Novel Mathematical Model for Predicting the Dissolution Profile of Spherical Particles under Non-sink Conditions

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Summary

A mechanistic mathematical model was designed to predict dissolution patterns under non-sink conditions. Sulfamethoxazole was used as a model drug, and its physico-chemical properties such as solubility, density, and intrinsic dissolution rate constant etc, were investigated in order to apply these experimental values to the proposed model. Dissolution tests were employed as a way of validating the mathematical model, and it was found that the predictions given by the model were surprisingly accurate for all particle sizes. In addition, a simulation focused on forecasting the fraction of the drug that was dissolved at a certain time point when various initial particle diameters were used was also particularly valuable. Therefore, these results demonstrated that the model enables dissolution profiles to be analyzed under non-sink conditions.

Keywords
Mathematical model, Non-sink condition, Sulfamethoxazole, Dissolution rate control
Introduction

The quantitative prediction of drug dissolution profiles is critically important for elucidating the pharmacokinetic behavior of drugs. The determination of drug dissolution in vitro is one of the key elements in the pharmaceutical development process and is sometimes used as a surrogate for the assessment of bioequivalence. Therefore, many mathematical models for predicting drug dissolution, which can be roughly categorized into mechanistic and empirical methods, have been proposed.

The basic mechanistic models for solid dissolution were developed by Noyes-Whitney and later Nernst and Brunner. These familiar models are known as “diffusion-controlled models” today. Furthermore, based on these models, the “cube-root law” devised by Hixson and Crowell and other equations were developed. One of the significant advantages of these mechanistic models is that they allow easy prediction of a drug dissolution profile without requiring a dissolution test because physical parameters such as solubility, density, diffusivity etc, which are components of the equations, can be determined by more convenient experiments. In addition, since the crucial parameters that influence drug dissolution patterns have been clarified, the models may be useful for controlling drug dissolution patterns.

Although, to the best of our knowledge, perfect sink conditions, in which the bulk concentration of a drug is considerably less than its solubility, have been universally assumed in these models, discrepancies between the theoretical and experimental data have been found for water-insoluble drugs, suggesting that the development of new mechanistic models for predicting almost all kinds of drug dissolution is desired.

On the other hand, empirical and semiempirical models, not mechanistic models, have also been developed by numerous researchers. A general empirical equation called the Weibull model has been applied to the drug dissolution process by Langenbucher et al., and this model can be adapted to almost all kinds of drug dissolution (Goldsmith, Vudathala). Korsmeyer et al. also developed a semiempirical model called the Korsmeyer-Peppas model. This Korsmeyer-Peppas model is surprisingly simple, but is capable of predicting many kinds of drug dissolution profiles. Although both the Weibull and Korsmeyer-Peppas models are able to describe drug dissolution profiles even if the drug is water-soluble or not, a dissolution test is required to determine the parameters of the equations because these models
are not mechanistic. Therefore, empirical and semiempirical models are difficult to apply to the control of drug dissolution patterns as desired.

It has been estimated that more than 40% of the new chemical entities developed through a high throughput drug discovery program have poor water solubility.\(^{12,13}\) In order to effectively develop pharmaceutical products, the establishment of a new mechanistic model that is independent of drug solubility is desired. The purpose of the present study is to derive an adequate equation that describes the dissolution patterns of poorly water-soluble drugs under non-sink conditions and to validate the equation experimentally using sulfamethoxazole (SMX) as a model drug.

**Theory**

The amount \((W)\) of a drug flowing through a unit cross-section of the available surface area \((S)\) in unit time \((t)\) is known as flux \((J)\).

\[
J = \frac{dW}{Sdt}
\]  
(1)

Based on Fick’s first law, flux is expressed as follows:

\[
J = -D \frac{dC}{dx}
\]  
(2)

in which \(D\) is the diffusion coefficient of a drug molecule, \(C\) is its concentration, and \(x\) is the distance moved perpendicular to the available surface.

Using the following assumptions, equation (2) becomes equation (3).

- The particle is in a well-stirred solution, and a boundary layer of constant thickness \((h)\) exists around the particle.
- The concentration at the interface between the solid and the solution is saturated \((C_s)\), and solubility is independent of particle size.
- During dissolution, a pseudo-steady-state is established with only minimal solid dissolution, after which the overall mass transport rates across the inner and outer surfaces of the diffusion layer are assumed to be equal.
\[ J = \frac{D}{h} (Cs - C) \quad (3) \]

where \( C \) is bulk solution concentration. Substituting equation (1) into equation (3) gives:

\[ \frac{dW}{dt} = -kS(Cs - C) \quad (4) \]

where \( k \) represents the dissolution rate constant per unit area (intrinsic dissolution rate constant) \( (k = D/h) \). Since sink conditions, in which the bulk concentration of a drug \( (C) \) is considerably less than its solubility \( (Cs) \), have been universally assumed (Fig. 1 (a)), term \( (Cs - C) \) of equation (4) is approximated by \( Cs \). However, in the present study, this term is not approximated since we assumed the non-sink conditions, in which there are not significant differences between \( C \) and \( Cs \), as illustrated in Fig. 1 (b).

On the other hand, for \( N \) monodispersed spherical particles, the drug amount present in the system is:

\[ W = \frac{N\pi\rho}{6}X^3 \quad (5) \]

where \( \rho \) is the density of the particle, and \( X \) is the diameter of particle.

Differentiating both sides of equation (5) with time gives:

\[ \frac{dW}{dt} = \frac{N\pi\rho}{2}X^2 \frac{dX}{dt} \quad (6) \]

Here, we assume that the available surface area \( (S) \) is equal to the particle surface area:

\[ S = N\pi X^2 \quad (7) \]

From equations (4), (6), and (7), we get the following ordinal differential equation:

\[ \frac{dX}{dt} = -\frac{2k}{\rho} (Cs - C) \quad (8) \]

Using \( X_0 \) for the initial particle diameter and \( V \) for the volume of solvent, concentration \( C \) is represented as:

\[ C = \frac{N\pi\rho}{6V} (X_0^3 - X^3) \quad (9) \]

Substituting equation (9) into equation (8) gives:
\[ \frac{1}{a + bX^3} \frac{dX}{dt} = -\frac{2k}{\rho} \]  \hspace{1cm} (10)

where \( a \) and \( b \) are constants:

\[ a = Cs - \frac{N\pi\rho}{6V} X^3 \]  \hspace{1cm} (11)

\[ b = -\frac{N\pi\rho}{6} \]  \hspace{1cm} (12)

Solving equation (10) gives:

\[ F(X) - F(X_0) = -\frac{2k}{\rho} t \]  \hspace{1cm} (13)

where the function \( F \) is defined as follows:

\[ F(X) = \frac{1}{6b} \left( \frac{b}{a} \right)^{2/3} \left[ \ln \left( \frac{X - (a/b)^{1/3}}{X^2 - (a/b)^{1/3} X + (a/b)^{2/3}} \right) + 2\sqrt{3} \arctan \left( \frac{2}{\sqrt{3}} \frac{(b/a)^{1/3} X - 1}{\sqrt{3}} \right) \right] \]  \hspace{1cm} (14)

The symbolic calculus was conducted using Maple. Rearranging equation (13) gives:

\[ X = F^{-1} \left( F(X_0) - \frac{2k}{\rho} t \right) \]  \hspace{1cm} (15)

where \( F^{-1} \) is the inverse function of the function \( F \).

The fraction of the drug dissolved (%Dissolved) is defined using equation (15):

\[ \%Dissolved = \frac{100}{X_0^3} \left( F^{-1}(X) - \frac{2k}{\rho} t \right)^3 \]  \hspace{1cm} (16)

where \( F^{-1}(X) \) was calculated using the software Excel and Maple.

The fraction of the drug dissolved under sink conditions (%Dissolved\textsubscript{sink}) can also be derived from the cube-root law:

\[ \%Dissolved\textsubscript{sink} = 100 \left( 1 - \frac{2kCs}{\rho X_0} t \right)^3 \]  \hspace{1cm} (17)
Materials and Methods

Materials

Sulfamethoxazole (SMX) was purchased from Wako Pure Chemical Ind. Ltd. (Osaka, Japan). All of the reagents used were of the highest grade available from commercial sources.

Preparation of SMX

SMX crystals were prepared by the recrystallization method. Briefly, after SMX had been completely dissolved in boiled ethanol, the solution was filtered immediately. The filtrate was then spontaneously cooled to room temperature. The separated SMX crystals were then recovered and desiccated for 3 hours at 40°C. After drying-out the SMX crystals, they were classified by sieving. Next, the sieved crystals were washed with distilled water to remove the micro particles adhered to their surfaces and then desiccated for 3 hours at 40°C.

Dissolution study

The dissolution behavior of SMX was examined in accordance with the paddle method listed in the Japanese Pharmacopoeia (15th edition). The test solution was 900 ml phosphate buffer saline (PBS; pH 7.4) at 30.0 ± 0.5°C, and the paddle rotation speed was 50 rpm. At 1, 3, 5, 10, 15, and 20 minutes, the samples (5 ml) were withdrawn. The solution was then filtered through a membrane filter (0.45 μm). Then, the absorbance was determined at 264 nm with a spectrophotometer (UVmini, SHIMADZU), and the SMX concentration was calculated from the absorbance of a standard solution.

Determination of initial particle diameter

About 40 mg of SMX were measured, and the number of particles was counted with the eye. The initial particle diameter, $X_0$, was obtained using the following equation:

$$X_0 = \sqrt[3]{\frac{6w}{n \pi \rho}}$$

(18)

where $w$ is the mass of SMX, $n$ is the number of the particles, and $\rho$ is the density of SMX.

Determination of the solubility of SMX
Three hundred mg of SMX were added to 50 ml of pH 7.4 PBS containing 15v/ν% ethanol at 30°C, and the mixture was agitated for 48 hours. The solubility of SMX was determined in the same manner as described in the dissolution study.

**Determination of the dissolution rate constant per unit area**

In order to determine \( k \), the fixed disk method was used. An SMX disk with a diameter of 1.3 cm (surface area = 1.33 cm\(^2\)) was prepared by compressing 400 mg of the drug powder at a pressure of 1 tf. The disk was placed in a JP dissolution test apparatus and rotated at 50 rpm in PBS at pH 7.4 and 30°C. Five ml of the solution were withdrawn at appropriate intervals and, after adequate dilution, the SMX concentration was calculated spectrophotometrically by the same method as used in the dissolution study.

**Determination of density**

SMX density was measured using a pycnometer.
Results and Discussion

**Determination of physico-chemical parameters of SMX**

Fig. 2 shows the dissolution profile of SMX in a fixed disk with a surface area of 1.33 cm². From the Nernst equation, the following equation (19) was obtained and then was fitted to the experimental data using the least squares method.

\[
\ln \frac{C_s}{C_s - C} = \frac{kS}{V} t \quad (19)
\]

As shown in Fig. 2, good agreement was observed between the theoretical (solid line) and experimental values (symbols). From the slope of equation (19), \( k \) was determined. The value of \( k \) as well as the solubility and the density of the particles are shown in Table 1. Table 2 also shows the initial diameters of the sieved particles as calculated by equation (18).

**Application of the mathematical model to the dissolution behavior of SMX particles**

Fig. 3 (a) shows the dissolution behavior of SMX particles with an initial diameter of 387 \( \mu \)m. The broken and solid curves represent the theoretical values predicted under sink conditions by equation (17) and under non-sink conditions by equation (16), respectively, and the symbols represent the experimentally obtained data. Good agreement was observed between the theoretical values under non-sink conditions (solid curve) and the experimental values (symbols); whereas, a significant deviation from the theoretical values was observed under sink conditions (broken curve). As the cube-root law (equation (17)) was originally applied to compounds with relatively high water solubility, it might be inappropriate to apply it to high doses of poorly water-soluble drugs. In addition, Fig. 3 (b) and (c) show the dissolution behaviors of SMX with initial particle diameters of 520 \( \mu \)m and 609 \( \mu \)m, respectively. As expected, good agreement was obtained between the theoretical values under non-sink conditions (solid curve) and the experimental values (symbols) in both cases, suggesting that the equation derived in the present study is able to predict the dissolution profile of SMX. Furthermore, since this mathematical model was derived without assuming specific physico-chemical properties of SMX, it is considered that this model could allow the prediction of the dissolution profile of other water-insoluble drugs.

However, the experimental values of SMX dissolution at the early and late stages were
shown to be slight higher and lower, respectively, than the predicted values. These deviations may have been caused by the particle size inhomogeneity. Namely, in this study, since we classified the SMX particles by sieving, SMX particle size inhomogeneity remained to some degree. To easily understand this phenomenon, a schematic explanation of the changes in particle size that occurred throughout the dissolution study was constructed (Fig. 4). First, we defined a numerical size distribution function \( n \) as follows:

\[
n(X) = \begin{cases} 
N_L(X = X_L) & \\
N_S(X = X_S) & \\
0 & \text{otherwise}
\end{cases}
\]  

(20)

where \( N_L \) is the number of particles with a larger initial diameter of \( X_L \), and \( N_S \) is the number of particles with smaller initial diameter of \( X_S \). The sum of \( N_L \) and \( N_S \) must equal \( N \) (equation (21)).

\[
N_L + N_S = N \quad (21)
\]

\( N_L \) and \( N_S \) are also constrained by the following equation:

\[
\frac{N_L}{N_L + N_S} r_L^3 + \frac{N_S}{N_L + N_S} r_S^3 = 1 \quad (21)
\]

in which \( r_L \) and \( r_S \) are the coefficients that satisfy the following equations:

\[
r_L = \frac{X_L}{X_0} \quad (22)
\]

\[
r_S = \frac{X_S}{X_0} \quad (23)
\]

If a theoretical system satisfies equations (20) – (23), the mass of the particles in the system \( w \) is given by:

\[
w = \frac{N_L \pi \rho}{6} X_L^3 + \frac{N_S \pi \rho}{6} X_S^3 = \frac{N \pi \rho}{6} X_0^3 \quad (24)
\]

Fig. 4 (a) shows a schematic explanation of this system, and Fig. 4 (b) shows the conditions assumed by equation (16). The model derived in this study cannot distinguish between Fig. 4 (a) and (b), which gave us identical predictions. However, at the early stage of dissolution, the experimental values of SMX dissolution were slight higher. Since the rate of dissolution is affected by \( S \) as shown in equations (4), the sum of the available surface area of \( X_S \) and \( X_L \)
might be larger than that of \( X_0 \), and consequently higher dissolution might be observed. However, this tendency will be changed with time, especially when \( t = t_{\text{disap}} \), where \( t_{\text{disap}} \) is the time when a smaller proportion of the drug has disappeared. The disappearance of a smaller fraction of the drug considerably decreases the available surface area. Therefore, the dissolution rate decreases too, and lower dissolution is observed. Therefore, it was found that since particles with a range of sizes were applied to this system, an unsatisfactory result might be obtained during the early and late stages of dissolution.

**Effect of initial particle size on the dissolution behavior of SMX**

In equation (16), the parameters \( C_s, \rho, \) and \( k \) are characterized by a combination of the drug used and the conditions of the system (solvent, paddle speed), and \( N \) is restricted by the initial dose and initial diameter (equation (18)). However, since the initial diameter \( X_0 \) is only an arbitrary parameter, setting the initial diameter is a way of controlling drug dissolution patterns. Treating \( t \) as a constant \((\bar{t})\) and \( X_0 \) as a variable, equation (16) can be regarded as a function of \( X_0 \), as shown in equations (25) and (26).

\[
X = F^{-1}\left( F(X_0) - \frac{2k}{\rho} \tau \right) \quad (25)
\]

\[
\%\text{Dissolved} = \frac{100}{X_0^3} \left( F^{-1}(X) - \frac{2k}{\rho} \tau \right)^3 \quad (26)
\]

Using this manner, we could resolve some drug development problems. For example, imagine a situation in which more than 85% of a generic drug needs to be dissolved within 15 minutes in order to achieve bioequivalence. The question is what size of particle is needed to achieve this goal. Fig. 5 shows the \( \%\text{dissolved} \) of SMX at \( \tau = 15 \) in the case of an initial dose of 2.5 g. As shown in Fig. 5, the initial diameter that provides the desired dissolution behavior is less than 66 \( \mu \text{m} \).
Conclusions

We have developed a novel equation that describes the dissolution profiles of water-insoluble drugs, and the equation has been validated experimentally. Furthermore, deeper insight into the dissolution of particles was obtained from the equation. Therefore, the equation enables the analysis of dissolution profiles under non-sink conditions.

References
Figure legends

Fig. 1. Steady-state concentration gradient around a planar surface under sink conditions (a) and non-sink conditions (b).

Fig. 2. Dissolution profile of SMX from a fixed disk with an available surface area of 1.33 cm². [open circles: experimental values, solid line: equation (19)]. Each symbol represents the mean ± S.D. (n=3).

Fig. 3. Dissolution profile of SMX particles with initial particle diameters of 387 μm (a), 520 μm (b), and 609 μm (c). [open circles: experimental values, solid curve: prediction under sink model, broken curve: prediction under non-sink model]. Each symbol represents the mean ± S.D. (n = 3).

Fig. 4. Schematic explanation of changes in particle size throughout the dissolution study. (a) In the presence of a range of particle sizes and (b) when using a uniform particle size.

Fig. 5. Simulated %dissolved of SMX after 15 minutes of a dissolution test. The initial amount of SMX was 2.5 g.
**Fig. 1.**

(a) Saturated layer

(b) Saturated layer
Fig. 2.

$\ln \left( \frac{C_s}{(C_s - C)} \right)$

[Graph showing a linear relationship between $\ln \left( \frac{C_s}{(C_s - C)} \right)$ and time (min).]
Fig. 3.
Fig. 4.

\( t = 0 \)

(a) \( N_L \)
\( X_L = r_L X_0 \)
\( N_S \)
\( X_S = r_S X_0 \)

(b) \( N \)
\( X_0 \)

Early stage

\( t = t_{\text{disap}} \)

(a) \( N_L \)
\( \cdots \)
\( \cdots \)

(b) \( N \)
\( \cdots \)

\text{disappeared}
Fig. 5.
Table 1. Physico-chemical parameters of SMX.

<table>
<thead>
<tr>
<th>Physico-chemical parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Solubility ($C_s$)</td>
<td>5.30 $\mu$g/ l</td>
</tr>
<tr>
<td>Density of particles ($\rho$)</td>
<td>1.32 g/ cm$^3$</td>
</tr>
<tr>
<td>Rate constant ($k$)</td>
<td>0.048 cm/ min</td>
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</table>

Table 2. Initial diameter of sieved SMX

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Number of particles (number/ g)</th>
<th>Initial diameter (µm)</th>
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</thead>
<tbody>
<tr>
<td>300 – 420 µm</td>
<td>24963</td>
<td>387</td>
</tr>
<tr>
<td>500 – 600 µm</td>
<td>10290</td>
<td>520</td>
</tr>
<tr>
<td>600 – 710 µm</td>
<td>6437</td>
<td>608</td>
</tr>
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