Stability Analysis and Analytical Solution of a Nonlinear Model for Controlled Drug Release: Travelling Wave Fronts

Chontita Rattanakul, and Yongwimon Lenbury

***Abstract*—**In this paper, the process of drug dissolution and release from a planar matrix is investigated based on two coupled nonlinear partial differential equations proposed by Göran Frenning in 2003. In the modelling the process drug adsorption has been disregarded, assuming concentration-independent diffusion coefficients, using perfect sink conditions, and specializing to a planar geometry, The concentration profile of the mobile, or diffusing, the resulting model is rather complex and has been investigated only numerically and only approximate solution have been possible. In this paper it is shown that an analytical solution can be obtained exactly in the form of a travelling wave front. We describe the method for finding the analytical solutions using the travelling wave coordinate when the wave is assumed to be moving at constant speed. The model system of partial differential equations is transformed into two coupled ordinary differential equations, which is analysed interms of the stability of its steady state. Analytical solutions are derived in three possible cases, giving travelling wave solutions. We then discuss a comparison between the exact solutions obtained here and the "analytical short-time approximation" as well as the curves obtained from the modified Higuchi formula reported by Frenning in 2003.

***Keywords*—**Delay differential equations; omega limit set; persistence; signal transduction; stability.

I. Introduction

ONE of the most important means of drug-delivery is the utilization of the matrix systems. The objectives of controlled delivery systems are to reduce the frequency and/or to increase the effectiveness of the drug through drug localization at the target site, in order to reduce the dose required to provide uniform drug delivery.

Controlled drug delivery requires the knowledge of both physical and polymer sciences so that it is possible to produce well characterized and reproducible dosage forms, which control drug entry into the body according the specifications of the required drug delivery profile [l]. It is well documented that in this type of drug delivery, the rate of drug release is principally controlled by the delivery system itself, though it may be influenced by surrounding conditions, such as pH, enzymes, ions, motility and physiological conditions [2].

Mathematical modeling and computation has also become an important tool in the design of pharmaceutical products dealing with controlled-release mechanism. As explained in [3], when drug released from a matrix is controlled by diffusion through the polymeric matrix, its release kinetics obey Fick's 1st and 2nd laws [3]:

$$J = -DC_x \tag{1}$$

$$c_t = -DC_{xx} \tag{2}$$

where J represents the diffusional flux of the drug; D the is diffusional coefficient; C is the concentration of the drug; and x is the distance of diffusion.

When drug release is dominated by surface erosion, Hopfenberg's equation has been found to give good prediction of drug delivery in spherical, cylindrical, and planar geometrical forms [4].

According to [3], we may distinguish between two conceptually different scenarios, depending on the relative magnitudes of the drug concentration and solubility in the matrix. 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 [3]. In this type of release, all drugs may be assumed to be completely dissolved in before any release has occurred, and the drug concentration in the matrix can therefore be solved from the heat conduction equation [3].

In the second, more general, type of drug release from a matrix, 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 distinctly more complex. For this more general situation when drug loading is much higher than drug solubility ($C_0 \gg C_s$), the model proposed by Higuchi [5] has shown to perform well for planar matrix under the perfect sink assumption, although it was originally formulated for drug release from ointment bases containing drugs in suspension.

Manuscript May 17, 2012: Revised version received May 17, 2012. This work was supported in part by the Centre of Excellence in Mathematics, CHE, Thailand, and Mahidol University.

C. Rattanakul is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok, Thailand (e-mail: chontita.rat@mahidol.ac.th).

Y. Lenbury is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok, Thailand (corresponding author, phone: 662-201-5448; fax: 662-201-5343; e-mail: yongwimon.len@mahidol.ac.th).

The original Higuchi model has been subject to a great deal of generalizations and improvements [6-12]. Recently, a similar model has been studied by Frenning and Strømme [13], who investigated the problem of drug release from spherical pellet units into the finite volume of dissolution medium, under the assumption that some of the dissolved drug could become immobilized by absorption to the pellet constituents. In [14], this model was reformulated by disregarding drug absorption, and assuming that the diffusion coefficient is concentration-independent. Using perfect sink conditions, an "analytical short-time approximation" to the solution was derived [14].

It is the purpose of this paper to show that an exact solution can be obtained analytically in the form of a travelling wave front. We describe the method for finding the analytical solutions using the travelling wave coordinate in the situation that the wave is presumably moving at a constant speed. The analytical solutions are then discussed in comparison to the "analytical short-time approximation" derived in [14].

II. Referenced Model

In [14], a planar matrix system whose normal is in the x direction was investigated. The assumptions are 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 $x = L$.

The perfect sink condition assumes that the matrix is in contact with a well-mixed dissolution medium, the volume of which is sufficiently large so that it can be assured that the drug concentration is virtually zero at all times.

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

Letting $d(t,x)$ be drug concentration in the dissolved phase and $s(t,x)$ the 'concentration' of drug in the solid phase, it is then possible to describe drug dissolution and release by the following equations [14].

$$d_t = d_{xx} - s_t \tag{3}$$

$$s_t = -k_d s^{2/3}(\varepsilon c_s - d) \tag{4}$$

where t is the time, c_s the saturation constant, ε the porosity, D the drug diffusivity, k_d the dissolution rate.

The initial conditions are

$$d(0,x) = 0$$
$$s(0,x) = 1$$

which means that all drug is assumed to be present in the solid form in the initial state [14].

Similarly, the boundary conditions are

$$d_x\big|_{x=0} = 0$$
$$s(t,L) = 0$$

which follow from the assumption that the interface at $x = 0$ is impenetrable to the drug, while the drug concentration at $x = L$ is kept at zero as a consequence of the sink condition.

III. Model Analysis

3.1 Traveling wave coordinate

We introduce the travelling wave coordinate $z = x - vt$, where v is the constant velocity at which the wave is assumed to be moving. By substituting z in (3) and (4), we obtain a coupled system of ordinary differential equations with respect to z:

$$-vd' = Dd'' + vs' \tag{5}$$

$$-vs' = -ks^{2/3}(\gamma - d) \tag{6}$$

where $()'$ denotes the derivative with respect to z, k stands for k_d, and γ stands for εc_s.

Integrating (5) and combining with (6) lead us to a single second-order differential equation terms of d as

$$Dd'' + vd' + \frac{k}{v^{2/3}}\left(vd + Dd'\right)^{2/3}\left(\gamma - d\right) = 0 \tag{7}$$

Now, by letting $X = d$, and $Y = X'$, we can write (7) as

$$X' = Y \tag{8}$$

$$Y' = \frac{k}{Dv^{2/3}}\left(vX + DY\right)^{2/3}\left(X - \gamma\right) - \frac{v}{D}Y \tag{9}$$

3.2 Dynamical analysis

Before we derive the analytical solution, a stability analysis may be carried out on the model system written in the form of equations (3) and (4).

The system possess only one nontrivial equilibrium state in the feasible region, namely $(X_1, Y_1) = (\gamma, 0)$.

The Jacobian matrix of the system (8)–(9) about its steady state $(\gamma, 0)$ is

$$J = \begin{pmatrix} 0 & 1 \\ \dfrac{k(DY+vX)^{2/3}}{Dv^{2/3}} + \dfrac{2kv^{1/3}(X-\gamma)}{3D(DY+vX)^{1/3}} & \dfrac{2k(X-\gamma)}{3v^{2/3}(DY+vX)^{1/3}} - \dfrac{v}{D} \end{pmatrix}$$

At $(X_1, Y_1) = (\gamma, 0)$ the Jacobian becomes

$$J_{(\gamma,0)} = \begin{pmatrix} 0 & 1 \\ \dfrac{k}{D}\gamma^{2/3} & -\dfrac{v}{D} \end{pmatrix}$$

whose eigenvalues are

$$\lambda_{1,2} = \frac{1}{2}\left(-\frac{v}{D} \pm \sqrt{\left(\frac{v}{D}\right)^2 + 4\frac{k\gamma^{2/3}}{D}} \right)$$

which are real and opposite in signs. Therefore, the steady state $(X_1, Y_1) = (\gamma, 0)$ is a saddle point.

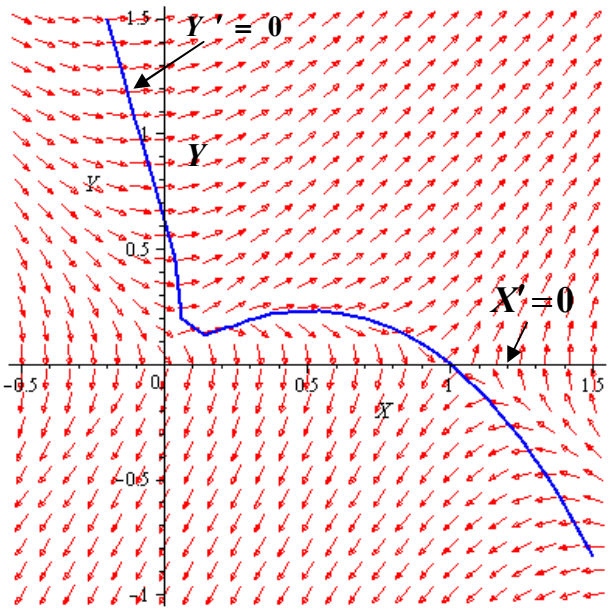

Fig. 1 Phase portrait of the system (8)-(9) in the case $\nu < 0$. Here $D = 0.8, k = 1, \nu = -1, \gamma = 1$.

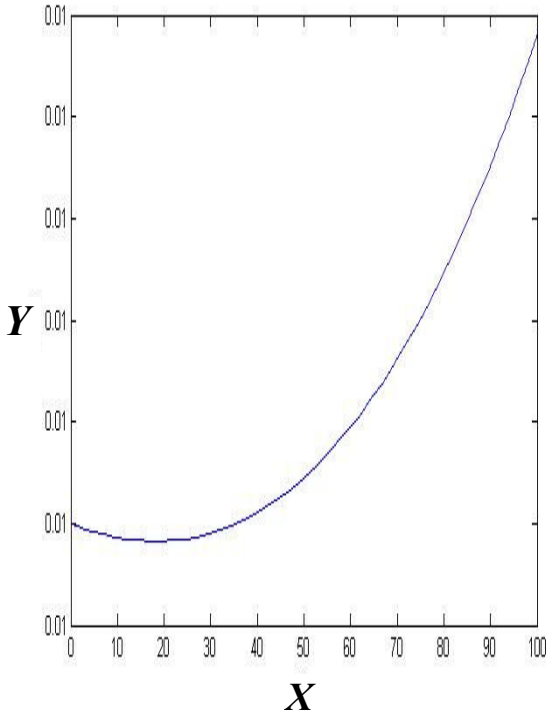

Fig 2 Computer simulation of the system (8)-(9), showing the solution trajectory in the (X,Y)-plane in the case that $D = 0.8, \nu = -1,\ k = 1, \gamma = 1,\ \ X(0) = 0,\ Y(0) = 0.01$.

In what follows, we are able to derive analytical solutions, in terms of the travelling wave coordinate, in 3 of the cases.

Fig.2 shows the solution trajectory in the phase plane starting from the initial point at $(X,Y) = (0, 0.1)$ and becoming unbounded as time passes. The corresponding plots of the concentration of dissolved drug d and its rate of change as functions of z for the same parameter values as in Fig. 1-2 are seen in Fig. 3 and 4 respectively

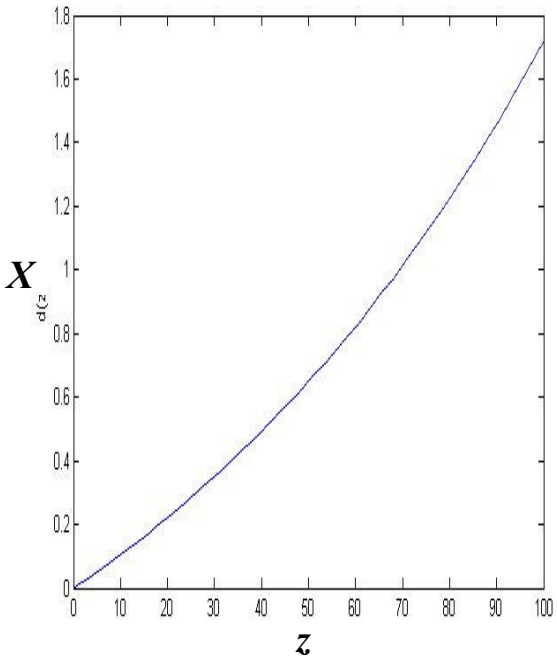

Fig. 3 Plot of d, the dissolved drug concentration, as a function of z for the same parameter values as in Fig. 1-2.

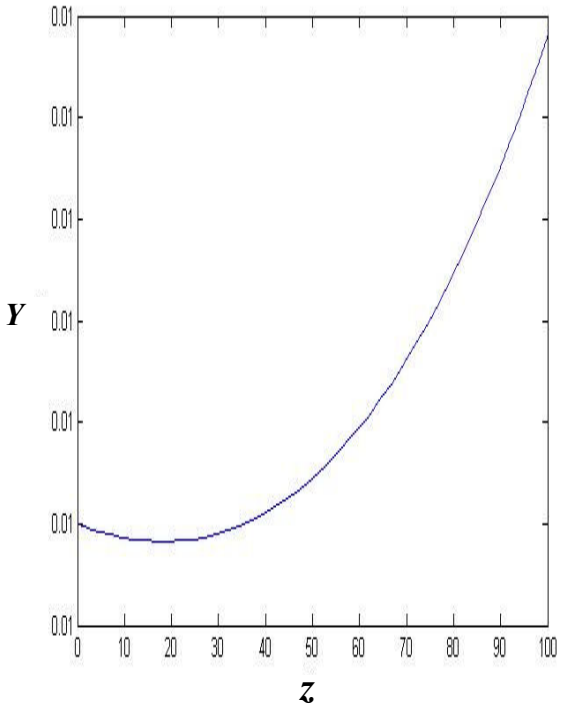

Fig. 4 Plot of d' as a function of z for the same parameter values as in Fig. 1-2.

IV. Analytical Solution

In order to derive an analytic solution for the model equation (5), we first let

$$C^{3/2} = \nu d + Dd' \tag{10}$$

We will seek a solution of the form

$$d' = AC^m + BC^n \tag{11}$$

so that we have

$$\frac{3}{2}C^{1/2}C' = \nu d' + Dd'' \tag{12}$$

Also, Eq. (10) gives

$$d = \frac{1}{\nu}C^{3/2} - \frac{D}{\nu}(AC^m + BC^n) \tag{13}$$

Substituting (12) and (13) into (7), we obtain

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

Rearranging the above equation yields

$$\frac{3}{2}C^{1/2}C' + \frac{k\gamma}{\nu^{2/3}}C - \frac{k}{\nu^{5/3}}C^{5/2} + \frac{kAD}{\nu^{5/3}}C^{m+1} + \frac{kBD}{\nu^{5/3}}C^{n+1} = 0 \tag{14}$$

On inspection, we observe that we may find exact solutions in the following two possible cases.

Case 1: $m = 0, n = -\frac{1}{2}$

For these values of m and n, Eq. (14) becomes

$$\frac{3}{2}C^{1/2}C' + \frac{k\gamma}{\nu^{2/3}}C - \frac{k}{\nu^{5/3}}C^{5/2} + \frac{kAD}{\nu^{5/3}}C + \frac{kBD}{\nu^{5/3}}C^{1/2} = 0 \tag{15}$$

By letting

$$AD = -\gamma\nu \tag{16}$$

equation (15) reduces to

$$\frac{3}{2}C^{1/2}C' - \frac{k}{\nu^{5/3}}C^{5/2} + \frac{kBD}{\nu^{5/3}}C^{1/2} = 0 \tag{17}$$

If we let

$$\alpha^2 = -\frac{1}{BD} > 0, \beta = -\frac{2kBD}{3\nu^{5/3}} < 0 \tag{18}$$

we can write Eq. (17) as

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

which can be easily solved, yielding

$$C = \frac{1}{\alpha}\tan(\alpha\beta z + \alpha K) \tag{19}$$

where K is the constant of integration.

Substituting (17) into (13), rearranging and using (16), one obtains

$$d = \frac{1}{\nu\alpha^{3/2}}\left(\tan^{3/2}(\alpha\beta z + \alpha K) + \cot^{1/2}(\alpha\beta z + \alpha K)\right) + \gamma \tag{20}$$

So that we have $d\big|_{z=0} = 0$, the following equation must be satisfied.

$$\tan^{3/2}\alpha K + \cot^{1/2}\alpha K = -\gamma\nu\alpha^{3/2} \tag{21}$$

We can then obtain the level of drug in solid form by integrating (5) so that

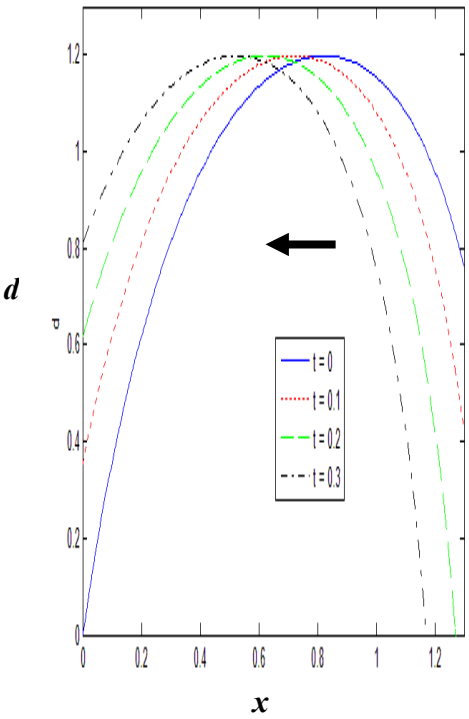

Fig. 5 Travelling wave solution in Case 1 for the concentration d of drug in the diluted form, given by (23), plotted as a function of x for different time.

$$\nu s = -C^{3/2} + \nu l$$

or,

$$s = -\frac{1}{\nu\alpha^{3/2}}\tan^{3/2}(\alpha\beta z + \alpha K) + l \tag{22}$$

where l is the constant of integration. Thus, a travelling wave solution is given as

$$d = \frac{1}{\nu\alpha^{3/2}}\left(\tan^{3/2}(\alpha\beta(x-vt)+\alpha K) + \cot^{1/2}(\alpha\beta(x-vt)+\alpha K)\right) + \gamma \tag{23}$$

$$s = -\frac{1}{\nu\alpha^{3/2}}\tan^{3/2}(\alpha\beta(x - vt) + \alpha K) + l \tag{24}$$

where $\alpha, \beta, A,$ and B are given by (16) and (18), and (21).

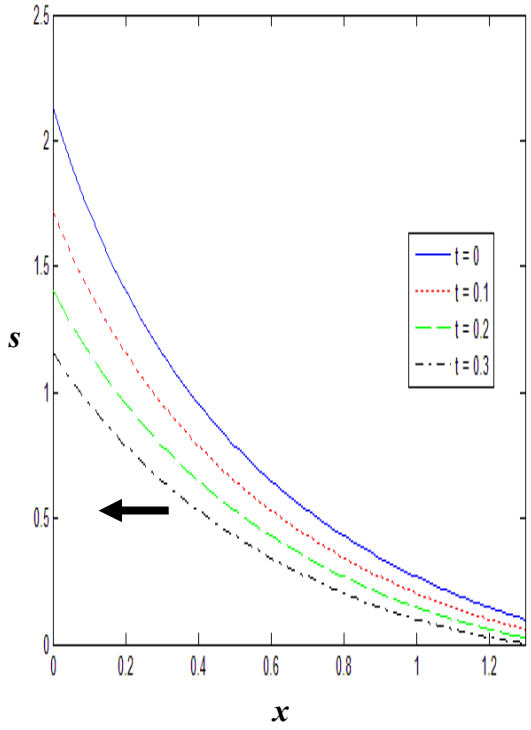

Fig. 6 Travelling wave solution in Case 1 for the concentration of drug s in the solid form, given by (24), plotted as a function of x for different time t.

The analytical travelling wave solution given by (23)-(24) is shown in Fig. 5 and 6 to move in the direction of decreasing x as time elapses. Here,

$\alpha = \frac{\pi}{3}$, K =1, $l = 0$, $\nu = -1$, k =1, and $\gamma = 2.836$

***Case 2*:** $m = \frac{3}{2}, n = 0$

In this case, equation (14) becomes

$$\frac{3}{2}C^{1/2}C' + \frac{k\gamma}{\nu^{2/3}}C - \frac{k}{\nu^{5/3}}C^{5/2} + \frac{kAD}{\nu^{5/3}}C^{5/2} + \frac{kBD}{\nu^{5/3}}C = 0 \quad (23)$$

If we let

$$BD = -\gamma\nu \quad (24)$$

then (23) reduces to

$$\frac{3}{2}C^{1/2}C' - \left(\frac{k}{\nu^{5/3}} - \frac{kAD}{\nu^{5/3}}\right)C^{5/2} = 0 \quad (25)$$

or

$$C' = -JC^2,$$

where

$$J = \frac{2k(AD-1)}{3\nu^{5/3}} \quad (26)$$

Solving (26), we obtain

$$C = \frac{1}{Jz + K} \quad (27)$$

where K is the constant of integration. Upon substitution (27) into (13) and using (24) we are led to

$$d = \frac{1-AD}{\nu}(Jz + K)^{-3/2} + \gamma \quad (28)$$

So that we have $d|_{z=0} = 0$, we need the following equation to be satisfied.

$$\frac{AD-1}{\nu K^{3/2}} = \gamma \quad (29)$$

Using (5) then gives

$$s = -\frac{1}{\nu(Jz + K)^{3/2}} + l \quad (30)$$

where l is the constant of integration.

Thus, a travelling wave solution to (3)-(4) is given as

$$d = \frac{1-AD}{\nu}(J(x - \nu t) + K)^{-3/2} + \gamma \quad (31)$$

$$s = -\frac{1}{\nu(J(x - \nu t) + K)^{3/2}} + l \quad (32)$$

where $\alpha, \beta, A,$ and B are given by (24), (26), and (29)

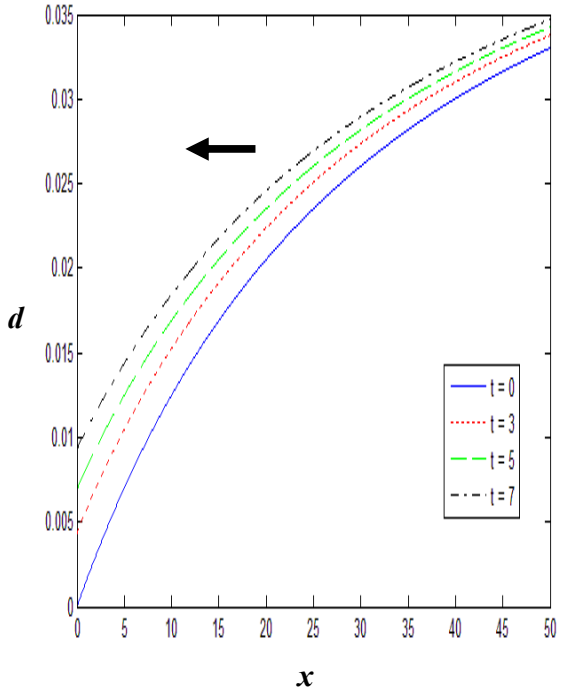

Fig. 7 Wave front solution in Case 2 for the concentration d of drug in the dissolved form, given by (31), plotted as a function of x for different time t.

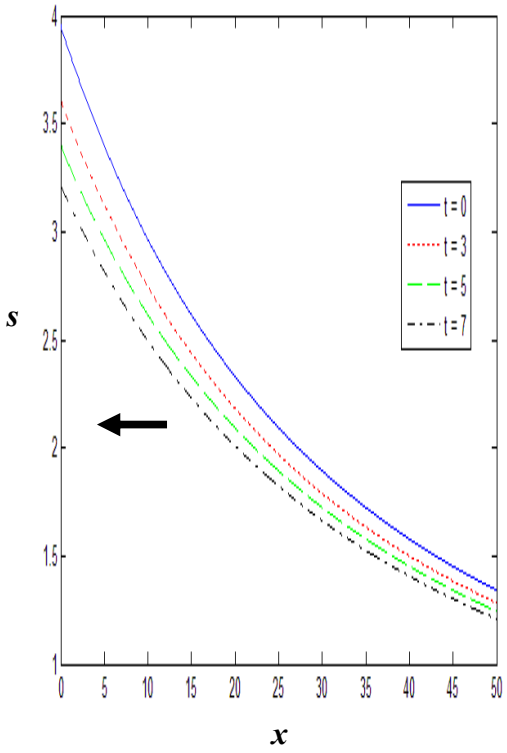

Fig. 8 Wave front solution in Case 2 for the concentration of drug s in the solid form, given by (32), plotted as a function of x for different time t.

The graphs of the wave front solution given in (31)-(32) are shown in Fig. (7)-(8) to move in the direction of decreasing x as time elapses. Here, $D = 0.02, K = 0.4, \nu = -1, k = 1, \gamma = 0.05,$ and $l = 0$.

Case 3: $m = \frac{3}{2}, n = n' + \frac{1}{2}$.

For convenience, we let

$$A = \frac{3a}{2}, B = \frac{3b}{2}$$

in (11), and drop the prime on the exponent n'. Thus, we are now looking for a solution in the form

$$d' = \frac{3}{2}\left(aC^{3/2} + bC^{n+1/2}\right) \tag{33}$$

such that

$$C' = A_0 C + B_0 C^n \tag{34}$$

Differentiating (33) and using (34), we obtain

$$d'' = \frac{3}{2}\left(\frac{3}{2}aC^{1/2} + b(n+\frac{1}{2})C^{n-1/2}\right)\left(A_0 C + B_0 C^n\right) \tag{35}$$

Substituting (33) and (35) in (7), choosing A_0 = a, and B_0 = b, and rearranging, we are led to

$$\frac{3D}{2}\left(\frac{3}{2}ab + \frac{b\nu}{D} + ab(n+\frac{1}{2})\right)C^{n+1/2} + \frac{3D}{2}\left(\frac{3a^2}{2} + \frac{a\nu}{D}\right)C^{3/2}$$
$$+\frac{3D}{2}b^2(n+\frac{1}{2})C^{2n-1/2} + \frac{k\gamma}{\nu^{2/3}}C$$
$$-\left(\frac{k}{\nu^{5/3}} - \frac{3akD}{2\nu^{5/3}}\right)C^{5/2} + \frac{3kbD}{2\nu^{5/3}}C^{n+3/2} = 0 \tag{36}$$

Upon observation, we see that if we let $n = -\frac{1}{2}$ then Eq. (36) can be written as

$$\left(\frac{9}{4}abD + \frac{3}{2}b\nu\right)C^0 + \left(\frac{k\gamma}{\nu^{2/3}} + \frac{3kbD}{2\nu^{5/3}}\right)C + \left(\frac{9}{4}a^2D + \frac{3}{2}a\nu\right)C^{3/2}$$
$$+\left(\frac{3akD}{2\nu^{5/3}} - \frac{k}{\nu^{5/3}}\right)C^{5/2} = 0 \tag{37}$$

Thus, if we let

$$\frac{k\gamma}{\nu^{2/3}} + \frac{3kbD}{2\nu^{5/3}} = 0, \text{ or } b = -\frac{2\gamma\nu}{3D}$$
$$\frac{3akD}{2\nu^{5/3}} - \frac{k}{\nu^{5/3}} = 0, \text{ or } a = \frac{2}{3D} \tag{38}$$

then (37) will be satisfied.

With the above choice in (38), we are in the case where $\nu = -1$, and (34) becomes

$$C' = aC + bC^{-1/2}$$

which can be easily solved to yield

$$C(z) = \frac{1}{a^{2/3}}\left(b - e^{\frac{3az}{2}+k}\right)^{2/3} \tag{39}$$

Substituting (39) into (10), 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

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

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

$$d = \left[\gamma - \frac{3}{2}(x - \nu t)e^k\right]e^{(x-\nu t)/D} - \gamma \tag{40}$$

and, similarly to the previous cases,

$$s = \gamma - \frac{3}{2}De^{(x-\nu t)/D+k} + l \tag{41}$$

l being a constant of integration.

The graphs of the wave front solution given in (40)-(41) are shown in Fig. (9)-(10) with $\nu = -1,$ $\gamma = 200,$ $D = 50e^{-2},$ $k = 0.2,$ and $l = 1 - \gamma + \frac{3}{2}De^{k+2}$.

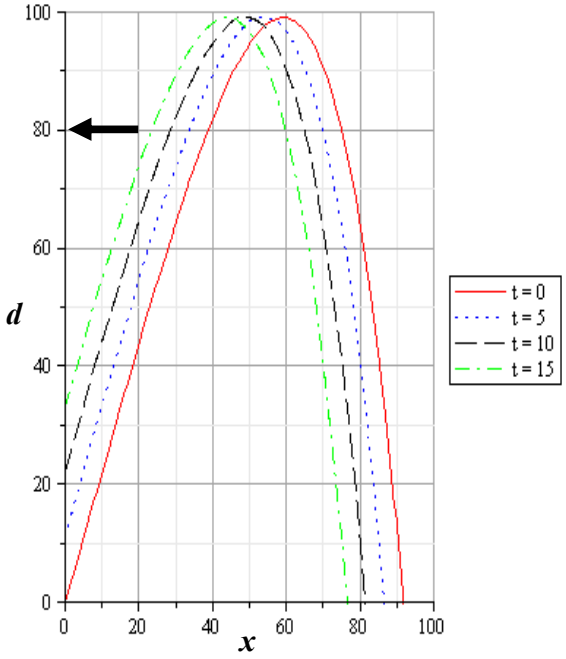

Fig. 9 Wave front solution in Case 3 for the concentration d of drug in the dissolved form, given by (40), plotted as a function of x for different time t.

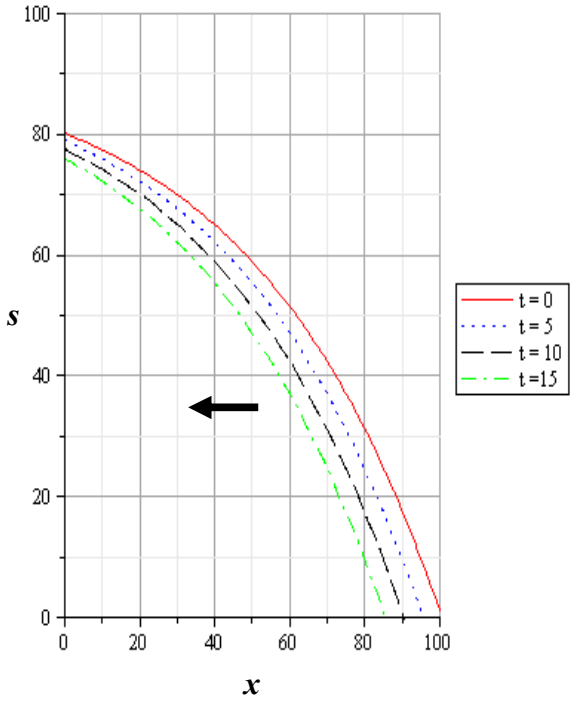

Fig. 10 Wave front solution in Case 3 for the concentration d of drug in the dissolved form, given by (41), plotted as a function of x for different time t.

V. Discussion

To illustrate that the analytic solution can allow us to investigate the impact of different values of the system's physical properties, such as the saturation constant, the porosity, the drug diffusivity, or the dissolution rate, on the waveform structures, we show in Fig. 11 the plot of the travelling wave front of concentration of drug in dissolved form for a different set of parametric values, namely, $\gamma = 200,\ D = 2,\ k = 0.2,$ and $\nu = -1$.

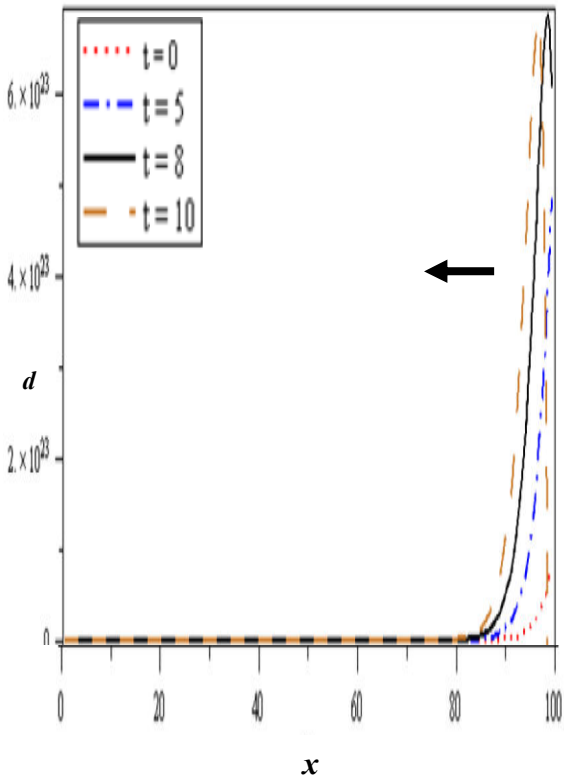

Fig. 11 Wave front solution in Case 3 for the concentration d of drug in the dissolved form, given by (40), plotted as a function of x for different time t: $\gamma = 200,\ D = 2,\ k = 0.2, \nu = -1$, and $d\big|_{z=0} = 0$.

Finally, to put our analytical solution in the context of numerical and approximate solutions reported in earlier literatures, we refer to the results shown in [5] and [14]. In [14], fractions of released drug calculated numerically using the model consisting of (3) and (4) is shown for different values of saturation constant c_s. The curves are compared with the "analytical short-time approximation" as well as the curves obtained from the modified Higuchi formula.

We observe that the Higuchi solution and the analytical short-time approximation are close to the exact solution only during the exponential phase of drug release, but offer quite a poor estimate of the released drug near the saturation period.

Our exact solution is therefore extremely valuable as it can be used to accurately investigate effects of different values of physiological or physical factors in the controlled drug release system, such as different saturation constants, diffusivity, or porosity. These parameters and their impact on drug delivery are of great importance in the design of pharmaceutical products which are well characterized and in reproducible dosage forms, capable of controlling drug entry into the body according the specifications of the required drug delivery profile.

VI. Conclusion

Intensive continuing research, both experimentally and theoretically, has been on going, especially in the last decade or so, on the topic of controlled-release technology, due to its crucial role in the formulation of pharmaceutical products [1-14, 22-25].

Here, we have added to the current knowledge by showing that an exact solution can be derived for the model of drug release formulated by Frenning [14] where the lateral dimensions of the system are assumed to be much larger than its thickness L. The boundary at x = 0 is assumed to be impenetrable to the drug, while the matrix is in contact with the liquid at $x = L$. The matrix is assumed to be in contact with a well-mixed dissolution medium, the volume of which is large enough to ensure that the drug concentration is virtually zero at all times.

The resulting model is relatively complex, involving a nonlinear fractional power of the dependent variable. Previous works have been able to obtain numerical solution and, only by restriction their attention to the initial phase of drug release, an 'analytical approximate solution' can be found.

We have relied on the work in [17-19], using the travelling wave coordinate, and appropriate choice of combination of powers of the solution and its derivative, we have shown that an exact solution for the concentrations of drug in the solid and dissolved forms can be found as functions of the travelling coordinate, while the travelling wave velocity v is found to be negative as expected.

The methodologies for obtaining the exact solution presented in this study can be applied to other problems [20, 21] which admit travelling wave solutions. In the case that the system is described by a model consisting of coupled partial differential equations, they can be reduced to a single second order differential equation which is more easily solved. In Fig. 1, we can see that the drug concentration in the dissolved form increases (as t tends to infinity) while the wave of the dissolved drug concentration wave front is moving at a constant speed of 1.0.

It might be wondered whether it would have been better to simply solve the model equations for numerical solutions. To answer such a question, the model system should be solved numerically so that the numerical simulation could be compared with the analytical solution, which is the subject for our future work.

It can be argued at this juncture that the ability to derive the exact solution could be quite valuable in the investigation of impacts of various conditions on drug delivery, since the ability to accurately predict the outcome of different choices of material, composition, drug properties, and others, on the release mechanism and kinetics is of crucial importance in terms of medical treatment and health care purposes.

Acknowledgment

This research is supported by Mahidol University and the Centre of Excellence in Mathematics, CHE, Thailand, and Mahidol University.

References

[1] J.E. Mockel, B.C. Lippold, Zero order drug release from hydrocolloid matrices, Pharm. Res., Vol.10, 1993, pp. 1066-1070.
[2] J. Heller, Biodegradable polymers in controlled drug delivery, Crit. Rev. Ther. Drug Carrier Syst., Vol. 1, N0 1, 1984, pp. 39-90.
[3] J. Crank, The Mathematics of Diffusion, Oxford University Press, London, 1975.
[4] P. Colombo, R. Bettini, G. Massimo, P.L. Catellani, P. Santi, N.A. Peppas, Drug diffusion front movement is important in drug release control from swellable matrix tablets, J. Pham. Sci. Vol.87, 1995, pp. 991 997.
[5] T. Higuchi, Rate of release of medicaments from ointment bases containing drugs in suspension, J. Pharmac. Sci., 50 (1961), 874–875.
[6] T.J. Roseman, W. Higuchi, Release of medroxyprogesterone acetate from a silicone polymer, J. Pharm. Sci., Vol. 59, 1970, pp. 353-357.
[7] K. Tojo, Intrinsic release rate from matrix-type drug delivery systems, J. Pharm. Sci., Vol.74, 1985, pp. 685-687.
[8] D.R. Paul, S.K. McSpadden, Diffusional release of a solute from a polymeric matrix, J. Membr. Sci. Vol.1, 1976, pp. 33-48.
[9] P.I. Lee, Diffusional release of a solute from a polymeric matrix-approximate analytical solutions, J. Membr. Sci., Vol.7, 1980, pp. 255-275.
[10] A.L. Bunge, Release rates from topical formulations containing drugs in suspension, J. Control. Release, Vol.52, 1998, pp. 141-148.
[11] M.J. Abdekhodaie, Y.-L. Cheng, Diffusional release of a dispersed solute from planar and spherical matrices into finite external volume, J. Control. Release, Vol.43, 1997, pp. 175-182.
[12] Y. Zhou, X.Y. Wu, Theoretical analyses of dispersed-drug release from planar matrices with boundary layer in a finite medium, J. Control. Release, Vol.84, 2002, pp. 1-13.
[13] G. Frenning, M. Strømme, Drug release modeled by dissolution, diffusion, and immobilization, Int. J. Pharm., Vol.250, 2003, pp. 137-145.
[14] G. Frenning, Theoretical investigation of drug release from planar matrix systems: effect of a finite dissolution rate, J. Control. Release, Vol.92, 2003, pp. 331-339.
[15] D. Sun, V.S. Manoranjan, H.-M. Yin, Numerical solution for a coupled parabolic equations arising induction heating processes, Discrete and Continuous Dynamical System, 2007, pp. 956-964.
[16] R.L. Burden, J.D. Faires, A.C. Reynolds, Numerical Analysis 2nd Edition, Prindle, Weber and Schmidt. Inc, USA, 1981.
[17] M.O. Gomez, C.M. Chang, V.S. Manoranjan Exact solution for contaminant transport with nonlinear sorption, Appl. Math. Lett., Vol.9, 1996, pp. 83-87.
[18] V.S. Manoranjan, T.B. Stauffer, Exact solution for contaminant transport with kinetic langmuir sorption, Water Resources Research, Vol.32, No.3, 1996, pp. 749-752.
[19] C.M. Chang, V.S. Manoranjan, Travelling wave solutions of a contaminant transport model with nonlinear sorption, Mathl. Comput. Modelling., Vol.28, No.9, 1998, pp. 1-10.
[20] E. Kreyszing, Advanced Engineering Mathematics 8th Edition, John Wiley and Sons. Inc, USA, 2003.
[21] P. Prasertsang, V.S. Manoranjan, Y. Lenbury, Analytical travelling wave solutions of a dental plaque model with nonlinear sorption, Nonlinear Studies, Vol. 18, No. 1, 2011, pp. 87-97.

[22] S.-P. Tang, An exploratory research on the nanovectors for drug delivery and for gene therapy, WSEAS Transactions on Biology and Biomedicine, Volume 5, Issue 12, 2008, pp. 313-321.
[23] S.-P. Tang, An experimental comparing analysis research on the nanovectors for drug delivery and for gene therapy, WSEAS Transactions on Biology and Biomedicine, Vol. 7, No. 1, 2010, pp. 11-20.
[24] T. Schroder., A. Quintilla., J. Setzier., E. Birtaian., W. Wenzel., and S. Brase., Joint experimental and theortical Investigation of the propensity of peptoids as drug carriers. WSEAS Transductions on Biology and Biomeducine, Vol. 4, Issue 10, 2007, pp. 145-148.
[25] T. Hara, S. Iriyama, M. Ohya, Estimation of drug shape in drug delivery system by simulation, Proceedings of the 10th WSEAS International Conference on Mathematics and Computers in Biology and Chemistry, 2009.