A Novel Dissolution-Diffusion Model for Investigation of Drug Release from Polymeric Microspheres

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Abstract
A new model was developed for drug release from microspheres. Drug dissolution, diffusion, moving front, and size distribution were considered as main release mechanisms. The proposed dissolution-diffusion model was solved numerically for analysis of dissolved drug concentration profiles. In comparison with Fickian diffusion model and Koizumi model, the proposed model is characteristic of the whole release process without limitation of dissolution rate or solubility. Further, the in vitro controlled release kinetics of nifedipine loaded microspheres of PLA and PLGA was investigated by the proposed modelling method.

Keywords: microspheres, drug release, model, dissolution, diffusion

1. Introduction
Absorption of many drugs is dissolution dependent. Conventional formulations of many drugs are known to have a short elimination half life with significant fluctuations in plasma drug concentrations. Drugs dispersed in polymers in the form of microspheres can improve physical stability and dissolution properties, while the transfer resistance of polymer matrix controls the rate of drug release.

Basically, drug release is possible to be distinguished into two cases, depending on the relative magnitudes of the drug loading and solubility. In the first case, drug concentration in microspheres is much lower than solubility of drug. Drug is assumed molecularly dispersed in the polymer matrix. Drug release is only dependant on diffusion. Crank (1975) presented a diffusion model for the circumstance. However, the mass transfer process is more complex with an initial drug concentration higher than the solubility of the drug in the carrier material. A well-known mathematical model describing such a case is perhaps the Higuchi model (Higuchi, 1961). The principles of pseudo steady state, and linear drug concentration gradient were applied in the model. Based on Higuchi’s work, Koizumi (1995) derived an approximate solution for drug release in an explicit form. Many of these models are only adequate for soluble drugs.

Harland (1988) proposed a diffusion-dissolution model, in which a linear dissolution term was added in Fick’s second law of diffusion. Later, Wong (2001) used this model in the investigation of in vitro controlled release kinetics of human immunoglobulin G (IgG) loaded microspheres. Modeling study suggested that mechanisms of drug release

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were mainly diffusion and dissolution controlled. However, the influence of moving boundary resulting from drug dissolution was not considered. The model is thus not applicable to the process when the dissolution front moved.

In this paper, a novel drug release model is proposed, which considers the effects of drug diffusion, dissolution, and moving boundary.

2. Dissolution-diffusion Model

2.1 Model formulation

First, it assumes that initially all the drugs exist in solid phase dispersed in microspheres, while the medium immerses into microspheres. The solid drug dissolves gradually into the liquid phase due to concentration gradient. The dissolution boundary moves towards the spherical center, while undissolved drug nucleus reduces until dissolves completely.

Distinguished with previous works, we consider that the drug dissolution occurs in both solid and liquid phase from the moving front to the spherical center. In addition, restricted with dissolution rate, drug concentration at the dissolution front is less than solubility. At the last stage, when drug dissolves completely, the release process is controlled entirely by diffusion in the liquid phase. Thus, considering the effects of drug accumulation, diffusion flux, and dissolution, the dynamic mass balances of drug in both solid and liquid phase in a microsphere are established, resulting in coupled non-linear partial differential equations.

In liquid phase, accumulation of the drug is equal to the amount of drug diffused and dissolved:

\[
\frac{\partial C_L(r,t)}{\partial t} = D \left( \frac{\partial^2 C_L(r,t)}{\partial r^2} + \frac{2}{r} \frac{\partial C_L(r,t)}{\partial r} \right) + k \text{sgn}(C_s(r,t)) \times (C_{\text{sat}} - C_L(r,t))
\]

(1)

where \(C_L\) and \(C_S\) represent drug concentration in solid and liquid phase in microspheres, \(r\) is the radial position, \(D\) is the diffusion coefficient, \(k\) is the dissolution constant, \(t\) is release time, \(C_{\text{sat}}\) represents the solubility of drug in the release medium.

For drug in the solid phase, concentration variation is the same to dissolution rate:

\[
\frac{\partial C_S(r,t)}{\partial t} = -k \text{sgn}(C_S(r,t)) \times (C_{\text{sat}} - C_L(r,t))
\]

(2)

where \(\text{sgn}(x)\) is a step function from 0 to 1 at \(x = 0\).

At time \(t = 0\), all drugs are presented in the solid form. The initial condition is \(C_L(r,0) = 0\) and \(C_S(r,0) = C_m\). The boundary condition at \(r=0\) follows symmetry considerations, where there is no drive force of mass transfer at the center of microspheres.

It assumes the medium are mixed adequately and perfect sink conditions achieved, the resistance of mass transfer in the boundary layer at the surface of microsphere is neglected. At the same time, since drug concentration in release medium is much smaller than in microspheres, it is assumed to be zero at the surface.

By solving the couple partial differential equations, the concentration distributions in both phases in the microsphere are obtained. The drug remaining in the microspheres is calculated by integrating concentration along the radial coordinate. Ultimately the cumulative released drug is calculated by the following equation:
\[ \frac{M_L}{M_w} = 1 - 3 \int_{0}^{R} \frac{r^2 (C_S + C_r)}{R^3 C_{in}} dr \]  

(3)

### 2.2 Computation of the model

No analytical solution can be obtained for the coupled nonlinear partial differential equations. In this paper, the PDEs were numerically solved with the method of lines.

1. With the finite difference method, the variables discretization is made.
2. Cubic Hermite polynomials are applied in the \( r \) variable approximation so that the trial solution is expanded in serials.

\[ C_m(r, t) = \sum_{i=1}^{S} \left( a_{i,m}(t) \phi_i(r) + b_{i,m}(t) \theta_i(r) \right), \quad m = 1, \ldots, M \]  

(4)

where \( \phi_i(r) \) and \( \theta_i(r) \) are the standard basis functions for the cubic Hermite polynomials with the knots \( r_1 < r_2 < \cdots < r_N \), \( M \) is the number of equations.

3. According to the collocation method, coefficients of the approximation were obtained so that the trial solution satisfied the differential equation at the two Gaussian points in each subinterval.

\[ \begin{align*}
  p_{2j-1} &= r_j + \frac{3 - \sqrt{3}}{6} (r_{j+1} - r_j), \\
  p_{2j} &= r_j + \frac{3 - \sqrt{3}}{6} (r_{j+1} + r_j), \quad j = 1, \ldots, N
\end{align*} \]  

(5)

4. By collocation approximation, the differential equations are transferred to a system of \( 2MN(\text{N}-1) \) ordinary differential equations with \( 2MN \) unknown coefficient functions, \( a_{i,k} \) and \( b_{i,k} \). The basic form is shown as follows,

\[ \frac{d}{dt} a_{i,m} \phi_i(p_j) + \frac{d}{dt} b_{i,m} \theta(p_j) = f_n \left( p_j, t, C_i(p_j), C_N(p_j), \ldots, C_r(p_j), C_r(p_j), \ldots, C_N(p_j) \right) \]  

(6)

5. Combined with the initial conditions, the one order initial value problem of the system of ODEs is formed. Since the system is typically stiff, it is solved with Gear's backward differentiation formulas.

Finally, discrete drug concentrations in both solid and liquid phase were obtained. Then, the cubic spine interpolation of discrete values were computed, and substituted to Equation (3) to calculated integral quantities: the accumulative drug release percentage.

### 3 Analysis of the Release Models

#### 3.1 Transfer Mechanism of Drug Release

The amounts of undissolved and dissolved drug in microspheres during release process are calculated. The effect of dissolution rate on release kinetics was examined. The microspheres diameter is assumed of 1µm, and diffusion coefficient is \( 10^{-13} \text{ cm}^2/\text{s} \). Three cases with different dissolution rate or solubility are considered. Calculated drug concentration profiles are shown in Figure 1.
Initially, when drug is not dissolved, the dissolution rate is all the same everywhere in microspheres. As time goes, undissolved spherical drug nucleus lapses to the center of microspheres. In the first case, concentration in liquid phase increases as drug dissolved. After 10 hours, it reaches maximum and then holds constant, when dissolution and diffusion reaches balance. Accordingly, the drug release profile keeps constant.

In the case of $k = 1/s$, dissolution rate is large enough, drug release is only limited by solubility. Dissolved drug reaches saturation concentration at the very beginning. The dissolution process is in concordance with Koizumi model. After very short time of dissolution, the undissolved drug concentrations within the moving front of dissolution hold constant. As dissolution processes, the dissolution front move inward, and concentration gradient of dissolved drug from the front to the surface is developed.

Consider a critical situation, where $k=1/s$, and $C_{sat}/C_{in}=1$. Since drug loading is smaller than saturation, the limitation of both solubility and dissolution rate are neglected. At the very beginning, drug has all dissolved in the aqueous phase. Thus, only concentration profiles in the liquid phase were given. Drug release was entirely governed by diffusion through polymer matrix.

3.2 Comparison of the Release Models

The cumulative drug released profiles of the four cases are shown in Figure 2. Three kinds of models (dissolution-diffusion model, Koizumi model, Fick’s diffusion model) are evaluated. The curve (a) is the case that finite dissolution rate and solubility are both neglected. Drug release only depends on diffusion. The release profiles of both models
coincide completely, which indicates the basic diffusion model can be regarded as a special case of the dissolution-diffusion model when there is no limitation of finite dissolution rate and solubility.

The case with drug loading much higher than saturation concentration is plotted as curve (b). The profile calculated with the dissolution-diffusion model is similar to that with Koizumi model. It is derived under the assumption of instantaneous dissolution, which limits the applicability of this model to the instances where drugs dissolve fast in comparison with the diffusion process. In this case, diffusion model is not applicable.

As \( k=1 \times 10^{-4}/\text{s} \), the limitation of finite dissolution rate constant must be considered. The basic diffusion model and Koizumi model can not reflect the influence of this parameter. Whereas, the dissolution-diffusion model proposed in our work can successfully describes the release characteristic, as shown in curves (c). The release process is composed of two stages. In first stage of release, the effect of dissolution is dominant, and the profiles are approximately linear, corresponding to the stage of constant concentration in microspheres. As dissolution processes, the solid drug starts to exhaust, the release process shifts to diffusion controlled. The release rate decrease gradually.

\[ \text{Cumulative drug released} \]

\[ t, \text{h} \]

\[ \begin{align*}
\text{Diffusion model} & \quad 0.0 \quad 0.2 \quad 0.4 \quad 0.6 \quad 0.8 \quad 1.0 \\
\text{Koizumi model} & \quad 0.0 \quad 0.2 \quad 0.4 \quad 0.6 \quad 0.8 \quad 1.0 \\
\text{Dissolution-Diffusion model} & \quad 0.0 \quad 0.2 \quad 0.4 \quad 0.6 \quad 0.8 \quad 1.0
\end{align*} \]

**Fig. 2.** Comparison of drug released profiles of different models and parameters.

(a) \( k=1/\text{s}, C_{\text{sat}}/C_{\text{in}}=1 \); (b) \( k=1/\text{s}, C_{\text{sat}}/C_{\text{in}}=0.1 \);

(c). \( k=1 \times 10^{-4}/\text{s}, C_{\text{sat}}/C_{\text{in}}=0.1 \)

4. Simulation of in vitro Drug Release

Based on the presented release model, the effects of physicochemical and structural properties on release kinetics are revealed from the examination of model parameters, which would provide insight into the drug controlled release process. Model parameters are evaluated from fitting the experimentally measured drug release data to the diffusion/dissolution model. The fitting procedure is a nonlinear least squares optimization problem, solved by using a modified Levenberg-Marquardt algorithm with finite-difference Jacobian matrix.

The release profiles calculated from the diffusion-dissolution model are plotted in Figure 3 together with the experimental data. Good agreements are achieved between modeling results (solid curves) and experimental value (symbols) in three cases.

The parameters of three types of polymeric microspheres are given in Tables 1. The effective diffusion efficient of PLA is greater than PLGA microspheres. This may ascribe to PLGA microspheres having a denser structure. The hydrophilic PLGA solidifies at a slower rate, thereby shrinks more in the solvent evaporation process.

\[ \text{Cumulative drug released} \]

\[ t, \text{h} \]

\[ \begin{align*}
\text{PLA} & \quad 0.0 \quad 0.2 \quad 0.4 \quad 0.6 \quad 0.8 \quad 1.0 \\
\text{PLGA85:15} & \quad 0.0 \quad 0.2 \quad 0.4 \quad 0.6 \quad 0.8 \quad 1.0 \\
\text{PLGA50:50} & \quad 0.0 \quad 0.2 \quad 0.4 \quad 0.6 \quad 0.8 \quad 1.0
\end{align*} \]

**Fig. 3.** Comparison of the dissolution-diffusion model to the measured release profiles of nifedipine in phosphate buffer.
Another reason is possibly due to the stronger interaction between PLGA and the drug, which seem to slow the drug release rate of drug in the polymer matrix. In addition, the more compatible polymer provides better drug dispersion, which facilitates dissolution of the drug. Consequently, PLGA microspheres have a higher dissolution rate. For the comparison of two PLGA microspheres, the higher release rate is found in PLGA85:15 microspheres, mainly due to their smaller particle size.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Size, µm</th>
<th>D, cm²s⁻¹</th>
<th>k, s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA</td>
<td>3.80</td>
<td>5.08e-13</td>
<td>3.70e-3</td>
</tr>
<tr>
<td>PLGA85:15</td>
<td>2.55</td>
<td>4.11e-13</td>
<td>6.39e-3</td>
</tr>
<tr>
<td>PLGA50:50</td>
<td>2.74</td>
<td>3.96e-13</td>
<td>7.26e-3</td>
</tr>
</tbody>
</table>

From the above analysis, it is known that release profiles depend on the comprehensive effects of diffusion resistance, compatibility, and particle size. The modeling study helps to reveal the effects of these factors. The findings from modeling study helps design and control of microsphere structures to achieve desirable release performance.

5. Conclusion

Drug release from the microspheres is predominantly controlled by drug diffusion. There is, however, significant limitation from slowly dissolution rate, especially for hydrophobic drugs. A new dissolution-diffusion release model is developed, which takes diffusion, finite dissolution rate, and moving front of dissolution into consideration. The release profile has been determined numerically. The new model facilitates quantitative description of drug release kinetics, and yields release characteristics in good agreement with those observed experimentally.

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