In Vitro Dissolution Tests Corresponding to the *in Vivo* Dissolution of Clarithromycin Tablets in the Stomach and Intestine

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The correlation between *in vivo* and *in vitro* dissolution of clarithromycin (CAM) tablets was examined. *In vivo* dissolution rate constants in the stomach and the intestine were obtained from analysis of the urinary excretion data of CAM following oral administration to humans in the fasting or postprandial state using a pharmacokinetic model including gastrointestinal transit.

In the present study, the flow-through cell method with moderate agitation was used, as the *in vitro* dissolution test related to the *in vivo* dissolution rate constants. Both the effects of pH of the dissolution medium and the volumetric solvent flow rate on the dissolution rate in the flow-through cell method were examined. The pH of the dissolution medium and the flow rate were related to the *in vitro* dissolution rate. Therefore, the conditions of the flow-through cell method in correlation with the *in vivo* dissolution rates in the stomach and intestine were determined by controlling the flow rate at pH 3.0 and 6.8 dissolution medium. The urinary excretion of CAM, simulated by substituting the *in vitro* dissolution rate constants into the equation, were consistent with the *in vivo* data. The *in vitro* tests corresponding to the *in vivo* dissolution in the stomach and intestine following a single oral administration in the fasting or postprandial state for a CAM tablet were established.

Key words *in vitro–in vivo* correlation; flow-through cell method; dissolution rate; clarithromycin tablet; pharmacokinetic model

In the development of oral solid dosage forms, if the rate of dissolution of a drug formulation is the limiting factor in drug absorption, dissolution testing is useful for predicting drug absorption. Therefore, numerous attempts have been made to determine the correlation between *in vitro* release and *in vivo* performance.[1] Four levels of in *vitro–in vivo* correlation have been defined by the USP subcommittee on biopharmaceutics.[2] The highest level of correlation is a 1 : 1 relationship between *in vitro* and *in vivo* dissolution. *In vivo* dissolution profiles can be obtained by the Wagner–Nelson method[3] or the Roo–Riegelman method[4] (model dependent method) and by the direct mathematical deconvolution method[5] (model independent method).

In general, however, it is not easy to obtain *in vitro* dissolution profiles correlated with *in vivo* dissolution profiles, since physiological conditions such as gastric emptying and the pH profile in the gastrointestinal tract are individually specific. In particular, drug release from formulations containing drugs with pH-dependent solubility is significantly affected by pH in the gastrointestinal tract. Therefore, in order to adapt dissolution test parameters to physiological conditions, methods of dissolution with changes in pH during testing have been developed.[6] However, these dissolution methods are more complicated than conventional methods such as the paddle method. Moreover, in these dissolution methods, the effect of gastrointestinal transit rate on absorption cannot be taken into consideration.

In the present study, the *in vivo* dissolution rate constants in the stomach and intestine were obtained from the urinary excretion of clarithromycin (CAM) following oral administration to humans in the fasting or postprandial state using the pharmacokinetic model (Chart 1) described in our previous paper.[7] We then attempted to estimate the *in vivo* behavior of drugs, including gastrointestinal transit, using these parameters.

Furthermore, we examined the *in vitro* dissolution tests corresponding to the *in vivo* dissolution rates in the stomach or intestine separately. When the dissolution test for CAM tablets using the paddle method with conventional conditions was carried out,[8] the *in vitro* dissolution rate was found to be higher than the *in vivo* dissolution rate. In the present study, therefore, the flow-through cell method with moderate agitation was used as the *in vitro* dissolution test.

Materials and Methods

Materials CAM and tablets containing 200 mg (potency) of CAM were supplied by Taisho Pharmaceutical Co., Ltd. All other chemicals used were of reagent grade.

***In Vivo* Data and Pharmacokinetic Analysis** The urinary excretion data for CAM after a single oral administration to humans reported by Suwa *et al.*[9] were used.

The equation for cumulative urinary excretion was derived from the pharmacokinetic model,[7] and was assumed to proceed with first-order kinetics for the entire process.

Cumulative urinary excretion (E_t) can be expressed by the following equation in terms of time (t):

$$E_t = A_0 \cdot F_s \cdot \left(\alpha \cdot e^{-k_{el} \cdot t} + \frac{\beta \cdot k_{el}}{K_2} \cdot e^{-K_2 \cdot t} - \frac{\gamma \cdot k_{el}}{K_1} \cdot e^{-K_1 \cdot t} + \frac{K_1 \cdot k_{d1} + k_{d2} \cdot k_g}{K_1 \cdot K_2} \right) \quad (1)$$

where

$$\alpha = \frac{\{k_{d2} \cdot k_g + k_{d1} \cdot (K_1 - k_{el})\}}{\{(K_1 - k_{el}) \cdot (K_2 - k_{el})\}} \quad (2)$$

$$\beta = \frac{\{k_{d2} \cdot k_g - k_{d1} \cdot (K_2 - K_1)\}}{\{(K_2 - K_1) \cdot (K_2 - k_{el})\}} \quad (3)$$

$$\gamma = \frac{k_{d2} \cdot k_g}{\{(K_2 - K_1) \cdot (K_1 - k_{el})\}} \quad (4)$$

A_0 and F_s represent the dose and fraction of drug absorbed, respectively. k_g, k_{d1}, k_{d2}, k_{ex} and k_{el} represent the rate constants for

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gastrointestinal transit rate, dissolution in stomach, dissolution in intestine, exclusion, and elimination, respectively, and K_1 and K_2 are defined as follows:

$$K_1=(k_{d2}+k_{ex}) \quad (5)$$

$$K_2=(k_{d1}+k_g) \quad (6)$$

Pharmacokinetic parameters of Eq. 1 were calculated by simultaneously fitting the individual urinary excretion data for CAM after oral administration in the fasting and postprandial states with MULTI[10] using nonlinear least-squares regression analysis.

***In Vitro* Dissolution Test** The dissolution test was carried out using Dissotest-100 (Toyamasangyo, Osaka, Japan) as the flow-through cell apparatus. The flow-through cell method was used in accordance with Supplement I in the Pharmacopoeia of Japan, Twelfth Edition. Into a 22.6 mm inner diameter cell were placed one glass bead 5 mm in diameter and 1 g of glass beads 1 mm in diameter, along with one tablet on a holder. After an assembly of two filters was attached, the dissolution medium, warmed at 37 °C, was introduced through the bottom of the cell by using a piston pump. Britton–Robinson buffer solution with a pH range of 3.0 to 7.8 was used as the dissolution medium. A CAM tablet was tested in each experiment using dissolution media of pH 3.0 5.0, 6.0, 6.5, 6.8, 7.2 and 7.8 at a 10 ml/min flow rate for studying the effect of pH on the dissolution. The effect of flow rates on dissolution was tested with flow rates of 0.5, 1.5, 3 and 5 ml/min at pH 3.0 of the dissolution medium, and with flow rates of 1.5, 5, 10 and 15 ml/min at pH 6.8 of the dissolution medium. During each experiment, fresh dissolution medium was pumped through a cell, and the elute was collected in separate fractions during different times periods, *i.e.*, 0—5, 5—10, 10—15, 15—20, 20—30, 30—45, 45—60, 60—90 and 90—120 min. The elute was filtered through a membrane filter with a 0.45 μm pore size.

Then, the amount of CAM released into the dissolution medium was quantitatively determined by HPLC with the following operating conditions: ultraviolet absorption photometer detector: wavelength, 210 nm; column: 4.6 mm i.d. × 15 cm stainless-steel column packed with ODS-80TM (Tosoh): column temperature, 50 °C; mobile phase: a mixture of 1/15 M monobasic potassium phosphate and acetonitrile (13 : 7); and a flow rate of 1 ml/min.

Determination of *in Vitro* Dissolution Rate Constant The *in vitro* dissolution rate constants with first-order kinetics were calculated by fitting each dissolution value for a CAM tablet with MULTI[10] using nonlinear least-squares regression analysis.

Results and Discussion

Figure 1 shows the urinary excretion data for CAM obtained after a single oral administration of 200 mg CAM tablets to healthy volunteers in the fasting or postprandial state, as reported by Suwa *et al.*[9] The fitted lines were obtained by nonlinear least-squares regression analysis. The pharmacokinetic parameters obtained are listed in Table 1. The parameters[7] obtained from the serum concentration data were nearly equal to that obtained from the urinary excretion data.

For a single oral administration in the fasting state, the *in vivo* dissolution rate of CAM in the stomach was higher than that in the intestine. Therefore, we attempted to characterize flow-through cell methods corresponding to the stomach and intestine separately.

On the other hand, following postprandial administration, the *in vivo* dissolution rate in the stomach was nearly equal to that in the intestine. Consequently, for postprandial administration, we used the same condition for flow-through cell method corresponding to the stomach and the intestine. For CAM tablets, the dissolution from granules disintegrated is the rate-determining step, since the rate of disintegration is much larger than that of dissolution. Therefore, although in the pharmacokinetic model (Chart 1) solid drug in the intestine compartment is assumed to be dissolved from granules gastric-emptied following first order kinetic, the dissolution test for the intestine was carried out by the whole tablet. In order to characterize the flow-through cell method, the effects of the pH of the dissolution medium and the volumetric solvent flow rate on dissolution rate for CAM were examined. These correlations may be useful for adapting the *in vitro* dissolution rate to the *in vivo* dissolution rate.

Relationship between pH of Dissolution Medium and *in Vitro* Dissolution Rate Constant (Kd_{vitro}) To clarify the effect of pH of the dissolution medium on the *in vitro* dissolution rate in the flow-through cell method for CAM, we tested the pH range of 3.0 to 7.8 at 10 ml/min flow rate. As the pH value increased, the *in vitro* dissolution rate decreased, as shown in Fig. 2.

The *in vitro* dissolution rate constants with first-order kinetics, Kd_{vitro}, were calculated by fitting the *in vitro* dissolution profiles for each dissolution medium pH. As can be seen in Fig. 3, the plot of $\log(Kd_{vitro})$ against each pH of dissolution medium yielded a straight line with the following equation:

$$\log(Y)=-0.588\cdot X+3.918 \qquad r=0.996 \quad (7)$$

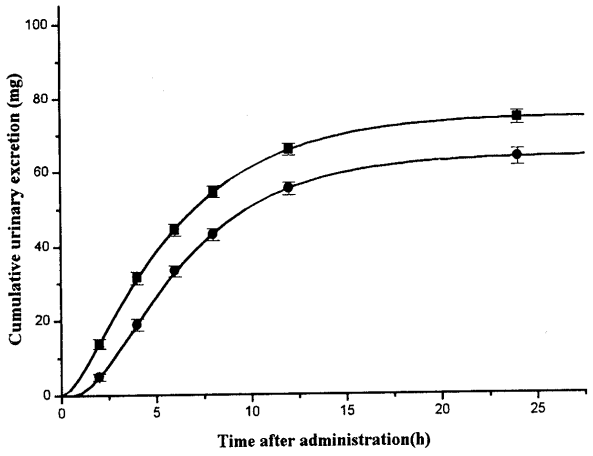

Fig. 1. Cumulative Urinary Excretion of CAM Following Oral Administration to Healthy Volunteers in Fasting or Postprandial State

Values are expressed as means ± S.E. for 8 volunteers. The solid lines were obtained by non-linear least-squares regression analysis. Key: ●, postprandial; ■, fasting.

Table 1. Effect of Food on Pharmacokinetic Parameters for a Single Oral Administration of CAM (200 mg) to Healthy Volunteers

State	k_{d1} (h^{-1})	k_{d2} (h^{-1})	k_g (h^{-1})	k_{ex} (h^{-1})	t_0 (h)	F (%)	k_{e1} (h^{-1})
Fasting	1.873 ± 1.412	0.254 ± 0.208	4.499 ± 6.476	0.047 ± 0.081	0.260 ± 0.492	40.2 ± 8.9	0.305 ± 0.070
Postprandial	0.407 ± 0.482	0.464 ± 0.503	0.449 ± 0.534	0.089 ± 0.124	0.799 ± 0.641	36.2 ± 5.9	

Results are expressed as the mean ± S.D. of 8 volunteers.

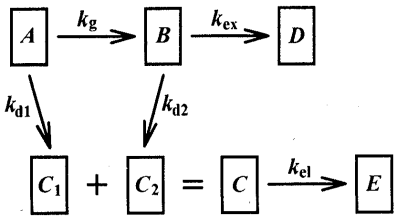

Chart 1. A Simplified Version of the Pharmacokinetic Model Including *in Vivo* Dissolution and Gastrointestinal Transit Parameters

A, and *B* represent the amounts of solid drug in the stomach and undissolved drug in the intestine. C_1, C_2, and *C* represent the amounts of drug dissolved in the stomach and absorbed in the intestine, drug dissolved in the intestine and absorbed in the intestine, and the total amount of drug absorbed in the gastrointestinal compartment, respectively. *D* and *E* represent the amounts of undissolved drug and of urinary excretion of drug.

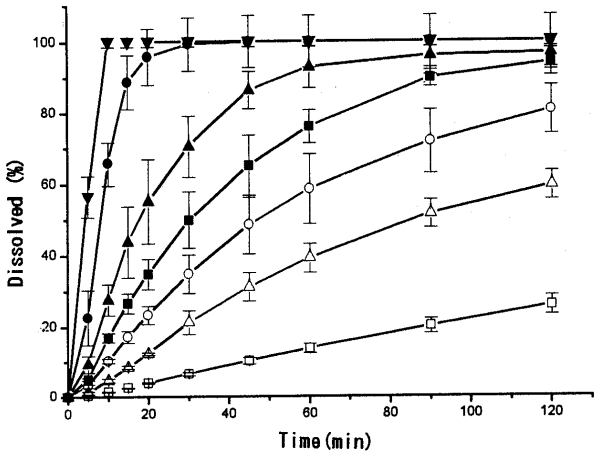

Fig. 2. The Effect of pH of Dissolution Medium on the *in Vitro* Dissolution Rate

Key: ▼, pH 3.0; ●, pH 5.0; ▲, pH 6.0; ■, pH 6.5; ○, pH 6.8 △, pH7.2; □, pH 7.8.

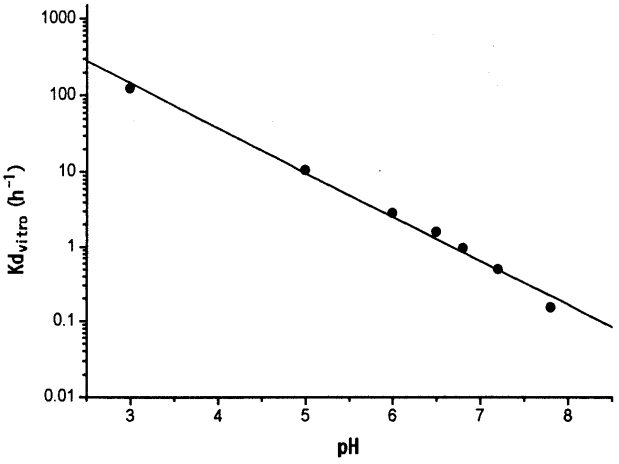

Fig. 3. Relationship between pH of Dissolution Medium and *in Vitro* Dissolution Rate Constant (Kd_{vitro})

This finding indicates that logalism of the *in vitro* dissolution rate is proportional to the dissolution medium pH. This appears to be due to the pH-dependent solubility of CAM.

Wagner[11] reported that under sink conditions, the dissolution rate could be represented as

$$\frac{dC}{dt} = K\frac{S}{V}C_s \tag{8}$$

where *C* is the concentration of solute at time *t*, C_s is the equilibrium solubility of the solute at the experimental temperature, *K* is a constant with dimension length/time, *S* is the surface area of solute available for dissolution, and *V* is the volume of the dissolution medium. In general, since sink conditions are maintained in the flow-through cell method, the dissolution rate can be considered to depend on drug solubility. Thus, the following correlation can be obtained:

$$Kd_{vitro} \propto C_s \tag{9}$$

And the correlation can be rewritten as follows:

$$\log(Kd_{vitro}) \propto \log(C_s) \tag{10}$$

In addition, the relationship between pH and solubility of a weak base drug can be explained using Henderson–Hasselbach's equation.

$$\mathrm{pH} = \mathrm{p}K_a + \log\left(\frac{C_b}{C_i}\right) \tag{11}$$

where pK_a is the dissociation constant, C_i is the solubility of the dissociated molecule, and C_b is the solubility of the undissociated molecule. In the case of CAM, in which a weak base drug which exhibits pK_a 8.76, C_s is nearly equal to C_i, since C_s is much lagrer than C_b below pH 7.8. Therefore, Eq. 11 is given by:

$$\log(C_s) = -\mathrm{pH} + \mathrm{p}K_a + \log(C_b) \tag{12}$$

The following correlation can be obtained:

$$\log(C_s) \propto \mathrm{pH} \tag{13}$$

These correlations suggest that log (Kd_{vitro}) may be proportional to pH.

Relationship between Kd_{vitro} and C_s The solubilities of CAM at each pH were calculated by using the pK_a and C_b of CAM reported by Nakagawa *et al.*[12] An approximately linear relationship was found between the logarithms of the solubility for CAM calculated and the logarithms of the *in vitro* dissolution rate constant as shown in Fig. 4. The linear regression of these data produces Eq. 14.

$$\log(Y) = 1.533 \cdot \log(X) + 2.890 \qquad r = 0.995 \tag{14}$$

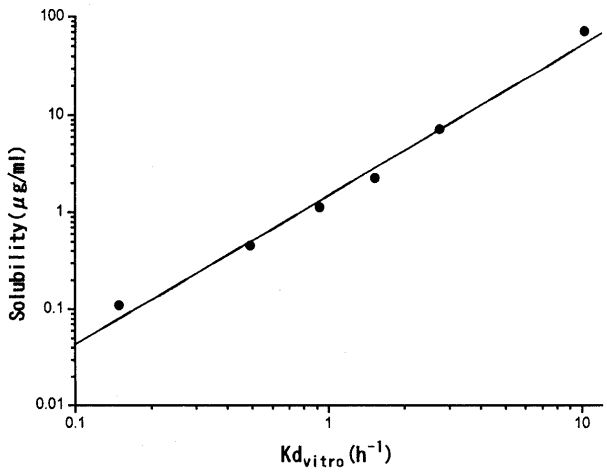

Fig. 4. Relationship between Solubility and Kd_{vitro}

From Eq. 10, derived from Eq. 8 reported by Wagner, Eq. 14 can be explained.

Relationship between Kd_{vitro} and Flow Rate To confirm the effect of volumetric solvent flow rate on the dissolution rate in the flow-through cell method, we changed the flow rate from 0.5 to 5 ml/min at pH 3.0 and from 1.5 to 15 ml/min at pH 6.8. As the flow rate increased, the *in vitro* dissolution rate also increased, as shown in Fig. 5. Kd_{vitro} was calculated by fitting the *in vitro* dissolution profiles at each flow rate. As can be seen in Fig. 6, the plot of Kd_{vitro} against the flow rate yielded a straight line with the following equations:

$$Y=2.2292\cdot X+0.0217 \quad r=0.995 \text{ at pH } 3.0 \tag{15}$$

$$Y=0.0917\cdot X-0.0087 \quad r=1.000 \text{ at pH } 6.8 \tag{16}$$

These findings indicate that the *in vitro* dissolution rate is proportional to the flow rate.

In the flow-through cell method, the dissolution rate can be determined using the following equation[13]:

$$\frac{dm}{dt}=C_e\cdot Q \tag{17}$$

where m is the amount of drug dissolved, C_e is the concentration during t time, and Q is the flow rate of the dissolution medium. This relationship also shows that the *in vitro* dissolution rate is proportional to flow rate.

Determination of Conditions for the Flow-Through Cell Method Corresponding to *in Vivo* Data The above findings proved that the *in vitro* dissolution rate is related to both the pH of dissolution medium and flow rate. Therefore, the *in vitro* dissolution rate can be controlled by the pH of the dissolution medium and flow rate. In the present study, the conditions under which the flow-through cell method would correlate with the *in vivo* dissolution rate were determined by controlling the flow rate. In the fasting state, the dissolution medium of pH 3.0 for the stomach and pH 6.8 for the intestine were used. The gastric pH of human is 1 to 3.5.[14] Though macrolide antibiotics were inactivated by gastric acid, CAM is relatively stable in acidic solution.[12] In particular, CAM is stable above pH 3. Moreover, the 5-*O*-desosaminyl-6-*O*-methylerythronolide, the degradation product by acid, was only slightly detected in the urinary excretion of CAM following oral administration.[9] Therefore, the pH of the stomach can be estimated to be about pH 3. And in general, since the

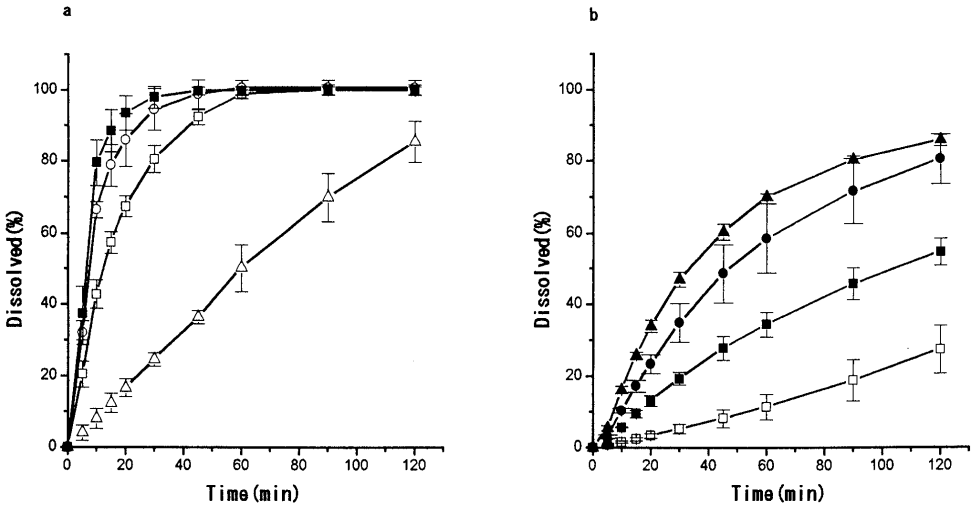

Fig. 5. The Effect of Flow Rate on the *in Vitro* Dissolution Rate

Key: a, at pH 3.0; △, 0.5 ml/min; □, 1.5 ml/min; ○, 3 ml/min; ■, 5 ml/min; b, at pH 6.8; □, 1.5 ml/min; ■, 5 ml/min; ●, 10 ml/min; ▲, 15 ml/min.

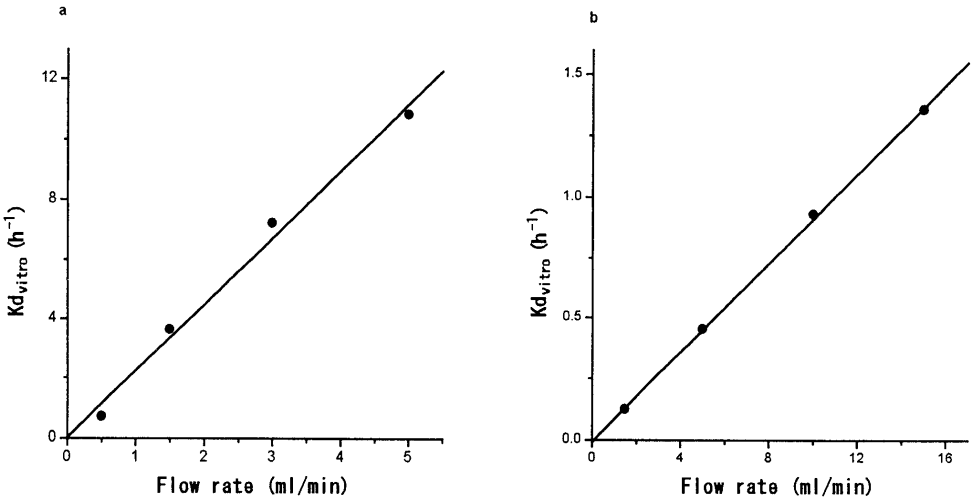

Fig. 6. Relationship between Flow Rate and Kd_{vitro}

Key: a, at pH 3.0 of dissolution medium; b, at pH 6.8 of dissolution medium.

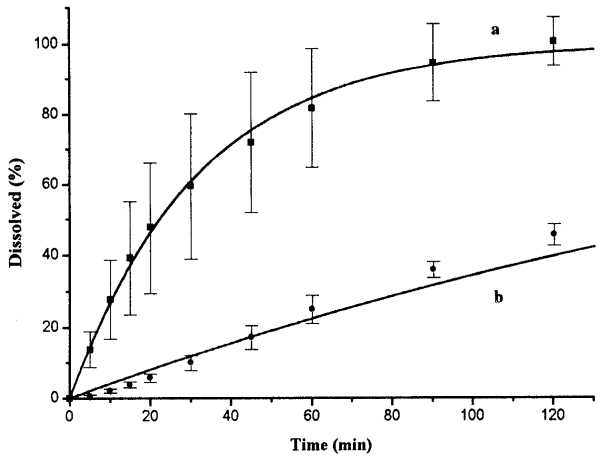

Fig. 7. Relationship between *in Vivo* Dissolution and *in Vitro* Dissolution for Oral Administration in Fasting State

Key: a, simulated *in vivo* dissolution in stomach; b, simulated *in vivo* dissolution in intestine; ■, *in vitro* dissolution data for stomach; ●, *in vitro* dissolution data for intestine.

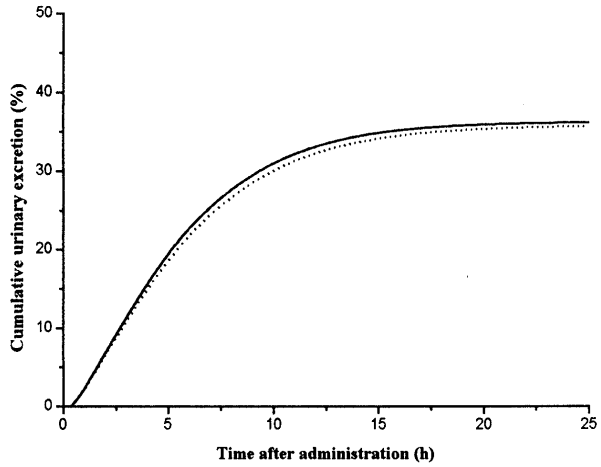

Fig. 8. Correlation between Fitting Curve Obtained from *in Vivo* Data and Predicted Curve Obtained from *in Vitro* Dissolution for Cumulative Urinary Excretion of CAM Following Oral Administration in Fasting State

The dotted line was obtained by fitting the cumulative urinary excretion data of CAM following oral administration in fasting state. The solid line was predicted from *in vitro* dissolution profiles for the stomach and intestine.

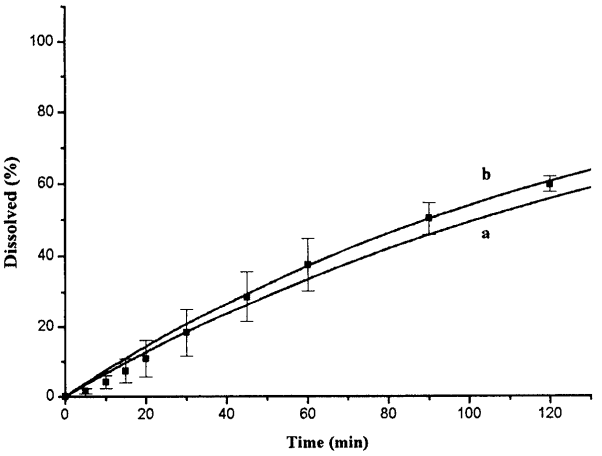

Fig. 9. Relationship between *in Vivo* Dissolution and *in Vitro* Dissolution after a Meal

Key: a, simulated *in vivo* dissolution in stomach; b, simulated *in vivo* dissolution in intestine; ■, *in vitro* dissolution data in stomach and intestine.

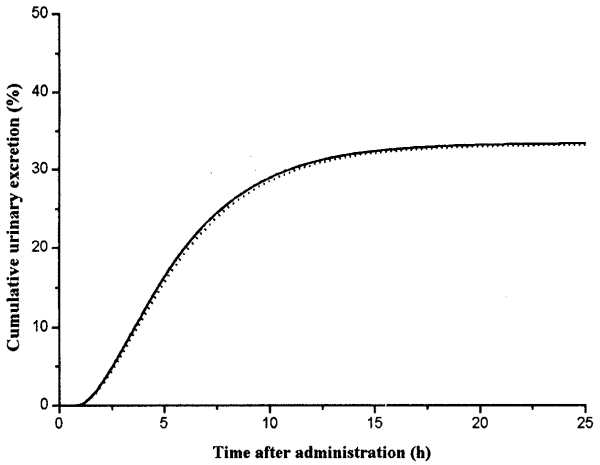

Fig. 10. Correlation between Fitting Curve Obtained from *in Vivo* Data and Predicted Curve Obtained from *in Vitro* Dissolution for Cumulative Urinary Excretion of CAM Following Oral Administration after a Meal

The dotted line was obtained by fitting the cumulative urinary excretion data of CAM following oral administration after a meal. The solid line was predicted from the *in vitro* dissolution profile.

pH in the intestine of human is 5 to 7,[14] a pH of 6.8 for the intestine was selected. In contrast, the same dissolution medium of pH 6.8 for the stomach and the intestine in the postprandial state were used, since the pH in the stomach may be increased by food.[15]

Since the *in vivo* dissolution rate constant in the stomach in the fasting state was $1.873\,h^{-1}$, as shown in Table 1, the flow rate at pH 3.0 of the dissolution medium was 0.8 ml/min, from Eq. 15. It seems reasonable to assume that the flow rate is 0.8 ml/min, since the gastric secretion rate in the fasting state is 0.08—3 ml/min.[16] Similarly, since the *in vivo* dissolution rate in the intestine in the fasting state was $0.254\,h^{-1}$, the flow rate at pH 6.8 of the dissolution medium was 2.9 ml/min, from Eq. 16. For a single postprandial oral administration, since the *in vivo* dissolution rate in the stomach is nearly equal to that in the intestine, the average of the values of the *in vivo* dissolution in the stomach and intestine was used, and the flow rate at pH 6.8 of dissolution medium was found to be 4.9 ml/min using Eq. 16.

Also, it can be assumed that these flow rates in the test are reasonable, because the flow rates of the intestinal contents in the fasting and fed state are 0.33—1.8 ml/min, 3.0—8.3 ml/min, respectively.[17]

***In Vitro–in Vivo* Correlation for Dissolution of a CAM Tablet** In order to correspond to the *in vivo* dissolution of a CAM tablet in the stomach in the fasting state, the flow-through cell method was used with a flow rate of 0.8 ml/min at pH 3.0 of the dissolution medium. The *in vitro* dissolution data were consistent with the *in vivo* dissolution profile, as shown in Fig. 7.

Similarly, the conditions for the intestine in the fasting state were used with a flow rate of 2.9 ml/min and a dissolution medium of pH 6.8. The *in vitro* dissolution data were also consistent with the *in vivo* dissolution profile, as again shown in Fig. 7.

Figure 8 shows the urinary excretion of CAM after a single oral administration in the fasting state simulated by substituting the *in vitro* dissolution rate constants

obtained into the equation for cumulative urinary excretion.

For postprandial administration, the same conditions of the flow-through cell method were used with dissolution medium of pH 6.8 at a flow rate of 4.9 ml/min. The dissolution data obtained were consistent with the *in vivo* dissolution profiles, as shown in Fig. 9. Figure 10 shows the urinary excretion of CAM following a single postprandial oral administration simulated by substituting the *in vitro* dissolution rate constants into Eq. 1. In the case of a single postprandial oral administration, the line obtained was also consistent with the *in vivo* data.

Conclusion

In vitro dissolution tests corresponding to *in vivo* dissolution in the stomach and intestine following a single oral administration in the fasting or postprandial state for CAM tablet were established.

Little difference was found between *in vitro* and *in vivo* dissolution, and a good *in vitro–in vivo* correlation was obtained. The values of urinary excretion of CAM predicted by substituting the *in vitro* dissolution rate constants and the *in vivo* gastrointestinal transit rate into the pharmacokinetic model fit the actual experimental data well. In the case of different subjects, the prediction obtained from the *in vitro* dissolution may deviate a little from the *in vivo* urinary excretion. However, this method is useful for the study of formulation, quality control and minor changes in formulation, since the *in vitro* dissolution corresponding to the urinary excretion in the biobatch can be obtained. And, for oral solid dosage forms containing CAM, this method is useful for predicting *in vivo* performance.

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