter than in humans, which may be attributed to the shorter gastric emptying time of beagle dogs than of humans. Wagner pointed out that the average gastric emptying time of enteric-coated tablets was 3.61 h with a standard deviation of 1.47 h in humans, and the average natural logarithm of gastric emptying time was 4.48 (corresponding to 1.47 h) with a standard deviation of 0.386 in beagle dogs.[12]

Though the results were obtained from different beagle dogs, the average *MRT*s of tablets C, D, E and F (Table II) were larger than that of *i.v.* injection (Table I), which suggested that the mean dissolution and absorption times of these tablets were about 3.5 h in beagle dogs.

TABLE II. Bioavailability Parameters of Pyridoxal Phosphate Enteric-Coated Tablets and Results of ANOVA and Multiple Range Test in Beagle Dogs

Parameter	Tablet						Result of ANOVA	Multiple range test[a]
	A	B	C	D	E	F		
Plasma concentration (μg/ml)								
$C_{0.5}$	0.004±0.002	0.005±0.002	0.026±0.012	0.012±0.004	0.176±0.019	0.271±0.096	$p<0.05$	F>E>C>D>B>A
C_1	0.006±0.003	0.021±0.018	0.590±0.152	0.162±0.056	0.504±0.146	0.763±0.058	$p<0.01$	F>C>E>D>B>A
C_2	0.298±0.130	0.179±0.086	0.693±0.104	0.508±0.076	0.480±0.091	0.568±0.038	$p<0.01$	C>F>D>E>A>B
C_4	0.208±0.072	0.152±0.057	0.381±0.044	0.352±0.041	0.384±0.041	0.310±0.025	$p<0.01$	E>C>D>F>A>B
C_6	0.224±0.084	0.122±0.037	0.227±0.023	0.225±0.029	0.208±0.017	0.197±0.017	n.s.	
C_8	0.139±0.046	0.089±0.025	0.150±0.016	0.153±0.021	0.152±0.014	0.142±0.012	n.s.	
C_{24}	0.020±0.008	0.025±0.005	0.026±0.007	0.032±0.006	0.020±0.004	0.023±0.005	n.s.	
C_{max}	0.427±0.132	0.264±0.086	0.957±0.085	0.583±0.059	0.868±0.084	0.818±0.043	$p<0.01$	C>E>F>D>A>B
T_{max} (h)	3.14 ±0.66[b]	3.50 ±0.86[b]	1.67 ±0.26	2.42 ±0.29	1.96 ±0.38	1.08 ±0.14	$p<0.01$[c]	F<C<E<D
MRT (h)	11.18 ±3.08[b]	9.09 ±1.10[b]	7.51 ±0.82	9.67 ±1.13	6.88 ±0.51	7.41 ±0.71	n.s.[c]	
AUC (μg·h/ml)								
AUC_{24}	2.724±0.777	1.834±0.472	4.267±0.358	3.675±0.303	3.895±0.181	4.039±0.235	$p<0.01$	C>F>E>D>A>B
AUC_∞	2.893±0.793	1.993±0.515	4.553±0.349	4.028±0.380	4.104±0.512	4.331±0.714	$p<0.01$	C>F>E>D>A>B

Values are mean±S.E. *a*) The multiple range test was done by the least-significant-difference method. The mean values for treatments not underscored by the same line differ significantly. *b*) Mean for beagle dogs that absorbed the drug. *c*) ANOVA was performed according to a randomized block design. n.s., not significant at $p=0.05$.

TABLE III. Power of ANOVA in Bioavailability Test of Pyridoxal Phosphate Tablets in Humans

Parameter	Φ	$1-\beta^{a)}$	$\Delta^{b)}$	$n^{c)}$
$V_{0.5}{}^{d)}$	0.453	<0.36	0.684	21
$V_{1.5}{}^{d)}$	0.605	<0.36	0.512	12
$V_{2.5}{}^{d)}$	0.369	<0.36	0.839	32
$V_{3.5}{}^{d)}$	0.442	<0.36	0.701	22
$V_{4.5}{}^{d)}$	0.296	<0.36	>1.0	50
$V_{max}{}^{e)}$	0.582	<0.36	0.533	13
$E_{22}{}^{f)}$	0.756	<0.36	0.410	8
$E_{\infty}{}^{g)}$	0.760	<0.36	0.408	8

a) Power for $n=2$ and $\Delta=0.2$ at $\alpha=0.05$. *b*) Minimum detectable difference for $n=2$ at $\alpha=0.05$ and $1-\beta=0.8$. *c*) Number of subjects required per group estimated for $\Delta=0.2$ at $\alpha=0.05$ and $1-\beta=0.8$. *d*) Excretion rate of pyridoxic acid at time t. *e*) Peak excretion rate of pyridoxic acid. *f*) Cumulative amount of urinary excretion of pyridoxic acid within 22 h. *g*) Cumulative amount of urinary excretion of pyridoxic acid through 0 to infinity.

TABLE IV. Power of ANOVA in Bioavailability Test of Pyridoxal Phosphate Tablets in Beagle Dogs

Parameter	Φ	$1-\beta^{a)}$	$\Delta^{b)}$	$n^{c)}$
$C_{0.5}$	0.237	<0.36	1.0	77
C_1	0.513	<0.36	0.603	17
C_2	0.406	<0.36	0.763	27
C_4	0.475	<0.36	0.653	20
C_6	0.357	<0.36	0.867	34
C_8	0.409	<0.36	0.759	26
C_{24}	0.333	<0.36	0.851	39
C_{max}	0.597	<0.36	0.523	13
AUC_{24}	0.646	<0.36	0.480	11
AUC_{∞}	0.565	<0.36	0.548	14

a) Power for $n=2$ and $\Delta=0.2$ at $\alpha=0.05$. *b*) Minimum detectable difference for $n=2$ at $\alpha=0.05$ and $1-\beta=0.8$. *c*) Number of subjects required per group estimated for $\Delta=0.2$ at $\alpha=0.05$ and $1-\beta=0.8$.

Power Analyses

The results of ANOVA of bioavailability tests in both humans and beagle dogs are summarized in Tables III and IV. The number of human subjects per group required to detect a 20% difference at $\alpha=0.05$ and $1-\beta=0.8$ in the bioavailability test of I was large relative to those for other drugs such as diazepam, flufenamic acid, and so on, though the dosage forms are different.[10] The low power was considered to be partially due to the existence of the basal excretion of pyridoxic acid (one of the metabolites of I) and its variance.[1] The absorption of I from an enteric-coated tablet is thought to be affected more by the gastric emptying rate and the gastric acidity of the subjects than is the case for plain tablets or capsules. Though the minimum detectable differences in the human study were nearly 40% at $\alpha=0.05$ and $1-\beta=0.80$, the differences in most of the bioavailability parameters were more than 50%, and thus were significant.

Despite the extremely low concentration of endogenous II and the small variances of the gastric emptying rate in beagle dogs, the power was low ($1-\beta<0.36$), as found in humans. Minimum detectable differences were slightly larger in beagle dogs than in humans and a

larger number of subjects per group was needed to detect a 20% difference at $\alpha=0.05$, $1-\beta=0.8$, as has often been found in bioavailability tests in our laboratory (*e.g.*, with diazepam, griseofulvin, nalidixic acid and cyclandelate).[10]

Dissolution Rates

Typical dissolution curves are shown in Fig. 2, and T_{lag} and T_{50} determined by various dissolution methods are summarized in Table V. Fairly similar curves were obtained by the paddle, rotating basket, beaker and Solubility Simulator methods, while the oscillating basket method gave a different curve from the other dissolution methods. In the paddle, rotating basket, beaker and Solubility Simulator methods, I dissolved very slowly not only from tablet A but also from tablets D and E, while the latter two showed good bioavailabilities and had

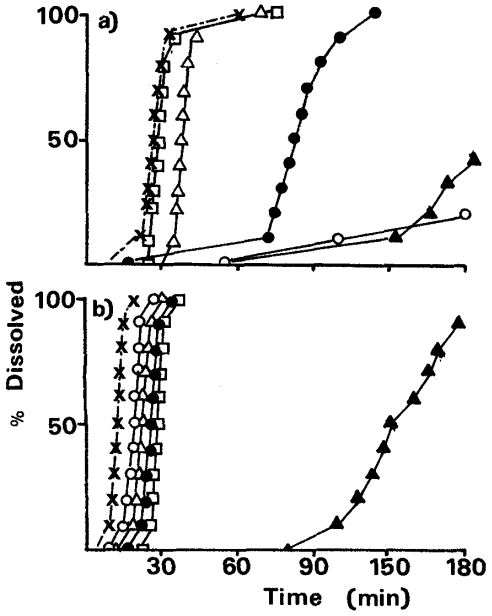

Fig. 2. Dissolution Profiles of Pyridoxal Phosphate Tablets Measured by the Paddle Method at pH 7.5 (a) and by the Oscillating Basket Method at pH 5.9 (b)

▲, tablet A; □, tablet B; △, tablet C; ●, tablet D; ○, tablet E; ×, tablet F.

TABLE V. T_{lag} and T_{50} of Dissolution of Pyridoxal Phosphate Tablets in Various Dissolution Methods (min)

Dissolution method	pH	Parameter	Tablet					
			A	B	C	D	E	F
Oscillating basket	7.5	T_{lag}	52± 6	20± 4	8±2	9± 1	14± 1	10± 2
		T_{50}	71± 8	22± 4	18±4	27± 2	26± 2	15± 1
	6.6	T_{lag}	>180	20± 4	11±0	7± 2	16± 2	11± 3
		T_{50}	>180	24± 2	21±3	26± 4	24± 4	18± 2
	5.9	T_{lag}	>180	20± 1	11±2	16± 1	10± 1	6± 0
		T_{50}	>180	28± 2	23±1	26± 2	20± 1	13± 0
Rotating basket	7.5	T_{lag}	>180	27± 4	34±6	34±16	35± 7	26± 6
		T_{50}	>180	30± 3	48±2	48±13	>180	31± 9
	6.6	T_{lag}	50±14	25± 2	29±5	55±24	31±16	21± 6
		T_{50}	>180	31± 2	40±8	113±61	>180	28± 4
Paddle	7.5	T_{lag}	61±23	25± 3	32±8	11± 2	55±19	6± 8
		T_{50}	160±12	27± 1	38±8	82±61	>180	28± 4
	6.6	T_{lag}	38± 4	21± 3	28±1	14±11	15±11	19± 5
		T_{50}	>180	29± 2	36±1	82±31	>180	26± 5
Solubility Simulator	7.5	T_{lag}	52±11	30± 3	24±6	38±11	36± 9	12±11
		T_{50}	>180	38± 4	35±5	>180	>180	27± 9

Values are means±S.D.

TABLE VI. T_{lag} Values Determined by the Oscillating Basket Method with Pretreatment with Acidic Solution (min)

pH	Tablet				
	A	B	C	D	E
6.6	13.8±2.5	9.5±1.0	7.5±2.0	11.0±1.1	7.0±1.5
7.5	8.8±1.0	8.1±0.8	9.1±2.3	9.9±0.8	6.9±1.9

Values are means±S.D.

lower values of apparent critical dissolution pH, (4.5 and 5.5). In these methods, however, I dissolved very rapidly from tablet B, which showed as low bioavailability as tablet A. On the other hand in the oscillating basket method at pH 6.6 and 5.9, I dissolved from tablet A at the slowest rate, and from tablet B at a slower rate than from tablets C, D and E. The differences of values of T_{lag} and T_{50}s between tablet B and tablets C, D and E were slightly more distinguishable at pH 5.9.

When they had been pretreated in acidic solution, all the tablets tested showed similar and relatively short T_{lag} in the oscillating basket method (Table VI) and no differences were found among the five tablets. MPM 47® seemed to be contained as a coating material in tablet A, based on the infrared (IR) spectra.[1] As MPM 47® undergoes degradation during the pretreatment with acidic solution for such a long time (2 h), the lag time in dissolution became shorter in the dissolution test with pretreatment.

Correlations between Bioavailabilities in Humans and in Beagle Dogs

Table VII shows the correlation coefficients between parameters showing the rate and extent of bioavailability of I in humans and beagle dogs. Correlation coefficients between T_{max} values in both species could not be calculated because I was not absorbed from tablets A and B in several subjects and dogs. Significant correlations were obtained between urinary excretion rates in humans and plasma levels in beagle dogs in the absorption phase, between V_{max} (peak excretion rate) and C_{max} and between E_{22} (cumulative amount of urinary excretion within 22 h) and AUC_{24} (Table VII, Fig. 3). Though the gastric emptying rate is considered to be faster in beagle dogs than in humans, beagle dogs seemed to be very useful as an animal model to predict the bioavailability of enteric-coated tablets of I in humans.

TABLE VII. Correlation Coefficients between Bioavailability Parameters in Humans and Beagle Dogs

Parameter	Beagle dogs					
	$C_{0.5}$	C_1	C_2	C_4	C_{max}	AUC_{24}
Humans						
$V_{0.5}$	0.850[a]	0.684	0.301	0.098	0.354	0.482
$V_{1.5}$	0.990[b]	0.851[a]	0.435	0.371	0.618	0.648
$V_{2.5}$	0.293	0.675	0.887[a]	0.970[b]	0.885[a]	0.869[a]
$V_{3.5}$	0.085	0.276	0.746	0.883[a]	0.612	0.668
$V_{4.5}$	0.285	0.147	0.635	0.779	0.512	0.503
V_{max}	0.581	0.918[b]	0.909[a]	0.885[a]	0.985[b]	0.937[b]
E_{22}	0.650	0.850[a]	0.856[a]	0.905[a]	0.940[a]	0.948[b]

a) Significant at $p=0.05$. *b*) Significant at $p=0.01$.

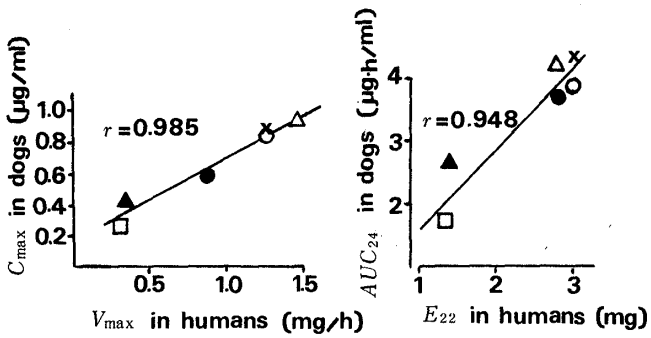

Fig. 3. Correlations between Bioavailabilities in Humans and Beagle Dogs

●, tablet A; □, tablet B; △, tablet C; ●, tablet D; ○, tablet E; ×, tablet F.

Correlations between Bioavailability in Humans and *in Vitro* Dissolution Rates

No significant correlations were found between bioavailability parameters in humans and dissolution parameters. The excretion rate of pyridoxic acid at 1.5 h ($V_{1.5}$), however, was significantly correlated with $1/T_{20}$, $1/T_{50}$ and $1/T_{70}$ in the oscillating basket method at pH 5.9 ($r=0.89$, 0.84 and 0.83, respectively), though V_{max} and E_{22} did not correlate significantly.

In spite of the significant correlations with the rate of bioavailability in humans, the differences of dissolution rates between tablet B and other enteric-coated tablets were not large enough for the oscillating basket method to distinguish tablet B clearly as a product with low bioavailability. On the other hand, other dissolution methods such as the paddle or rotating basket methods failed to reject tablet B as having poor bioavailability and to accept tablet E as having good bioavailability.

Dissolution rates of I from tablets A and B did not differ from those from tablets C, D and E, when the tablets were pretreated with acidic solution (Table VI). The enteric-coating films might suffer some damage during the pretreatment in acidic solution for 2 h. The accelerated *in vitro* disintegration after the pretreatment did not correlate with *in vivo* bioavailability. It is necessary to prove that an enteric-coated tablet does not disintegrate in acidic solution at all. However, the pretreatment with acidic solution did not seem to offer any advantage in the dissolution tests.

The bioavailability test of the enteric-coated tablets of I in beagle dogs was found to be of help to predict the bioavailability in humans, in contrast to the results on flufenamic acid capsules,[3] diazepam[4] and griseofulvin tablets.[5] The destructive conditions in the gastrointestinal tract of beagle dogs are more severe than in humans,[13,14] which was considered to account for the low correlations between bioavailabilities of these drugs from capsules or plain tablets in humans and beagle dogs. Compound I is so water-soluble that dissolution must occur rapidly once the coating film is broken, but the destruction of an enteric-coating film depends upon the pH of the surroundings rather than upon the general severity of the conditions. The good correlations observed in the present study suggested that the pH in the intestine of beagle dogs might be similar to that of humans, though the relationship between the pH in the stomachs of beagle dogs and humans has not yet been much investigated.[13,15]

Conclusion

The gastric emptying rates of enteric-coated tablets were found to be faster in beagle dogs than in humans. The bioavailability of enteric-coated tablets of I in beagle dogs, however, correlated significantly with that in humans, in both rate and extent, which suggested that beagle dogs may be useful as an animal model in bioavailability tests of enteric-coated tablets.

Various *in vitro* dissolution methods were tested, but only the oscillating basket method at pH 5.9 gave a good correlation of the reciprocal of the dissolution rate parameters with bioavailability parameters indicating the rate of bioavailability.

Thus, for enteric-coated tablets of I, the bioavailability test in beagle dogs was more helpful than the dissolution tests for predicting the bioavailability in humans.

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