Correlations between in Vivo and in Vitro Dissolution Rates of (α-Bromoisovaleryl)urea Polymorphs

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Correlations between the in vivo and in vitro dissolution rates of (α-bromoisovaleryl)urea polymorphs were investigated. The calculated dissolution rate constants obtained in the in vitro dissolution experiments were 0.135 and 0.133 (cm/min) for form I and form II, respectively. On the other hand, the crystals were administered intraduodenally into rats and the time course data of the plasma concentration were analyzed by the least-squares method on the basis of the Hixson–Crowell dissolution model for the intestinal dissolution process. The in vivo dissolution rate constants were obtained as 0.0629 and 0.0758 (cm/min) for form I and form II, respectively.

These in vivo and in vitro dissolution rate constants are based on the Noyes–Nernst dissolution theory and should be comparable in nature. Nevertheless, the in vivo rate constants were about a half of those in vitro. This result suggests that the stirring efficiency in the intestine is about a half of that of the in vitro dissolution experiment in this study.

Keywords—(α-bromoisovaleryl)urea; polymorph; pharmacokinetics; dissolution rate; dissolution rate constant; least-squares analysis; intestine; Noyes–Nernst model; Hixson–Crowell model

It is well known that the dissolution rate of crystals affects the absorption of drugs in the intestine. However, it has been considered difficult to relate the dissolution properties obtained in in vitro experiments to the in vivo pharmacokinetics, because the dissolution rate of crystals in the intestine is affected by the biological conditions, e.g. emptying time, secretions, or vermiculation of the intestine. Recently, Wataru et al. studied the effect of particle size of sulfadimethoxine on the oral bioavailability, and demonstrated a relationship between the dissolution rates obtained from the blood concentrations by the deconvolution method and those predicted by the Hixson–Crowell model on the basis of in vitro dissolution experiments.2) More recently, Tanigawara et al. presented a method for evaluating the dissolution rate from the blood concentration data by the use of statistical moment theory.3)

We have investigated the bioavailability and dissolution properties of the polymorphic forms of (α-bromoisovaleryl)urea.4,5) In the previous report,6) a pharmacokinetic study on the fate of the drug was presented, with a kinetic model having a single first-order rate process for the dissolution-absorption process. However, these studies did not deal with the quantitative relationship of the in vitro dissolution rates of the crystals to the time courses of blood concentration after the oral administration of crystalline drugs.

In this study, the dissolution rate constants of the polymorphic forms of (α-bromoisovaleryl)urea obtained in in vitro dissolution experiments were applied to an intestinal dissolution model, and the time course data of the plasma concentrations after intraduodenal administration of the polymorphs were analyzed by a least-squares curve-fitting method. The correlations of the in vivo and in vitro dissolution rate constants are discussed.

Experimental

Preparation and Identification of (α-Bromoisovaleryl)urea Polymorphs—(α-Bromoisovaleryl)urea polymorphs
(form I and form II) were prepared and identified as described previously.\textsuperscript{7} 

**Dissolution Experiments**—Powdered (\(\alpha\)-bromoisovaleryl)urea (about 2 g, 100—170 mesh) was suspended in 10 ml of 5\% gelatin solution, and immediately added to 190 ml of water stirred with a Teflon plate (3.5 × 6 cm) at 150 rpm in a double-walled beaker at 37 °C. The samples were treated and determined as described previously.\textsuperscript{4}

**Animal Experiments**—Wistar male rats, 180—220 g body weight, were fasted for one night before the experiment. The animals were cannulated with polyethylene tubing in the duodenal lumen and the femoral artery under ether anesthesia. Four mg (per 200 g body weight) of the powdered drug was suspended in 0.25 ml of 5\% gelatin solution and administered into the duodenum, as described previously.\textsuperscript{5} Blood samples were collected and the plasma concentrations of the drug were determined as in the previous study.\textsuperscript{5}

**Computations**—Computations were carried out on the same computers and with the same programs for least-squares analyses as described in the previous paper.\textsuperscript{6} Other programs for the model analyses and simulations presented here were written by the authors in Fortran.

**Theoretical**

The dissolution rate of a drug can generally be described by the Noyes–Nernst equation, which is based on the assumption that the dissolution process is rate-limited by diffusion from the thin layer of saturated solution at the solid surface into the bulk solution, as shown in Fig. 1.\textsuperscript{8,9} The equation is as follows:

\[
\frac{dC}{dt} = \frac{D \cdot S}{h \cdot V} (C_s - C) = k \cdot \frac{S}{V} (C_s - C) = K_a (C_s - C)
\]

where \(D\) is the diffusion coefficient, \(h\) is the thickness of the diffusion layer, \(S\) is the surface area of the solid, \(V\) is the volume of dissolution medium, \(C_s\) is the saturated concentration, \(C\) is the concentration in the bulk solution, \(k\) \((=D/h)\) is the dissolution rate constant which is used for the discussion in this paper, and \(K_a\) is the apparent dissolution rate constant in the Noyes–Nernst model.

The dissolved drug is immediately absorbed, because the absorption rate constant of (\(\alpha\)-bromoisovaleryl)urea after intraduodenal administration of the solution is very large, as shown in the previous report \((K_a = 0.712 \text{ min}^{-1})\).\textsuperscript{5} Therefore, it is considered that the dissolution of the drug in the intestine meets the sink condition \((C \ll C_s)\), and the particle size decreases in the process of absorption. The Noyes–Nernst equation can be transformed on the basis of the two assumptions described above in the following way\textsuperscript{10} to describe the dissolution of an individual particle in the sink condition;

\[
\frac{dW_i}{dt} = k \cdot S_i \cdot C_s = -k \cdot \pi \cdot a_i^2 \cdot C_s
\]

where \(W_i\) is the weight of the particle at time \(t\), \(S_i \ (= \pi \cdot a_i^2)\) is the surface area of the particle, and \(a_i\) is the diameter of the particle. The weight of the particle is expressed as follows;

\[
W_i = \frac{\pi \cdot a_i^3 \cdot \rho}{6}
\]

where \(\rho\) is the density of the particle. Differentiation of Eq. 3 with respect to time \((t)\) gives,

\[
\frac{dW_i}{dt} = \frac{\pi \cdot a_i^2 \cdot \rho \cdot da_i}{2 \cdot dt}
\]

By substituting Eq. 4 into Eq. 2 and rearranging the resultant equation, the following equation is obtained.

![Fig. 1. Schematic Illustration of the Noyes–Nernst Dissolution Model](image)

- \(C_s\): Saturated concentration.
- \(C\): Concentration in the bulk solution.
- \(h\): Thickness of diffusion layer.
\[
\frac{da_i}{\rho} = -2 \cdot k \cdot C_i \cdot dt
\]  
(5)

By integrating Eq. 5 from time 0 to time \( t \), the diameter of the particle is obtained as a function of time \( t \) as follows;
\[
a_i = a_i^0 - \frac{2 \cdot k \cdot C_i}{\rho} \cdot t
\]  
(6)

where \( a_i^0 \) is the diameter of the particle at time 0. The cube root of \( W_i \) can be expressed as follows after the substitution of Eq. 6 into Eq. 3.
\[
(W_i)^{1/3} = \left( \frac{\pi \cdot \rho}{6} \right)^{1/3} \cdot a_i = \left( \frac{\pi \cdot \rho}{6} \right)^{1/3} \cdot \left( a_i^0 - \frac{2 \cdot k \cdot C_i}{\rho} \cdot t \right)
\]  
(7)

The cube root of Eq. 3 at time 0 is as follows;
\[
(W_i^0)^{1/3} = \left( \frac{\pi \cdot \rho}{6} \right)^{1/3} \cdot a_i^0
\]  
(8)

After substituting Eq. 8 into Eq. 7, the following equation is obtained.
\[
3 \cdot \sqrt{W_i^0} - 3 \cdot \sqrt{W_i} = \left( \frac{\pi \cdot \rho}{6} \right)^{1/3} \cdot \frac{2 \cdot k \cdot C_i}{\rho} \cdot t
\]  
(9)

Assuming that the crystals are in the monodisperse state, the total weight of particles is expressed as follows;
\[
W = N \cdot W_i
\]  
(10)

where \( N \) is the number of particles. After substituting Eq. 10 into Eq. 9, the Hixson–Crowell cube root equation is obtained.\(^{11}\)
\[
3 \cdot \sqrt{W_0} - 3 \cdot \sqrt{W} = \left( \frac{\pi \cdot N \cdot \rho}{6} \right)^{1/3} \cdot \frac{2 \cdot k \cdot C_i}{\rho} \cdot t = \frac{2 \cdot k \cdot C_i \cdot 3 \cdot \sqrt{W_0}}{\rho \cdot a_0} \cdot t
\]  
(11)

where \( a_0 \) is the mean diameter of the particles at time 0, \( W_0 \) is the total weight of the drug at time 0, and \( W \) is the total weight of the undissolved drug at time \( t \). The derivation of this equation is based on the assumption that the shape factors for cubic (or spherical) particles are constant as long as they dissolved equally from all sides.

The following differential equation derived from Eq. 11 is used for the pharmacokinetic model analysis,
\[
\frac{dW}{dt} = -3 \cdot \frac{2 \cdot k \cdot C_i \cdot 3 \cdot \sqrt{W_0}}{\rho \cdot a_0} \cdot W_{2/3} = -K_d \cdot W^{2/3}
\]  
(12)

Fig. 2. Pharmacokinetic Model for in Vivo Behavior of (\( \alpha \)-Bromoisonovaleryl)urea after the Intraduodenal Administration of Crystals

- \( X_1 \): Amount of crystalline drug in intestine.
- \( X_2 \): Amount of dissolved drug in intestine.
- \( X_3 \): Amount of drug in central compartment.
- \( X_4 \): Amount of drug in peripheral compartment.
- \( C_d \): Concentration of drug in plasma.
- \( V_d \): Distribution volume.
- \( K_{p} \): Apparent dissolution rate constant in the Hixson–Crowell model.
- \( K_{a} \): First-order rate constant for absorption.
- \( K_{e} \): First-order rate constant for elimination.
- \( K_{t} \): First-order rate constant for transfer.
where $K_a$ is the apparent dissolution rate constant in the Hixson–Crowell model.

Based on this model of the dissolution process in the intestine, the pharmacokinetic model shown in Fig. 2 is presented for the analysis of the in vivo data in relation to the dissolution properties of the crystals in vitro. The rate of change in the amount of the drug in each compartment of the model is described by the following differential equations.

\[
\begin{align*}
\frac{dX_1}{dt} &= -K_a \cdot X_1 \cdot t^{2/3} \\
\frac{dX_2}{dt} &= K_a \cdot X_1 \cdot t^{2/3} - K_4 \cdot X_2 \\
\frac{dX_3}{dt} &= K_4 \cdot X_2 - (K_4 + K_5) \cdot X_3 + K_2 \cdot X_4 \\
\frac{dX_4}{dt} &= K_1 \cdot X_3 - K_3 \cdot X_4
\end{align*}
\]

(13)

where $X_0$ is the weight administered, and $F$ is the ratio of the dissolved drug in the gelatin solution to the dose at time 0, assessed from the in vitro experiments. Other expressions are shown in Fig. 2. Integrating under the initial conditions, as shown in the brackets following the equations at time 0, we obtain the plasma concentration of the drug as follows:

\[
C_3 = A \cdot e^{-K_a \cdot t} + B \cdot e^{-K_4 \cdot t} + C \cdot e^{-K_5 \cdot t} + D \cdot t^2 + E \cdot t + FF
\]

(14)

(see Appendix I)

However, Eq. 14 holds only while the crystals are present in the intestine. After the crystals are completely dissolved the following differential equations are obtained from the model shown in Fig. 2 without the crystal compartment.

\[
\begin{align*}
\frac{dX_2}{dt} &= -K_4 \cdot X_2 \\
\frac{dX_3}{dt} &= K_4 \cdot X_2 - (K_4 + K_5) \cdot X_3 + K_2 \cdot X_4 \\
\frac{dX_4}{dt} &= K_1 \cdot X_3 - K_3 \cdot X_4
\end{align*}
\]

(15)

The disappearance time of crystals ($T_0$) was obtained by calculation from the apparent dissolution rate constant ($K_a$) found by curve fitting analysis based on the model shown in Fig. 2. The mean $T_0$ values of form I and form II were 62.6 and 34.9 min, respectively. Integrating Eq. 15 under the initial conditions described in the brackets following the equations, which are the calculated amounts of the drug in the compartments at time $T_0$ obtained by simulation, we obtained the time function of the plasma concentration after $T_0$ as follows:

\[
C_3 = A \cdot e^{-K_a \cdot t} + B \cdot e^{-K_4 \cdot t} + C \cdot e^{-K_5 \cdot t}
\]

(16)

(see Appendix II)

In order to compare the dissolution parameters obtained in the in vitro and in vivo experiments, the following derivations were carried out.

Integrating the Noyes–Nernst equation (Eq. 1) under the condition of constant surface area, we obtain the following equation.

\[
\ln \left( \frac{C}{C_0} \right) = \frac{k \cdot S}{V} \cdot t = K_a \cdot t
\]

(17)

The in vitro dissolution rate constant ($k_{in\text{ vivo}}$) is calculated from the apparent dissolution rate constant ($K_a$) obtained in the in vitro dissolution experiment (Eq. 17) as follows;

\[
k_{in\text{ vitro}} = \frac{V}{S} \cdot K_a
\]

(18)

On the other hand, the in vivo dissolution rate constant ($k_{in\text{ vivo}}$) is calculated on Eq. 12 from the in vivo apparent dissolution rate constant ($K_d$) as follows;

\[
k_{in\text{ vivo}} = \frac{\rho \cdot a_0 \cdot K_d}{6 \cdot C_i \cdot \sqrt{W_0}}
\]

(19)
These two calculated dissolution rate constants \((k_{\text{intra}}\) and \(k_{\text{intra}}\)) should be comparable in nature because both rate constants are derived from the Noyes–Nernst dissolution theory (Eq. 1).

The derivations in this theory are based on the assumption of constant solubility with decreasing particle size in the intestinal compartment. On the other hand, it is known that the solubility of fine particles depends on the particle size\(^{14}\) as given in the Ostwald–Freundlich equation;

\[
\frac{R \cdot T}{M} \ln \frac{C_2^*}{C_1^*} = \frac{2}{\rho} \left[ \frac{1}{\gamma} \left( \frac{1}{r_2} - \frac{1}{r_1} \right) \right]
\]  

(20)

where \(C_1^*\) and \(C_2^*\) are the solubilities of particles with radii of \(r_1\) and \(r_2\), respectively, \(R\) is the gas constant, \(T\) is absolute temperature, \(M\) is molecular weight, \(\rho\) is density and \(\gamma\) is surface tension. In this experiment, the powdered drug was administered in gelatin solution. Therefore, the surface tension is reduced and it is assumed that the contribution of the particle size to the solubility in the intestine is negligible.

**Results and Discussion**

To obtain the dissolution parameters *in vitro*, plots based on Eq. 17 were drawn, as shown in Fig. 3. Linear plots were obtained. The apparent dissolution rate constants \((K_a)\) were obtained from the slopes as 0.447 and 0.457 \(\text{min}^{-1}\) for form I and form II, respectively. The saturated concentration values were obtained from the previous dissolution experiments in gelatin solution\(^1\) as 2.30 and 3.41 \(\mu\text{g/ml}\) for form I and form II, respectively. The condition of constant surface area assumed in the derivation of Eq. 17 should hold, since a large excess of crystals over that required for saturation was used, and the data were collected at the very early stage of the dissolution process, as shown in Fig. 3.

The *in vitro* dissolution rate constants \((k_{\text{intra}})\) were calculated by means of Eq. 18 as 0.135 and 0.133 \(\text{cm/min}\) for form I and form II, respectively. In this experiment, assuming that the powder is in the monodisperse particle state, the logarithmic mean diameter \((a_0 = 111.6 \mu\text{m})\) was used for the mean diameter of the particles.\(^{10}\) The density values of \((\alpha\)-bromoisovaleryl)urea polymorphs are given in the literature\(^{12}\) as 1.62 g/cm\(^3\) for form I and 1.56 g/cm\(^3\) for form II. Form these values, the surface area of the particles was calculated based on Eq. 3 as follows;

\[
S = \frac{6 \cdot W_0}{\rho \cdot a_0}
\]

(21)

The surface area of form I was 663.8 cm\(^2\) and that of form II was 689.3 cm\(^2\).

The intercepts of the straight lines shown in Fig. 3 suggest that a part of the drug had been dissolved before time 0 during the brief mixing of the crystals in the gelatin solution before the dissolution experiment.

The plasma concentration data after the intraduodenal administration of the polymorphs of \((\alpha\)-bromoisovaleryl)urea are shown in Fig. 4. The continuous lines in the figure are
calculated curves using the parameter values obtained by the least-squares curve-fitting analyses with the SALS program\(^{13}\) based on the model shown in Fig. 2 before and after \(T_0\) (time of consumption of crystals in the intestine) as described above. For the initial values of the parameters for the least-squares curve fitting, the values obtained in the previous experiment\(^{6}\) were used except in the case of \(K_d\). The calculated value from the \(k\) value obtained in the in vitro experiment described above was used as the initial value of \(K_d\).

It seems reasonable to assume the validity of the pharmacokinetic model based on the Hixson–Crowell model in the intestine compartment, because the calculated curves showed better agreement with the experimental data (Fig. 4) than the first-order absorption model presented in the previous study.\(^{6}\)

The parameter values obtained by the least-squares method are shown in Table I. The apparent dissolution rate constant (\(K_d\)) of form II was twice that of form I. The fraction of dissolved drug at the time of administration (\(F\)), caused by the mixing with the gelatin solution as suggested by the in vitro experiments mentioned above, of form II was 2.5 times

**Table I. Pharmacokinetic Parameters Obtained by the Least-Squares Method Based on the Model Shown in Fig. 2**

<table>
<thead>
<tr>
<th></th>
<th>(K_d) ((\mu g^{13} \cdot \text{min}^{-1}))</th>
<th>(K_1) ((\text{min}^{-1}))</th>
<th>(K_2) ((\text{min}^{-1}))</th>
<th>(K_{sl}) ((\text{min}^{-1}))</th>
<th>(V_d) (ml)</th>
<th>(F) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form I</td>
<td>(0.770 \pm 0.094)</td>
<td>(6.978 \pm 0.022)</td>
<td>(4.153 \pm 0.024)</td>
<td>(1.745 \pm 0.013)</td>
<td>(2.633 \pm 0.060)</td>
<td>(179.7 \pm 6.4)</td>
</tr>
<tr>
<td>Form II</td>
<td>(1.414 \pm 0.303)</td>
<td>(6.973 \pm 0.054)</td>
<td>(4.184 \pm 0.028)</td>
<td>(1.722 \pm 0.011)</td>
<td>(2.594 \pm 0.057)</td>
<td>(184.2 \pm 6.1)</td>
</tr>
</tbody>
</table>

**Table II. Dissolution Parameters Obtained in in Vivo and in Vitro Experiments**

<table>
<thead>
<tr>
<th></th>
<th>Apparent dissolution rate constant</th>
<th>Intrinsic dissolution rate constant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(K_d) ((\mu g^{13} \cdot \text{min}^{-1}))</td>
<td>(k_{in vivo}) (cm/min)</td>
</tr>
<tr>
<td>Form I</td>
<td>(0.770 \pm 0.094)</td>
<td>(0.447 \pm 0.015)</td>
</tr>
<tr>
<td>Form II</td>
<td>(1.414 \pm 0.262)</td>
<td>(0.457 \pm 0.033)</td>
</tr>
<tr>
<td>Mean</td>
<td>(0.694 \pm 0.0013)</td>
<td>(0.552 \pm 0.0008)</td>
</tr>
</tbody>
</table>

Fig. 4. Plasma Concentration after Intraluminal Administration of \((\alpha\)-Bromoisovaleroyl)urea Polymorphs

(a), form I; (b), form II. Points are each the mean ± S.E. of four rats. Continuous lines are those computed by the SALS program for the model shown in Fig. 2.
that of form I. Other kinetic parameter values were very similar for form I and form II. In the present model, the sink condition of the dissolution process in the intestine was confirmed by simulation of the concentration of the drug in the intestinal compartment, which showed that the maximum concentration was about 5—6% of the saturated concentration.

The parameter values obtained or calculated in the in vivo and in vitro experiments are listed in Table II. The apparent dissolution rate constants obtained in the in vivo experiment (K_d) showed significant differences (p < 0.05) between form I and form II, as mentioned above, but in the in vitro experiment, there was no significant difference between form I and form II. However, these two apparent dissolution rate constants are different in nature, and thus are not strictly comparable.

On the other hand, the dissolution rate constants (k) calculated from the apparent rate constants are essentially the same in nature as mentioned previously. The calculated dissolution rate constants either in vivo or in vitro did not show significant differences between form I and form II. However, there were significant differences (p < 0.05) between in vivo and in vitro values, and the dissolution rate constants in vitro are twice those in vivo, as shown in Table II.

In this study, it is demonstrated that the in vitro dissolution model can be introduced into the in vivo pharmacokinetics. However, the in vivo dissolution rate constants were about a half of those in vitro, and thus the dissolution process in the intestine was not fully reflected in the in vitro dissolution behavior. It is considered that this discrepancy is mainly caused by the stirring conditions, because, the calculated dissolution rate constant depends on the diffusion coefficient and the thickness of the saturated solution layer (k = D/ℓ) as mentioned previously, and the former depends on the temperature and viscosity of medium, while the latter depends on the stirring efficiency. It is considered that there are only very small differences of viscosity and temperature between the in vivo and in vitro experiments, because both experiments were carried out at the same temperature (37°C) in gelatin solution of same concentration. Therefore, it is concluded that the stirring efficiency of the intestine of rat is about a half of that in the in vitro dissolution experiment in this study.

This observation suggests that it is possible to introduce the dissolution parameters obtained in in vitro experiments into an in vivo study with the stirring factor of 0.5, and this has important implications for pharmacokinetic studies of the dissolution and absorption of crystalline drugs.

Appendix I

The time function of the plasma concentration in the model shown in Fig. 2 is as follows:

\[ C_3 = A \cdot e^{-k_a \cdot t} + B \cdot e^{-k_b \cdot t} + C \cdot e^{-k_c \cdot t} + D \cdot t^2 + E \cdot t + FF \]

where

\[ A = A_a + A_b; \quad B = B_a + B_b; \quad C = C_a + C_b \]

\[ K_a \cdot (K_2 - K_3) \cdot K_d \cdot \left[ X_a^{2/3} \cdot K_a^2 + \frac{2}{3} K_d \cdot X_a^{1/3} \cdot K_a + \frac{2}{9} K_d^2 \right] \]

\[ \frac{K_a \cdot (K_2 - K_3) \cdot K_d}{-K_a^2 \cdot (p - K_d) \cdot (q - K_3) \cdot V_d} \]

\[ A_b = \frac{X_b \cdot K_a \cdot (K_2 - K_3)}{V_d \cdot (p - K_3) \cdot (q - K_3)} \]

\[ K_a \cdot (K_2 - q) \cdot K_d \cdot \left[ X_a^{2/3} \cdot p^2 + \frac{2}{3} K_d \cdot X_a^{1/3} \cdot p + \frac{2}{9} K_d^2 \right] \]

\[ \frac{K_a \cdot (K_2 - p) \cdot K_d}{-p^2 \cdot (K_a - p) \cdot (q - p) \cdot V_d} \]
\[ B_n = \frac{X_b \cdot K_s \cdot (K_2 - p)}{V_d \cdot (K_s - p) \cdot (q - p)} \]

\[ C_s = \frac{K_s \cdot (K_2 - q) \cdot K_\nu \left[ \frac{X_s^{2/3} \cdot q^2 + \frac{2}{3} K_d \cdot X_s^{1/3} \cdot q + \frac{2}{9} K_s^2}{-q^3 \cdot (K_s - q) \cdot (p - q) \cdot V_d} \right] \]

\[ C_b = \frac{X_b \cdot K_s \cdot (K_2 - q)}{V_d \cdot (K_s - q) \cdot (p - q)} \]

\[ D = \frac{2}{9} \cdot K_d \cdot K_2 \]

\[ E = \frac{2}{9} \cdot K_s \cdot K_2^2 - \frac{2}{3} \cdot K_s \cdot K_2 \cdot X_s^{1/3} - \frac{1}{2} \cdot D \cdot V_d \cdot (K_s \cdot p + q \cdot p + K_s \cdot q) \]

\[ FF = \frac{V_d \cdot K_s \cdot p \cdot q}{V_d \cdot K_s \cdot p \cdot q} \]

\[ X_s = \{1.0 - F\} \cdot X_0; \quad X_b = F \cdot X_0 \]

\[ p = \frac{1}{2} \cdot \frac{[K_1 + K_2 + K_{s1}] + \sqrt{(K_1 + K_2 + K_{s1})^2 - 4K_2 \cdot K_{s1}}}{2} \]

\[ q = \frac{1}{2} \cdot \frac{[K_1 + K_2 + K_{s1}] - \sqrt{(K_1 + K_2 + K_{s1})^2 - 4K_2 \cdot K_{s1}}}{2} \]

### Appendix II

The time function of the plasma concentration after the time \( T_0 \) at which crystals are completely consumed by absorption is as follows:

\[ C_3 = A \cdot e^{-K_s \cdot t} + B \cdot e^{-P \cdot t} + C \cdot e^{-q \cdot t} \]

where

\[ A = \frac{K_s \cdot (K_2 - K_s) \cdot X_{o2}}{V_d \cdot (p - K_s) \cdot (q - K_s)} \]

\[ B = \frac{K_s \cdot (K_2 - p) \cdot X_{o2} + (K_s - p) \cdot (K_2 - p) \cdot X_{o3} + K_2 \cdot (K_s - p) \cdot X_{o4}}{V_d \cdot (K_s - p) \cdot (q - p)} \]

\[ C = \frac{K_s \cdot (K_2 - q) \cdot X_{o2} + (K_s - q) \cdot (K_2 - q) \cdot X_{o3} + K_2 \cdot (K_s - q) \cdot X_{o4}}{V_d \cdot (K_s - q) \cdot (p - q)} \]

### References and Notes

1) A part of this work was presented at the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1982.


12) A. Watanabe, *Yakugaku Zasshi*, 58, 565 (1928).