Different Travelling Wave Solutions for Controlled Drug Release Model in Planar Geometry

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Abstract: - Mathematical modelling and computation play an important role in the design of pharmaceutical products. The United States Food and Drug Administration Critical Path Initiative has recently identified model-based drug development, including drug and disease modeling, as an important goal (www.fda.gov/oc/initiatives/criticalpath). New discoveries and theories generated by model construction have been appearing in many prominent biologically related journals. In the formulation of pharmaceutical products, the use of controlled-release technology is becoming increasingly important. In 2003, Göran Frenning formulated and numerically investigated a mathematical model of the drug dissolution and release processes. The model can be expressed in terms of two coupled nonlinear partial differential equations. Later, Chontita and Lenbury (2012) explained how analytical solutions can be found for a system of reaction diffusion equations in the form of a travelling wave front using the travelling wave coordinate when the wave is assumed to be moving at constant speed. Here, we present certain travelling wave solutions of the model of controlled drug release, in a planar geometry, for different cases in which analytical solutions can be derived exactly.

Key-Words: - Controlled drug release, Analytical solution, Traveling wave coordinate.

1 Introduction

In recent years, the pharmaceutical industries have put their focus on the development of sustained release formulations due to its inherent advantages [1]. The aim of sustained release dosage forms is to release a drug at a predetermined rate so that they are designed to be able to maintain a constant drug level for a satisfactory period of time while incurring minimum side effects [1]. Intense research efforts have been carried out on sustained release in order to discover promising ways to decrease the side effect of drug by preventing the fluctuation of the therapeutic drug concentration in the body and improve a patient’s quality of life by reducing frequency of drug applications.

According to the review by Kumar et al. [1], due to increased complications and expense involved in marketing of new drug forms, the industry has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used since it is possible to prolong and control the release of the drug that is dissolved or dispersed. Numerous sustained release drug forms have been developed, and intense research has recently focused on the design of sustained release systems for poorly water soluble drugs.

To be able to produce well characterized and reproducible dosage forms, which control drug entry into the body according the specifications of the required drug delivery profile, knowledge of both physical and polymer sciences is required [2]. In this type of drug delivery, the rate of drug release is principally controlled by the delivery system itself, although several surrounding conditions, such as pH, enzymes, ions, motility and physiological conditions can also influence the outcome [3].

Mathematical modelling and computation play an important role in the design of pharmaceutical products. The United States Food and Drug Administration Critical Path Initiative [4] has recently identified model-based drug development, including drug and disease modeling, as an important goal. New discoveries and theories generated by model construction have been appearing in many prominent biologically related journals. In the formulation of pharmaceutical products, the use of controlled-release technology is becoming increasingly important. As explained in [5], when drug released from a matrix is controlled
by diffusion through the polymeric matrix, its release kinetics obey Fick’s 1st and 2nd laws [5]

\[ J = -DC_t, \quad (1) \]

\[ C_t = -DC_{ss}, \quad (2) \]

where \( J \) stands for the diffusional flux of the drug; \( D \) the represents diffusional coefficient; \( C \) represents the concentration of the drug; and \( x \) is the distance of diffusion.

When drug release is dominated by surface erosion, Hopfenberg’s equation gives comparatively good prediction of drug delivery in spherical, cylindrical, and planar geometrical forms [6]. If the drug concentration is sufficiently low so that all drugs can be dissolved, and the dissolution process proceeds rapidly enough, we may easily determine the release rate [5]. In this scenario of drug release, all drug may be assumed to be completely dissolved before any release has taken place and we can use the heat conduction equation to describe the drug concentration in the matrix.

In the second type of drug release, a more general type where the drug concentrations are higher, or the solubility is low, two forms of drugs, namely the solid and dissolved forms, coexist in the matrix, and the process becomes noticeably more complex. In this more general situation, drug loading is much higher than drug solubility \( (C_0 \gg C_s) \). The model proposed by Higuchi [7] has been found to perform well for planar matrix under the perfect sink assumption.

The original Higuchi model was formulated for drug release from ointment bases containing drugs in suspension. It has since been subject to a great deal of generalizations and modifications [8-12]. Recently, a similar model has been proposed and investigated by Frenning and Strømme [13], who focused on the problem of drug release from spherical pellet units into the finite volume of dissolution medium. It was assumed that some of the dissolved drug could become immobilized due to its absorption into the pellet constituents. In [13], the model in [13] was readjusted to disregard drug absorption, with the assumption that the diffusion coefficient is concentration-independent. An “analytical short-time approximation” to the solution was derived under the assumption of perfect sink conditions [14].

In [15], Rattanakul and Lenbury analytically obtained exact solutions to the model equations in the form of a travelling wave front by introducing the travelling wave coordinate in the situation that the wave is presumably moving at a constant speed.

Here, we present more travelling wave solutions of the model of controlled drug release, in a planar geometry, for different cases in which analytical solutions can be derived exactly.

2 Referenced Model

In [14], a planar matrix system whose normal is in the \( x \) direction was analyzed. It was assumed that the lateral dimensions of the system are much larger than its thickness \( L \), so that the process of drug release could be effectively considered to be one-dimensional. The boundary at \( x = 0 \) is assumed to be impenetrable to the drug, while the matrix is in contact with the liquid at \( x = L \) (see [14] for more detail).

The model assumes the perfect sink condition which means that the matrix is supposed to be in contact with a well-mixed dissolution medium, the volume of which is sufficiently large so that the drug concentration may be taken to be virtually zero at all times.

In order to simplify the analysis, Frenning [14] assumed further that liquid absorption occurs at a much faster rate than drug dissolution and subsequent release. This means that the matrix which contains finely dispersed solid drug can be assumed to be fully wetted in the initial state. Also, in the initial state, the entire drug is in the solid form.

If we let \( d(t,x) \) be drug concentration in the dissolved phase and \( s(t,x) \) the ‘concentration’ of drug in the solid phase, we can then describe the process of drug dissolution and release by the following equations [14].

\[ d_t = d_{xx} - s, \quad (3) \]

\[ s_t = -k_d s^{2/3} (\varepsilon C_s - d) \quad (4) \]

where \( t \) is the time, \( C_s \) the saturation constant, \( \varepsilon \) the porosity, \( D \) the drug diffusivity, \( k_d \) the dissolution rate.

According to [14], the initial condition

\[ d(0,x) = 0 \quad (5) \]

\[ s(0,x) = s_0 \quad (6) \]

should be imposed to assure that all drug is assumed to be present in the solid form in the initial state [14].

The boundary condition

\[ d_x|_{x=0} = 0 \quad (7) \]

is to be imposed if the interface at \( x = 0 \) is assumed to be impenetrable to the drug. However, if we relax the impenetrability condition to

\[ d_x|_{x=0} \ll 1 \quad (8) \]
instead, then the interface will be “almost” impenetrable to the drug. Finally, we impose the condition
\[ s(t,L) = 0 \] (9)
so that the drug concentration at \( x = L \) is kept at zero due to the perfect sink condition.

### 3 Analytical Solutions

In order to derive analytical solutions to the above model equations, we introduce the travelling wave coordinate \( z = x - vt \), where \( v \) is the constant velocity at which the wave is assumed to be moving. Upon substituting \( z \) in Eq. (3) and (4), we are led to the following system of nonlinear second order ordinary differential equations with respect to \( z \).

\[
-vd'' = Dd'' + vs'
\]
\[ -vs' = -ks^2/3 \left( \gamma - d \right) \] (10) (11)

where (') denotes the derivative with respect to \( z \), \( k \) stands for \( K_l \), and \( \gamma \) stands for \( \varepsilon c_l \).

By integrating (10) and using (11) the model is reduced to a single second-order differential equation terms of \( r \) which satisfy the following equation:

\[
C^{3/2} = vd + Dd'
\]
(12)

We shall derive analytic solutions for the model equation (12) which satisfy the following:

\[
C^{3/2} = vd + Dd'
\]
(13)

and seek a solution of the form

\[
d' = AC^m + BC^n \]
(14)

Thus, we have

\[
\frac{3}{2}C^{1/2}C' = vd' + Dd''
\]
(15)

On the other hand, Eq. (13) gives

\[
d = \frac{1}{v}C^{3/2} - \frac{D}{v} (AC^m + BC^n) \]
(16)

Substituting (15) and (16) into (12), we obtain

\[
\frac{3}{2}C^{1/2}C' + \frac{k}{v^{2/3}}C \left( \gamma - \frac{1}{v}C^{3/2} + \frac{D}{v} (AC^m + BC^n) \right) = 0
\]
(17)

Rearranging the above equation yields

\[
\frac{3}{2}C^{1/2}C' + \frac{ky}{v^{2/3}}C - \frac{k}{v^{5/3}C}C^{5/2} + \frac{kBD}{v^{5/3}C}C^{m+1} + \frac{kBD}{v^{5/3}C}C^{n+1} = 0
\]
(18)

The above derivation has been shown in Rattanakul and Lenbury [15], in which it was observed that we may find exact solutions in three possible cases: 1) \( m = 0, n = -1/2 \), 2) \( m = 3/2, n = 0 \), and 3) \( m = 3/2, n = n' + 1/2 \) for some appropriate \( n' \).

The analytic solutions given for Cases 1 and 2 in [15] did not satisfy the appropriate initial and boundary conditions at \( x = 0 \), namely conditions (5)-(9). Here, we give analytical solutions in 4 cases which satisfy physically meaningful initial and boundary conditions.

**Case 1:** \( m = 0, n = -1/2 \)

For these values of \( m \) and \( n \), we let

\[
AD = -v\gamma, \alpha^2 = -\frac{1}{BD} > 0, \beta = \frac{2kBD}{3v^{5/3}} < 0
\]
(19)

Thus, (17) is reduced to a simpler form which can be easily solved to yield [15]:

\[
C = \frac{1}{\alpha} \tanh(\alpha \beta z + \alpha K)
\]
(20)

Using the negative square root of \( C \) in (16), we can write the concentration of drug in solute form which satisfies (10)-(11) as

\[
d = \frac{1}{\alpha \gamma^{3/2}} \left( \tan^{3/2} \alpha(\beta(x - vt) + K) + \cot^{1/2} \alpha(\beta(x - vt) + K) \right) - \gamma
\]
(21)

From the integral of (10) and the positive square root of \( C \), we obtain the concentration of drug in solid form as

\[
s = -\frac{1}{\alpha \gamma^{3/2}} \tan^{3/2} \alpha(\beta(x - vt) + K) + l
\]
(22)

where \( l \) and \( K \) are constants of integration.

So that the solution satisfies condition (5), the following equation must be satisfied.

\[
\frac{1}{\alpha \gamma^{3/2}} \tan^{1/2} (\alpha K) \left( 3 \sec^2 (\alpha K) - \cos^2 (\alpha K) \right) = 0
\]
(23)

So that the solution satisfies condition (6), the following equation must be satisfied.

\[
\frac{\beta}{\alpha \gamma^{3/2}} \tan^{1/2} (\alpha K) \left( 3 \sec^2 (\alpha K) - \cos^2 (\alpha K) \right) = 0
\]
(24)

Finally, so that the solution satisfies condition (9), the following equation must be satisfied.

\[
\frac{1}{\alpha \gamma^{3/2}} \tan^{3/2} \alpha(\beta L + K) = l
\]
(25)

The analytical travelling wave solution given by (20)-(21), together with the conditions (19), (22)-(25), is shown in Fig. 1 to move in the direction of decreasing \( x \) as time elapses. Here, \( \alpha = 7\pi, K = \frac{1}{6}, L = 7.0582, l = 1.0043, \nu = -1, k = 10, \) and \( \gamma = 0.0170, s_0 = 1 \).
Fig. 1 Travelling wave solution in Case 1 for the concentration a) $d$ of drug in the diluted form and b) $s$ in the solid form, plotted as functions of $x$ for different time.
**Case 2:** $m = \frac{3}{2}, n = n' + \frac{1}{2}$.

This case, with $\nu = -1$, has already been described in [15]. However, to obtain a solution which can satisfy the appropriate initial and boundary conditions, we instead write

$$C(z) = \frac{1}{a^{2/3}} \left( \frac{3ae^{k} + b}{2e^{-b/2}} \right)^{2/3}$$

(26)

Substituting (26) into (13), we obtain

$$Dd' - d = C^{3/2} = \gamma + \frac{3D}{2} e^{\left(\frac{z}{D} + k\right)}$$

which can be directly solved, using an integrating factor, with $d|_{z=0} = 0$, to yield

$$d = \gamma + \frac{3}{2} z e^{z/D + k} - \gamma e^{z/D}$$

Therefore, we have derived an analytical solution in terms of the travelling wave coordinate as follows.

$$d = \left[ \frac{3}{2} (x - vt) e^k - \gamma \right] e^{(x - vt)/D} + \gamma$$

(27)

and, similarly to the previous case,

$$s = l - \gamma - \frac{3}{2} D e^{(x - vt)/D + k}$$

(28)

$l$ being a constant of integration.

The following equality assures that the solution satisfies the impenetrability condition:

$$\gamma = \frac{3}{2} D e^k$$

(29)

So that the solution satisfies the condition (6), we need the following equation to be satisfied.

$$l - \gamma - \frac{3}{2} D = s_0$$

(30)

So that the solution satisfies the condition (9), we need the following equation to be satisfied.

$$l - \gamma - \frac{3}{2} D e^{L/D + k} = 0$$

(31)

**Case 3:** $m = 3/2, n = 1$

For these values of $m$ and $n$, Eq. (11) becomes

$$\frac{3}{2} C^{1/2} C' + \frac{k\gamma}{\nu^{2/3}} C - \frac{k}{\nu^{5/3}} C^{5/2} + \frac{kAD}{\nu^{5/3}} C^{5/2} + \frac{kBD}{\nu^{5/3}} C^2 = 0$$

(32)

By letting $AD = 1$

Eq. (32) reduces to

$$\frac{3}{2} C^{1/2} C' + k\gamma C + kBD C^2 = 0$$

(33)

If we let

$$\alpha = -\frac{k\gamma}{3\nu^{2/3}}, \beta = -\frac{BD}{\gamma}$$

we can write Eq. (34) as

$$\frac{1}{2} C^{1/2} (1 + \beta^2 C) C' = \alpha$$

which can be easily solved, yielding

$$\tan^{-1}(\beta C^{1/2}) = \alpha \beta z + K$$

or

$$C = \frac{1}{\beta^2} \tan^2(\alpha \beta z + K)$$

(36)

where $K$ is the constant of integration.

Substituting (36) into (16), one obtains

$$d = \gamma \tan^2(\alpha \beta z + K)$$

(37)

So that the solution satisfies condition (5), we need $K = 0$. The solution then already satisfies (7).

We can then obtain the level of drug in solid form by integrating (10) so that

$$s = -\frac{1}{\nu^2} \tan^3(\alpha \beta z) + l$$

(38)

where $l$ is the constant of integration.

For $s|_{z=0} = s_0$, we need $l = s_0$. For $s|_{z=L} = 0$, the parameters have to satisfy the following condition

$$\tan^3(\alpha \beta L) = \nu^2 s_0$$

(39)

Thus, a travelling wave solution is given as

$$d = \gamma \tan^2(\alpha \beta (x - vt))$$

(40)

$$s = -\frac{1}{\nu^2} \tan^3(\alpha \beta z) + s_0$$

(41)

where $\alpha, \beta, A$, and $B$ are given by (33), (35), and (39).

**Case 4:** $m = 3/2, n = \frac{1}{2}$

In this case, equation (17) becomes

$$\frac{3}{2} C^{1/2} C' + \frac{k\gamma}{\nu^{2/3}} C - \frac{k}{\nu^{5/3}} C^{5/2} + \frac{kAD}{\nu^{5/3}} C^{5/2} + \frac{kBD}{\nu^{5/3}} C^2 = 0$$

(42)

If we again assume (40), then (49) reduces to

$$\frac{3}{2} C^{1/2} C' + \frac{k\gamma}{\nu^{2/3}} C + kBD C^2 = 0$$

(43)

If $C = u^2$, then $C' = 2uu'$ and one obtains

$$3u^2 u' + \frac{k\gamma}{\nu^{2/3}} u^2 + \frac{kBD}{\nu^{5/3}} u^3 = 0$$

(44)

or

$$u' - \eta u - \mu = 0$$

(51)

where
\[
\mu = - \frac{k \gamma}{3 \nu^{2/3}}, \eta = - \frac{kBD}{3 \nu^{5/3}}, AD = 1 \quad (52)
\]

Solving (51), we obtain
\[
\ln(\eta u + \mu) = \eta z + K
\]
which gives
\[
C^{1/2} = \frac{1}{\eta} \left[ \mu - \exp(K + \eta z) \right] \quad (53)
\]
where \( K \) is the constant of integration. By (16),
\[
d = \frac{1}{\nu} C^{3/2} - \frac{D}{\nu} (AC^{3/2} + BC^{1/2})
\]
We are thus led to
\[
d = \frac{3\nu^{2/3}}{k} \left[ \exp(K + \eta z) - \mu \right] \quad (54)
\]
Using (10), we obtain
\[
s = C^{3/2} + l = \frac{1}{\eta} \left[ \mu - \exp(K + \eta z) \right]^3 + l \quad (55)
\]
where \( l \) is the constant of integration.

4 Conclusion

We have extended our earlier work reported in [15] deriving more analytical solutions to a model of drug release from a planar matrix. The solutions are expressed in the travelling wave coordinate so that the wave front of drug dispersion can be graphed and investigated further in terms of how the shapes of the drug diffusion fronts changes with different values of physical parameters which is expected to be valuable for the design of controlled drug release forms which decrease the side effect of drug by preventing the fluctuation of the therapeutic drug concentration in the body and improve a patient’s compliance by reducing frequency of drug applications.

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