Optimization of the mathematical modeling of drug delivery from planar polymeric systems

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ABSTRACT
Analytical solutions for the case of dispersed–drug controlled release from non–erodible planar matrices, based on Refined Integral Method, are presented. A new adjusting equation is used for the dissolved drug concentration profile in the depletion zone of the matrix. In order to illustrate the validity and usefulness of the model, comparisons with experimental profiles reported in the literature are presented. A close match between the model predictions and the experimental data is observed. In addition, a comparison with a model reported previously by others authors is also presented. The results show that our model has a better performance than the previously reported equations in the prediction of the experimental release profiles. As conclusion, the obtained results show that the model can be employed in a broad range of drug delivery systems.

Keywords: Mathematical modeling, Refined Integral Method, Drug release.

INTRODUCTION
The modeling of the diffusional release of a dispersed or dissolved solute from a polymeric matrix is a problem of special interest in the area of the controlled release of pharmaceuticals or chemicals. The mathematical analysis of the release kinetics is often complicated by the presence of a moving diffusional front separating the undissolved core and the partially extracted region [1]. In the case of a planar non-erodible polymeric matrix, the first effort to analyze the kinetics of release was made by Higuchi [2]. This author proposed a pseudo–steady state approximation (PSSA) to obtain an analytical solution for the slab under perfect sink condition. Higuchi’s results have been applied frequently to the controlled release of drug in where the initial solute loading per unit volume (A) is greater than the solute solubility in the polymeric matrix (Cs). However in the limit of A → Cs, the PSSA introduces considerable error giving less precise results [3-4]. This drawback was removed by Paul and McSpadden [5] who achieved an exact solution for slabs under sink condition. Unfortunately, the exact solution involves a transcendental expression which is cumbersome for routine usage. Lee applied the Refined Integral Method (RIM) to develop an approximate explicit analytical solution which is simpler than McSpadden’s solution but more accurate than Higuchi’s results for small A/Cs ratio [3]. The difference is that the pseudo–steady state approximation assumes a linear concentration profile in the dissolved solute zone, which is valid only when the solute loading is in great excess of the solute solubility (A>>Cs). Instead, to obtain a more general analytical solution that can be used in a wide range of A/Cs ratios, Lee replaced the linear concentration distribution by an approximate function. This function was a polynomial of grade two. The purpose of the present work was to derive an explicit analytical solution for the case of dispersed–drug controlled release from non–erodible planar matrices that fits better the exact solution. In order to achieve the aim, a new adjusting equation for the dissolved drug concentration profile in the depletion zone was used.
MODEL DEVELOPMENT

The mathematical model is developed for planar single-layer devices containing solid drug particles. The system is schematically illustrated in figure 1.

![Figure 1: Schematic illustration of drug concentration profile in a non-erodible polymeric device. I. Dispersed drug zone; II. Dissolved drug zone; III. Release medium.](image)

The assumptions of the model to be mathematically formulated are the following: (i) The system is a planar single-layer device; (ii) The device is considered as an isotropic medium; (iii) The device is composed by a polymeric matrix that contains solid drug particles dispersed in its interior; (iv) The initial distribution of the drug in the polymeric matrix is homogeneous; (v) The initial drug loading in the matrix is higher than the maximum drug solubility in the polymer; (vi) For simplicity, all the drug particles have the same size and a spherical form; (vii) The polymeric matrix is inert, unswellable and non-erodible; (viii) The dissolution of the solid drug particles in the polymeric matrix occurs at a high rate and does not constitute a controlling step of the general release process; (ix) The rate controlling step of the release process is the drug diffusion across the polymeric matrix, which is described according to Fick’s laws; (x) The mass transport of drug is assumed to be effectively one-dimensional; (xi) The drug diffusion coefficient in the polymeric matrix is considered constant; (xii) Resistance to external mass transfer is negligible; (xiii) The volume of the release medium is considered infinite to ensure the “sink” condition; (xiv) There exist a drug depletion zone with a thickness $S$. This thickness increases with time and as more solid drugs elute out of the device, thus leading to the inward advancement of the interface of the dispersed–drug zone/depleted drug zone, phenomenon commonly referred to as “dissolution–diffusion moving front” (xv) The model formulated is valid till all solid drug particles dissolve in the polymer and no discrete crystals remains in the device. This stage is achieved when the “dissolution-diffusion moving front reaches $r = 0$; (xvi) At the initial time ($t = 0$), the elution medium has not been yet in contact with the device and therefore there is no depletion zone. It is considered that the “dissolution–diffusion moving front” is outside of the device ($S = R$); (xvii) At $r = 0$ there is an impermeable coating; there is no drug release through that surface. The approximate solution can be obtained using the Refined Integral Method. The proposed functional form which approximates the solute concentration distribution in the partially extracted region has the form:

$$\theta = a_0 + a_1 \frac{x}{\delta} + a_2 \left(\frac{x}{\delta}\right)^n \quad (1)$$

where $n$ is the adjusting exponent and

$$a_0 = 1 \quad (2)$$
Using the Fick’s laws and Eqs. (1-4), the position of the dissolution–diffusion moving front (δ) can be obtained:

\[ \delta = \left[ \frac{3(n+2)D_p t}{R^2 \left( \frac{3A}{2C_s} - 1 \right) (n+2) - a_2(n-1)} \right]^{1/2} \] (5)

The cumulative amount of solute released per unit area of the device (Q) is calculated from a mass balance equation and results in:

\[ Q = R\delta \left[ A + C_s \left( a_2 \left( \frac{1}{n+1} - \frac{1}{2} \right) - \frac{1}{2} \right) \right] \] (6)

The appropriate value of the adjusting exponent can be calculated from the following expression derived for a slab under perfect sink condition:

\[ \left( \frac{A}{C_s} - 1 \right)^{1/2} e^{\left( \frac{f_n}{4} \right)} \sum_{i=0}^{\infty} \frac{(-1)^i}{i!(2i+1)} = 1 \] (7)

where

\[ f_n = \frac{6(n+2)}{\left( \frac{3A}{C_s} - 2 \right)(n+2) - n \left( \frac{A}{C_s} - 1 \right) - 2 + n^2 \left( 1 - \frac{A}{C_s} \right)^2 + 4n \left( \frac{A}{C_s} - 1 \right) \}^{1/2} \] (8)

From Eq. (7), the values of \( n \) that minimize the error in the approximation of the exact solution can be calculated.

**RESULTS AND DISCUSSION**

In order to use the developed model to predict the drug release profiles, it is convenient to use suitable computational programs to simplify the calculations. These programs allow the creation of a "routine" in programming language to perform the simulations. Once the routine is created, the user only needs to load the values of the parameters that make up the model and then run the program. The values of \( n \) that minimize the error in the approximation of the exact solution were calculated from Eq. (7) using the computational software MATLAB®. The results are presented in figure 2. It shows that increasing \( A/C_s \) ratios increases the value of \( n \). For \( A/C_s \to \infty \), \( n \) tend to 3.
Figure 2: Values of the exponent $n$ calculated according to Eq. (7) for different $A/C_s$ ratios.

Once the appropriate value of $n$ is obtained, the cumulative amount of solute released per unit area of the device ($Q$) is calculated from Eq. (6). The result obtained through Eq. (6) was compared with the exact solution reported by Paul and McSpadden [5] and with the solution reported by Lee [3]. The comparison is presented in Table 1. The “percentages of error” for the Lee’s solution and for the Eq. (6) are plotted in figure 3 for different $A/C_s$ ratios. The “percentage of error” is defined as the subtraction between the values predicted by the tested model and the exact solution, divided by the value predicted by the exact solution and multiplied by one hundred. The tested models were the Lee’s solution and the Eq. (6). It can be observed that Eq. (6) gives better results. For $A/C_s > 1.4$, Eq. (6) is virtually identical to the exact solution (within 0.1%), whereas Lee’s equation requires $A/C_s > 4.5$ to have an accuracy within 0.1%. From figure 3 it can be seen that the percentage of error for Eq. (6) is always less than the corresponding percentage of Lee’s equation. Furthermore, the percentage of error for Eq. (6) is zero for almost the range of $A/C_s$ analyzed.

### Table 1: Comparison of the % deviation from the exact solution for solute release from planar matrices.

<table>
<thead>
<tr>
<th>$A/C_s$</th>
<th>Exact $^a$</th>
<th>Lee $^b$</th>
<th>% Error</th>
<th>This work</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>1.2102</td>
<td>1.2205</td>
<td>0.85</td>
<td>1.2099</td>
<td>-0.02</td>
</tr>
<tr>
<td>1.2</td>
<td>1.3011</td>
<td>1.2960</td>
<td>-0.39</td>
<td>1.2979</td>
<td>-0.25</td>
</tr>
<tr>
<td>1.3</td>
<td>1.3789</td>
<td>1.3700</td>
<td>-0.65</td>
<td>1.3766</td>
<td>-0.17</td>
</tr>
<tr>
<td>1.4</td>
<td>1.4513</td>
<td>1.4412</td>
<td>-0.70</td>
<td>1.4496</td>
<td>-0.12</td>
</tr>
<tr>
<td>1.5</td>
<td>1.5197</td>
<td>1.5094</td>
<td>-0.68</td>
<td>1.5185</td>
<td>-0.08</td>
</tr>
<tr>
<td>1.6</td>
<td>1.5849</td>
<td>1.5747</td>
<td>-0.64</td>
<td>1.5840</td>
<td>-0.06</td>
</tr>
<tr>
<td>1.7</td>
<td>1.6474</td>
<td>1.6376</td>
<td>-0.59</td>
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<tr>
<td>2.0</td>
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<td>1.8130</td>
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</tr>
<tr>
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<td>2.0301</td>
<td>2.0232</td>
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<td>2.2132</td>
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<tr>
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<tr>
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<td>2.6280</td>
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<tr>
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</tr>
<tr>
<td>10.9</td>
<td>4.5969</td>
<td>4.5960</td>
<td>-0.02</td>
<td>4.5969</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Paul and McSpadden, 1976.  
$^b$Lee, 1980.

Clearly one can see from these results that with the appropriate value of the $n$ adjusting exponent, the analytical solution is optimized. These results confirm that the error in the approximation of the exact solution can be minimized with the new adjusting equation. In order to illustrate the usefulness of the developed model in the analysis of controlled drug release from planar polymeric matrix-type systems, several examples of simulations are presented and compared with experimental profiles reported in the literature. Figure 4 presents
the release of 4–aminoazobenzene from a polymeric matrix of cellulose acetate with initial drug loading higher than solubility, calculated according to Eq. (6). The experimental data were reported by Charalambopoulou et al. [6]. The parameters employed in the model were taken from this work. It shows that the prediction of the model is in agreement with the experimental data for the different $A/C_s$ ratios. It can be observed in figure 4.a. that the straight line covers approximately the first 35 h of release. From that moment on, only dissolved drug remains in the device; therefore, the model is not applicable. The same situation can be seen in Fig. 4.b. for $A/C_s = 4.1$. Figure 5 shows experimental data reported by Roseman et al. [7] and the release profile calculated according to Eq. (6), for prostaglandin release from a polymeric matrix of silicone rubber with initial loading higher than solubility. The parameters employed were taken from Roseman et al. [7]. A close match between the model and the experimental data was observed. These examples confirm that the derived equations can be employed in a wide range of initial drug loading.

**CONCLUSIONS**

Analytical solutions were derived for the case of controlled dispersed–drug release from planar non–erodible polymeric matrices, based on Refined Integral Method. A new adjusting equation for the dissolved drug concentration profile in the depletion zone was used. The value of the exponent $n$ calculated from Eq. (7) increases the precision in the approximation of the exact solution. The derived model is of practical usefulness and relatively simple to use with the help of an adequate computational software. The utility of the model was corroborated by comparison with experimental profiles reported in the literature. The obtained results show that the model can be employed in a broad range of applicability.
REFERENCES


NOMENCLATURE

\[ A \] initial drug loading in matrix (g/cm\(^3\))
\[ C \] drug concentration in matrix (g/cm\(^3\))
\[ C_s \] maximum drug solubility in matrix (g/cm\(^3\))
\[ D_p \] drug diffusion coefficient in matrix (cm\(^2\)/s)
\[ n \] adjusting exponent (dimensionless)
\[ Q \] cumulative amount of drug released per unit area (g/cm\(^2\))
\[ r \] coordinate along the matrix thickness (cm)
\[ R \] matrix thickness (cm)
\[ S(t) \] position of dissolution–diffusion moving front (cm)
\[ t \] time (s)
\[ x \] r/R, coordinate along the matrix thickness (dimensionless)
\[ \delta(t) \] S(t)/R, position of the dissolution–diffusion moving front (dimensionless)
\[ \theta \] C/C_s, drug concentration in matrix (dimensionless)