Some New Solutions of a Reaction Diffusion Model for Controlled Drug Release using Travelling Wave Coordinate Transformation

Chontita Rattanakul, Yongwimon Lenbury

Abstract**—**Being able to deliver drugs to a targeted cell in the body would certainly enhance the future treatment of patients, especially those suffering from cancer. In such complex physical areas there is often a lack of well-formed conceptual ideas and sophisticated mathematical modelling in the analysis of the fundamental issues involved in the drug delivery process. Progress in many of these areas will be accelerated by means of accurate applied mathematical modelling which embodies the correct physical and chemical principles. In 2003, Göran Frenning proposed and numerically solved a mathematical model of the drug dissolution and release processes. The model consisted of two coupled nonlinear partial differential equations. Later, Chontita and Lenbury (2012) made use of appropriate transformation with travelling wave coordinate to derive analytical solutions the an equivalent set of ordinary differential equations when the wave was assumed to be moving at constant speed. Here, we present some new travelling wave solutions of the model of controlled drug release, in a planar geometry, for certain different cases in which analytical solutions can be derived exactly. We investigate how different values of important physical parameters effect the shapes of the travelling waves which should be useful for the proper design of the drug release system.

Keywords**—**Controlled drug release, Analytical solution, Traveling wave coordinate

I. Introduction

MATHEMATICAL and computer modelling has played an increasingly important role in pharmaceutical industry, providing valuable assistance in the design and manufacture of advanced materials and many nanodevices.

The United States Food and Drug Administration Critical Path Initiative has recently made model-based drug development, including drug and disease modeling, one of its important goals (www.fda.gov/oc/initiatives/criticalpath). Since it has now become commonly acknowledged that detailed and accurate modelling will accelerate the development of targeted drug delivery applications, new discoveries and theories generated by model construction have been appearing in many frequently cited biologically related literatures.

In the formulation of pharmaceutical products, the use of controlled-release technology is gaining increasing attention due to its inherent advantages [1]. The objective of the use of sustained release dosage forms is to be able to release the drug at a predetermined rate. They are therefore designed to be capable of maintain a sustained drug level for a satisfactory period of time without incurring side effects above an acceptable extent [1]. The need 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, has led to intense research on sustained release.

Moreover, according Kumar et al. [1], increased complications and expense involved in marketing of new drug forms necessitates the pharmaceutical industry to focus greater attention on design and manufacture of sustained release or controlled release drug delivery systems. The matrix system is popular and has found wide usage since it makes possible prolonged and controlled release of a drug that is dissolved or dispersed. In recent years, a number of sustained release drug forms have been marketed, and funding have become noticeably available for research which concentrates on the design of sustained release process 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]. Specifically, the drug sorption behaviour of a sorbent depends on many factors, including the structure and the chemical composition of the sorbent material.

According to Boutayeb and Chetouani [3], with drug delivery by the matrix system, 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.

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] according to the following equations.

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

C, Rattanakul is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400 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: scylb@yahoo.com).

$$C_t = -DC_{xx} \quad (2)$$

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

As explained in [6], 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. If the drug concentration is sufficiently low so that all drugs can be dissolved, and the dissolution process progresses fast enough, we may easily determine the release rate [5]. In such situation of drug release, all drug may be assumed to be completely dissolved before any release has taken place and we the heat conduction equation can be applied to determine the drug concentration in the matrix.

In the more general type of drug release, 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. In such a scenario the drug release process becomes noticeably more complex. For this more general situation where drug loading is much higher than drug solubility ($C_0 \gg C_s$), Higuchi [7] propose a model which has been found to perform well for planar matrix under the perfect sink assumption.

The Higuchi model, originally formulated for drug release from ointment bases containing drugs in suspension [7], has since been subject to several attempts at generalizations and modifications [8]-[12]. Then, in 2003, Frenning and Strømme [13] proposed a similar model which focuses on the release of drug from spherical pellets into a finite volume of dissolution medium. In formulating the model, it was assumed that some of the dissolved drug could become immobilized and absorped into the pellet constituents.

Later in the same year, Frenning [14] readjusted the model in [13] to disregard drug absorption, assuming that the diffusion coefficient is concentration-independent. He then derived an "analytical short-time approximation" to the solution under the assumption of perfect sink conditions [14].

In 2012, Rattanakul and Lenbury [15] analytically obtained exact solutions to the model equations by introducing the travelling wave coordinate in the situation that the wave is presumably moving at a constant speed which allows the transformation of the reaction diffusion equations into a system of ordinary differential equations. A stability analysis was carried out on the model system before deriving the wave front solutions written in a specifically convenient form.

Here, we derive more travelling wave solutions of the model of controlled drug release, in a planar geometry, will be derived for certain new cases in which analytical solutions can be derived exactly such that the solutions satisfy physically meaningful boundary and initial conditions. Plots of travelling wave fronts of drug diffusion in different cases are then presented.

II. Referenced Model

In [14], Frenning focused on a planar matrix system whose normal is in the x direction. 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 essentially be considered to be one-dimensional [14]. The boundary at $x = 0$ is assumed to be virtually impenetrable to the drug, while the matrix is assumed to be in contact with the liquid at $x = L$.

Under the perfect sink condition assumption, the matrix is supposed to be in contact with a well-mixed dissolution medium, the volume of which is large enough so that we can be assured that the drug concentration in the dissolution medium 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, the entire drug is present in the solid form [14]. As explained in [14], it is possible to describe drug dissolution and release by the following equations [14].

$$d_t = Dd_{xx} - s_t \quad (3)$$

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

where $d(t,x)$ is the concentration of drug in the dissolved phase, $s(t,x)$ that in the solid phase, t the time, c_s the saturation constant, ε the porosity, d the drug diffusivity, and k_d is the dissolution rate. The initial condition [14]

$$d(0,x) = 0 \quad (5)$$

$$s(0,x) = s_0 \quad (6)$$

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

$$d_x\big|_{x=0} = 0 \quad (7)$$

is imposed if the interface at $x = 0$ is supposed to be impenetrable to the drug. However, if we relax the impenetrability condition to

$$d_x\big|_{x=0} \ll 1 \quad (8)$$

instead, then the interface will be "almost" impenetrable to the drug. Finally, we impose the condition

$$s(t,L) = 0 \quad (9)$$

so that the drug concentration at $x = L$ is kept at zero due to the perfect sink condition.

We next introduce the travelling wave coordinate $z = \pm x - \nu t$, where ν is the constant velocity at which the wave is moving. By substituting z in (3) and (4), we obtain the following system of ordinary differential equations:

$$-\nu d' = Dd'' + \nu s' \quad (10)$$

$$-\nu s' = -ks^{2/3}(\gamma - d) \quad (11)$$

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), we are led to the following single second-order differential equation terms of d.

$$Dd'' + \nu d' + \frac{k}{\nu^{2/3}}(\nu d + Dd')^{2/3}(\gamma - d) = 0 \quad (12)$$

III. Wave front Solutions

We shall derive analytic solutions for the model equation (12) by writing the solution in a specifically convenient form as follows:

$$C^{3/2} = \nu d + Dd' \tag{13}$$

and seek a solution of the form

$$d' = AC^m + BC^n \tag{14}$$

Thus, we have

$$\frac{3}{2}C^{1/2}C' = \nu d' + Dd'' \tag{15}$$

On the other hand, Eq. (13) gives

$$d = \frac{1}{\nu}C^{3/2} - \frac{D}{\nu}(AC^m + BC^n) \tag{16}$$

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

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

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 some of the appropriate initial and boundary conditions at x = 0, namely conditions (5)-(9). Here, we describe how analytical solutions can be obtained in 4 cases which satisfy physically meaningful initial and boundary conditions with additional details to what has been discussed in [16].

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

For these values of *m* and *n*, we need to let

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

which reduces (17) into a simpler form that can be easily solved to yield [16]:

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

Keeping in mind that *d* should be increasing with z and *t*, while *s* should be decreasing, we realize that we need to use the negative square root of *C* in (16), so that the concentration of drug in solute form which will satisfy (10)-(11) can be written as

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

From the integrating (10) and using the positive square root of *C*, we obtain the "concentration" of drug in solid phase as

$$s = -\frac{1}{\nu\alpha^{3/2}}\tan^{3/2}\alpha(\beta(x-\nu t)+K) + l \tag{21}$$

where *l* and *K* are constants of integration.

So that the solution given by (20) satisfies condition (5), we need to set

$$\left(\tan^{3/2}\alpha K + \cot^{1/2}\alpha K\right) + \nu\gamma\alpha^{3/2} = 0 \tag{22}$$

So that the solution given by (20) satisfies condition (7), the following equation must be satisfied.

$$\frac{\beta}{\nu\alpha^{1/2}}\tan^{1/2}(\alpha K)\left\{3\sec^2(\alpha K) - \cos ec^2(\alpha K)\right\} = 0 \tag{23}$$

So that the solution given by (21) satisfies condition (6), we need to set

$$l = s_0 + \frac{1}{\nu\alpha^{3/2}}\tan^{3/2}\alpha K \tag{24}$$

Finally, so that the solution satisfies condition (9), we need to have

$$\frac{1}{\nu\alpha^{3/2}}\tan^{3/2}\alpha(\beta L + K) = l \tag{25}$$

In Fig. 1, the analytical travelling wave solution given by (20)-(21), subject to the conditions (19), (22)-(25), is shown to move in the direction of decreasing *x* as time elapses.

To investigate how varying the physical parameters may effect the shape of the diffusing drug wave front, we plot the solution in Fig. 2 with a different parameter values.

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

With these values of *m* and *n*, Eq. (6) becomes

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

As done in our earlier work [16], for simplicity, we consider the case that $AD = 1$. Then, the above equation is reduced to

$$\frac{3}{2}C^{1/2}C' + \frac{k\gamma}{\nu^{2/3}}C + \frac{kBD}{\nu^{5/3}}C^2 = 0 \tag{26}$$

If we now let

$$\alpha = -\frac{k\gamma}{3\nu^{2/3}}, \ \beta^2 = -\frac{BD}{\gamma\nu} \tag{27}$$

Then, Eq. (26) can be easily solved, to yield [16]

$$C = \frac{1}{\beta^2}\tan^2(\alpha\beta z + K) \tag{28}$$

where *K* is the constant of integration. Substituting (29) into (16), one obtains

$$d = \gamma\tan^2(\alpha\beta z + K) \tag{29}$$

So that the solution satisfies condition (5), we need to set *K* = 0. The solution then already satisfies (7). Thus, the level of drug in solid form is found by integrating (5) so that

$$s = -\frac{1}{\nu\beta^3}\tan^3(\alpha\beta z) + l \tag{30}$$

l being the constant of integration. For $s\big|_{z=0} = s_0$, we need to set $l = s_0$. For $s\big|_{z=L} = 0$, the parameters have to satisfy the following condition

$$\tan^3(\alpha\beta L) = \nu\beta^3 s_0 \tag{31}$$

Thus, a travelling wave solution can be written as

$$d = \gamma\tan^2\alpha\beta(x-\nu t) \tag{32}$$

and

CASE 1:

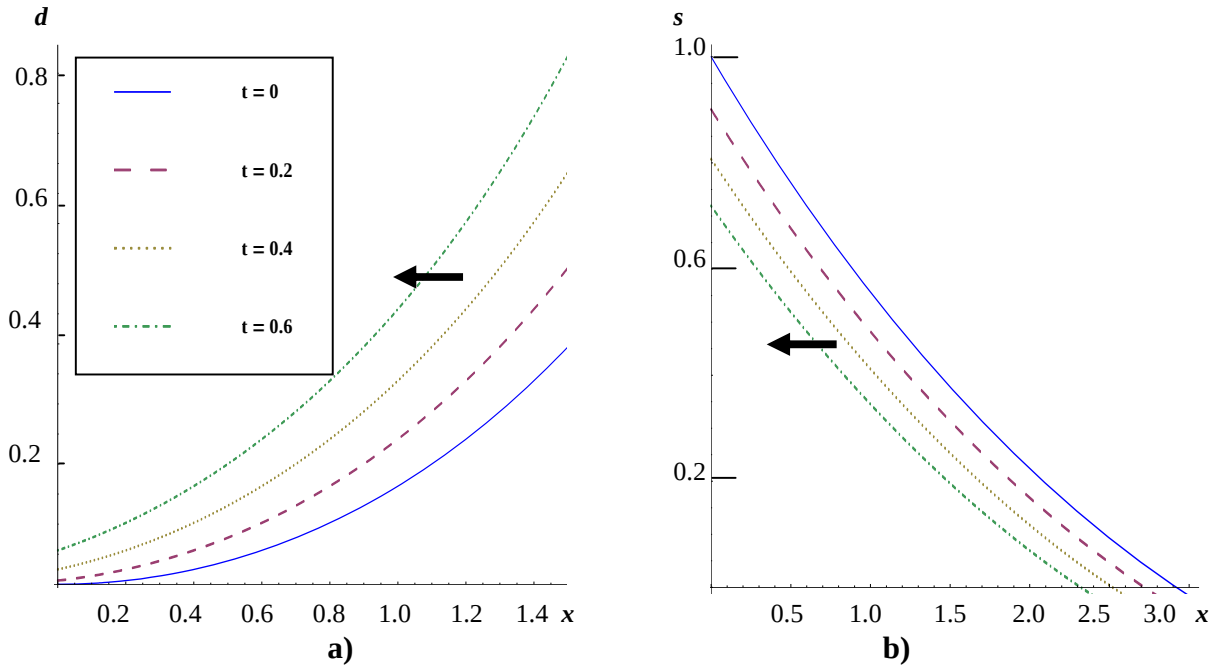


Fig. 1 Travelling wave solution in Case 1 with $\gamma = 0.0170$ for the concentration a) d of drug in the diluted form, and b) s in the solid form, plotted as functions of x for different time [16]. Here, $\alpha = 7\pi$, $K = \frac{1}{6}$, $L = 7.0582$, $l = 1.0043$, $\nu = -1$, $k = 10$, $\gamma = 0.0170$, and $s_0 = 1$.

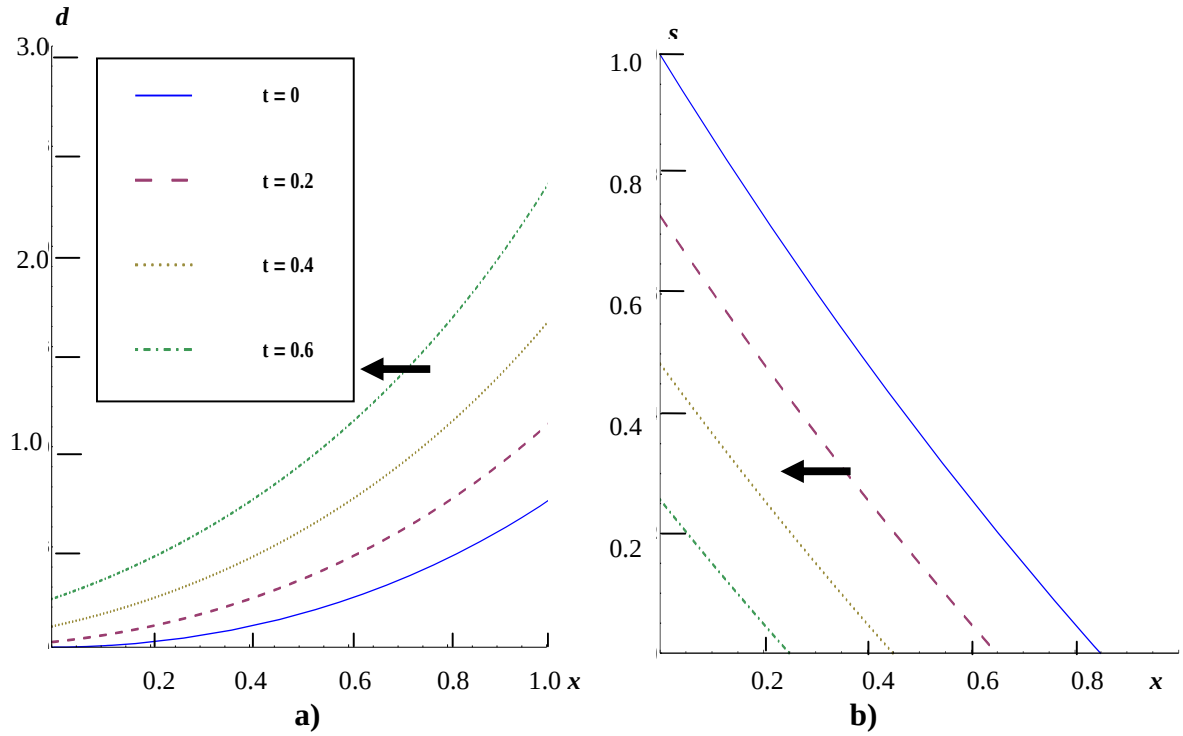


Fig. 2 Travelling wave solution in Case 1, with parameter values different from those used in Fig. 1, for the concentration a) d of drug in the diluted form, and b) s in the solid form, plotted as functions of x for different time. Here, $K = 1.5, \alpha = \frac{\pi}{9}, \nu = -1, \gamma = 8.5086, l = -1.12715, L = 0.849001$, and $k = 0.1$

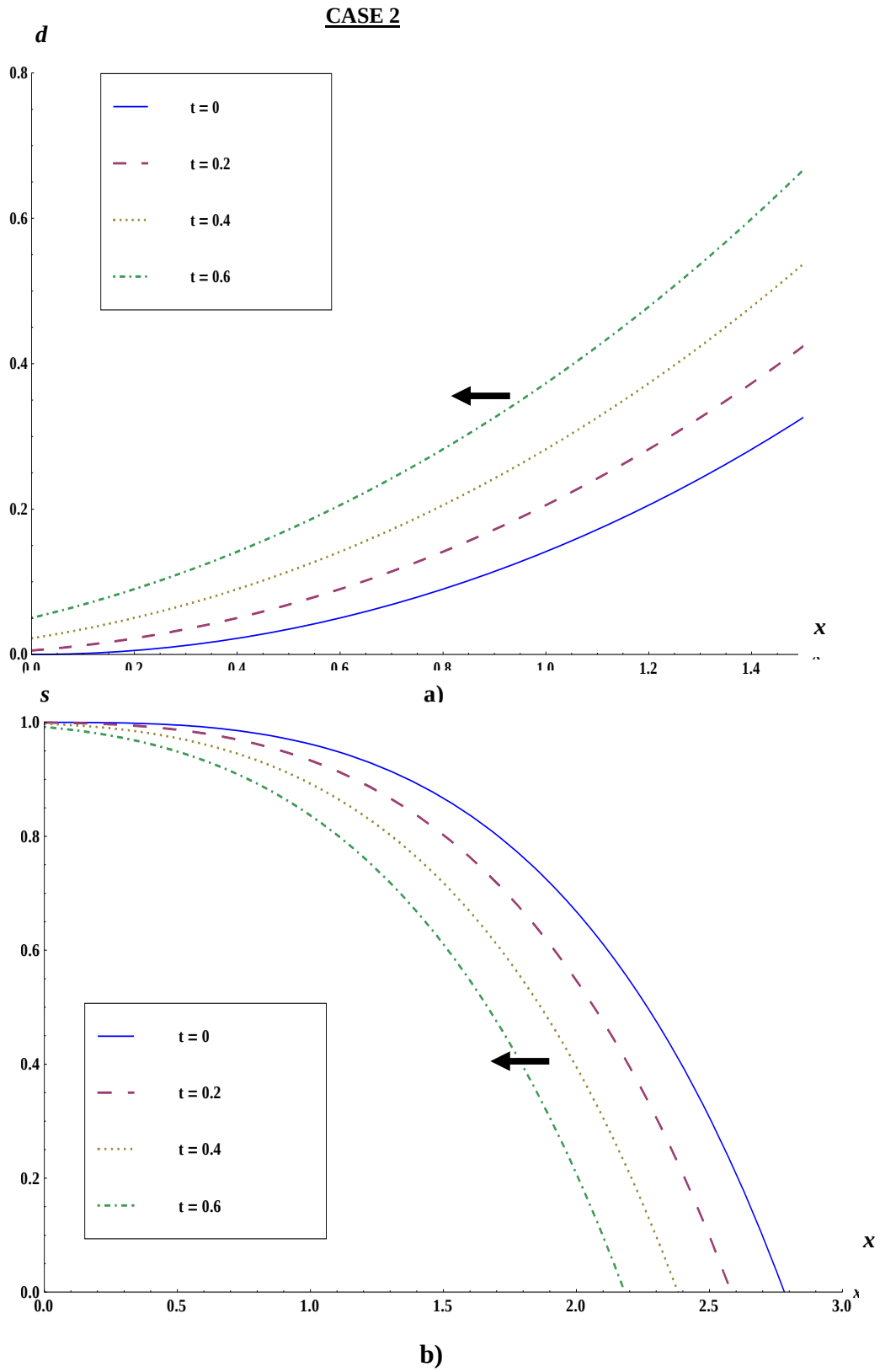


Fig. 3 Travelling wave solution in Case 2 for the concentration a) d of drug in the diluted form, and b) s in the solid form, plotted as functions of x for different time. Here, $\nu = -1, D = 1,\ \gamma = 5, L = 2.78189$, $k = 0.2,\ K = 0,\ s_0 = 1,\ \alpha = -0.3333$, $\beta = -0.5$, $A = 1, B = 1.25$.

where $\alpha, \beta, A,$ and B satisfy the conditions in (27), and (31). The plot of the travelling wave fronts given by (32)-(33), satisfying (27) and (31), is then shown in Fig. 3 to move in the direction of decreasing x as time elapses.

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

In this case, equation (17) becomes [16]

$$\frac{3}{2}C^{1/2}C' + \frac{k\gamma}{\nu^{2/3}}C - \frac{k}{\nu^{5/3}}C^{5/2} + \frac{kAD}{\nu^{5/3}}C^{5/2} + \frac{kBD}{\nu^{5/3}}C^{3/2} = 0 \quad (34)$$

If we again assume (27), then (34) reduces to

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

In order to simplify the above equation, we let $C = u^2$. Then, we have $C' = 2uu'$ which leads us to

$$3u^2u' + \frac{k\gamma}{\nu^{2/3}}u^2 + \frac{kBD}{\nu^{5/3}}u^3 = 0 \quad (35)$$

or

$$u' - \eta u - \mu = 0 \quad (36)$$

where

$$\mu = -\frac{k\gamma}{3\nu^{2/3}}, \eta = -\frac{kBD}{3\nu^{5/3}}, AD = 1 \quad (37)$$

Solving (36), we obtain

$$\ln(\eta u + \mu) = \eta z + K$$

which yields, with K a constant of integration,

$$C^{1/2} = \frac{1}{\eta}\left[\mu - \exp(K + \eta z)\right] \quad (38)$$

As described in [16], using (16) we are led to

$$d = \frac{3\nu^{2/3}}{k}\left[\exp(K + \eta z) - \mu\right] \quad (39)$$

Using (10), we then obtain

$$s = C^{3/2} + l = \frac{1}{\eta^3}\left[\mu - \exp(K + \eta z)\right]^3 + l \quad (40)$$

where l is the constant of integration.

In order that the condition (5) is satisfied, we need

$$\exp K = \mu \quad (41)$$

For the condition (6) to be satisfied, we need

$$\left(\mu - \exp(K)\right)^3 + \eta^3 l = \eta^3 s_0 \quad (42)$$

In order for the condition (8) to hold, we need

$$\left[\mu - \exp(K + \eta L)\right]^3 + l\eta^3 = 0 \quad (43)$$

Finally, so that the interface at $x = 0$ is virtually impenetrable, we set

$$\eta \exp K \ll 1 \quad (44)$$

Case 4: $m = \frac{3}{2}, n = n' + \frac{1}{2}$.

A travelling wave solution has already been given in [16] for this case with $\nu = -1$, namely

$$d = \left[\frac{3}{2}(x + t)e^k - \gamma\right]e^{(x+t)/D} + \gamma \quad (45)$$

$$s = l - \gamma - \frac{3}{2}De^{(x+t)/D+k} \quad (46)$$

the derivation of which may be seen in [16]. The solution in (45) already satisfies (5). To satisfy conditions (6), (8), and (9), the parameters need to satisfy the followings respectively.

$$l - \frac{3}{2}De^k - \gamma = s_0 \quad (47)$$

$$l - \frac{3}{2}De^{L/D+k} - \gamma = 0 \quad (48)$$

and

$$\left|\frac{3}{2}e^k - \frac{\gamma}{D}\right| \ll 1 \quad (49)$$

The plot of the solutions given by (45)-(49) is shown in Fig. 4.

Now, let's return to the solution we gave in [15], namely

$$d = \left[\gamma - \frac{3}{2}(x + t)e^k\right]e^{(x+t)/D} - \gamma \quad (50)$$

$$s = \gamma - \frac{3}{2}De^{(x+t)/D+k} + l \quad (51)$$

leaving the readers to find more detail of the derivation in this case from [15]. The solution in (50) already satisfies condition (5). In order that the conditions (6) and (8) hold, we need the following equation to be satisfied respectively.

$$\gamma - \frac{3}{2}De^k + l = s_0 \quad (52)$$

$$\gamma - \frac{3}{2}De^{L/D+k} + l = 0 \quad (53)$$

The impenetrable condition cannot be satisfied by this solution, but the drug being allowed to penetrate to some extent the interface $x = 0$ leads to an interesting situation where the level of drug drops at the tail of the wave which is no longer monotonically increasing, as seen in Fig. 5**.**

IV. Discussion and Conclusion

We have given new analytical solutions to a model of drug release from a planar matrix to add to our earlier work [15] and [16], as well as the collection of literatures in existence currently [17]-[19]. The solutions are expressed in the travelling wave coordinate which makes it convenient for us to investigate how the shape of the wave front of drug dispersion changes with different values of physical parameters.

In Fig. 6, plots of the wave fronts given by (50) and (51) in Case 4 are shown for different values of *k*, which corresponds to the dissolution rate. We see that as *k* increases, the dissolved drug level peaks more quickly but at a lower maximum value. This can be expected since for this case,

$$d_x = \frac{1}{D}\left[\gamma - \frac{3}{2}xe^k\right]e^{x/D} - \frac{3}{2}e^{k+x/D}$$

at $t = 0$, by (50). Therefore, $d_x = 0$ when $x = x_{\max}$,

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

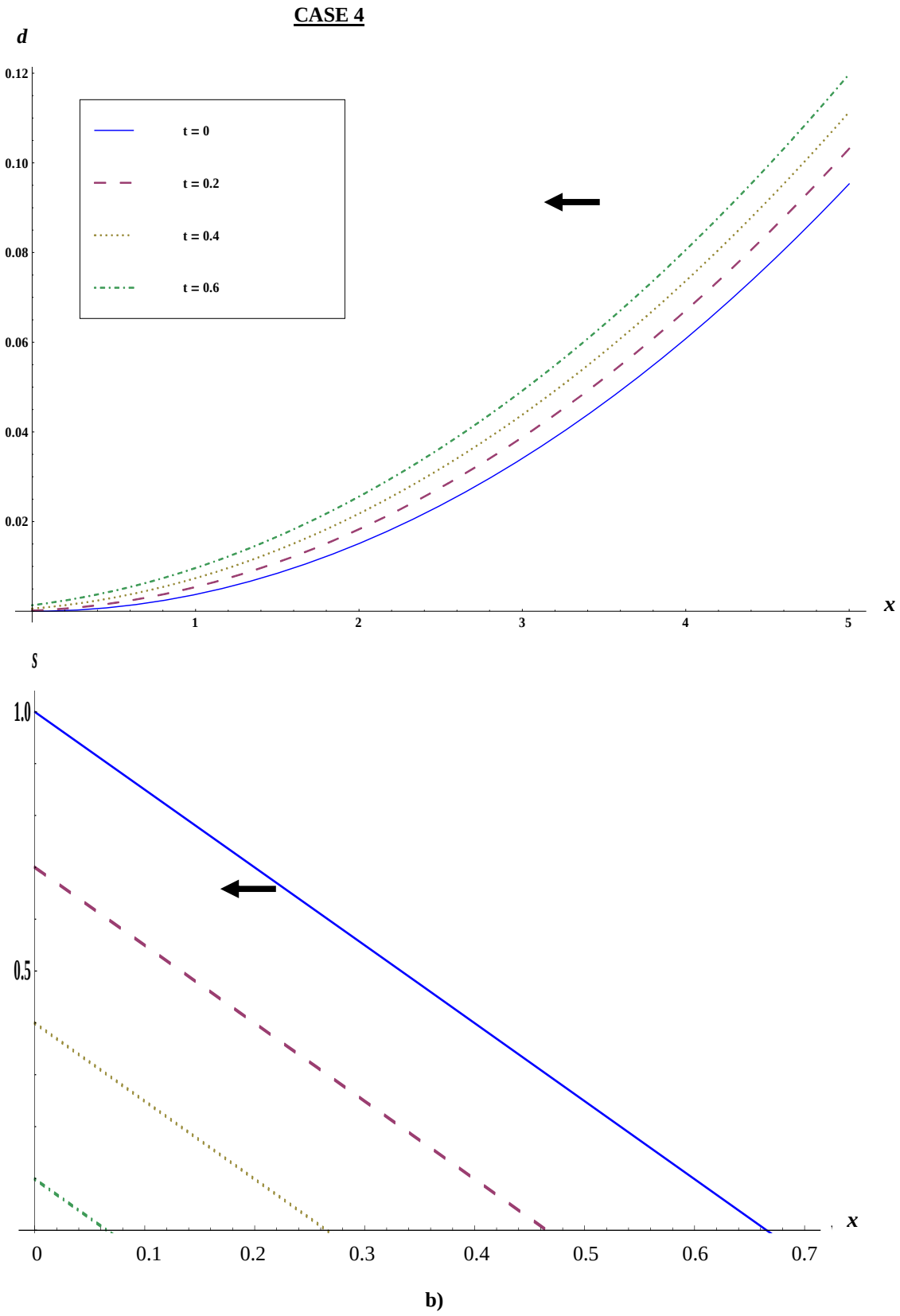


Fig. 4 Travelling wave solution in Case 4, given by (45)-(46), for the concentration a) d of drug in the diluted form and b) s in the solid form, plotted as functions of x for different time. Here, we used $\nu = -1, D = 200,\ \gamma = 300,\ l = 601,\ \ L = 0.6656,$ and $k = 0.00000001$.

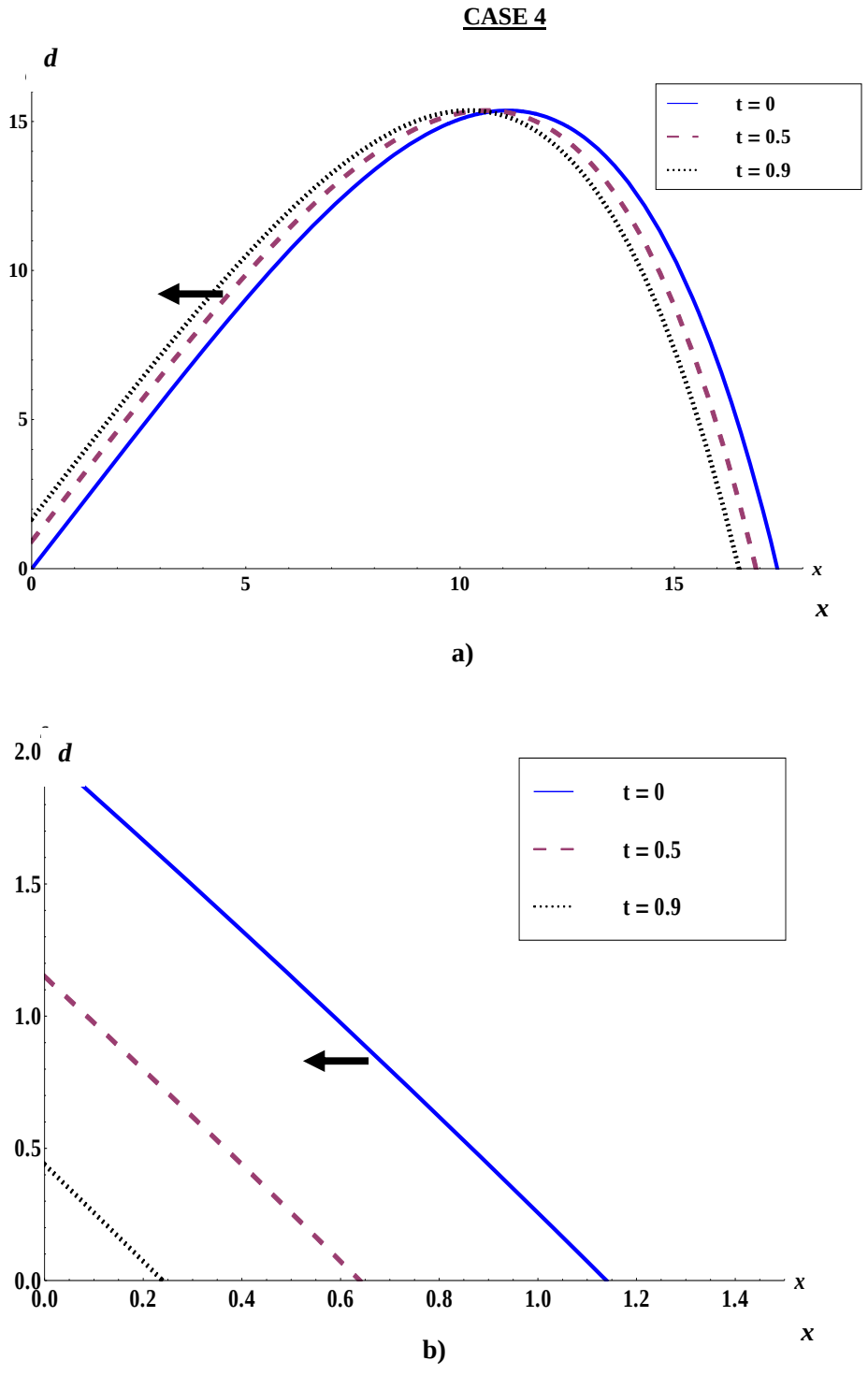
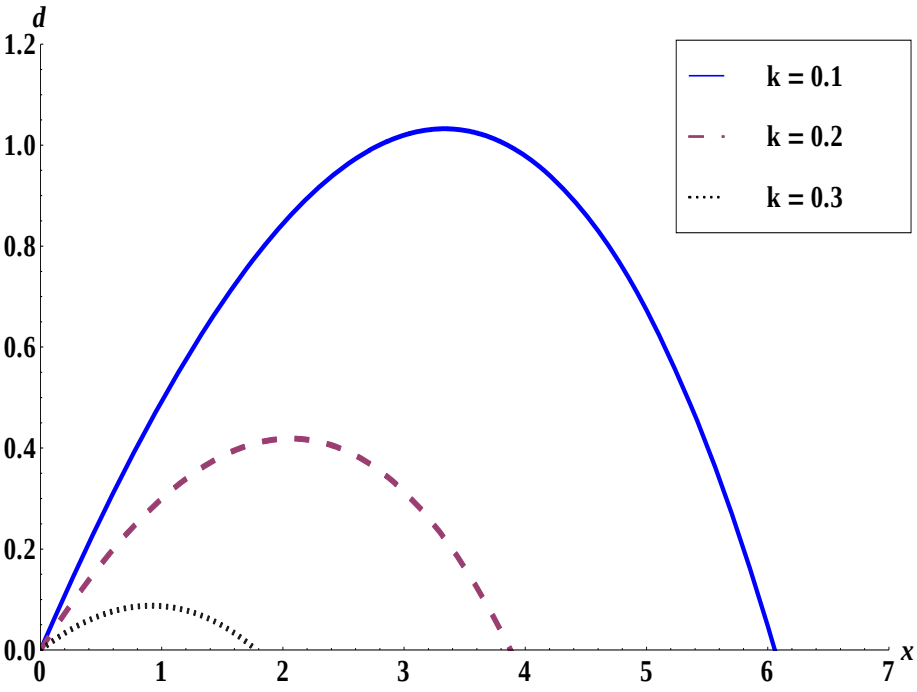
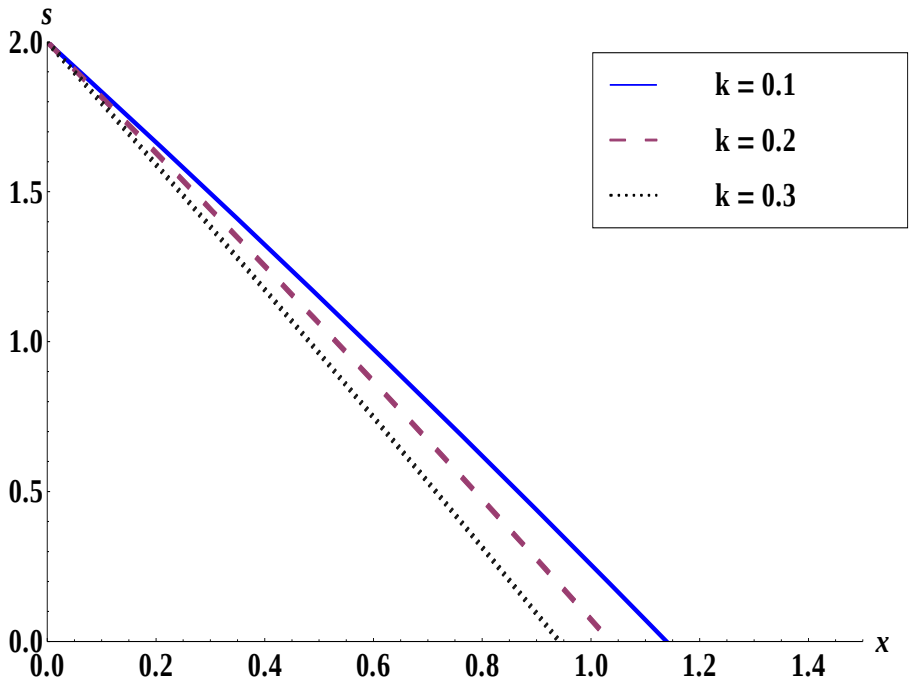


Fig. 5 Travelling wave solution in Case 4, given by (50)-(51), for the concentration a) d of drug in the diluted form and b) s in the solid form, plotted as functions of x for different time. Here, where $D = 10, s_0 = 2, \gamma = 35, k = 0.1,\ \ L = 1.13904, l = -16.4224$.



a)



b)

Fig. 6 Travelling wave solution in Case 4, given by (50)-(51), for the concentration a) d of drug in the diluted form and b) s in the solid form, at $t = 0$, plotted for different dissolution rates k. Here, $D = 10$, $s_0 = 2$, $\gamma = 22.1034$, while $k = 0.1, 0.2,$ and 0.3.

Then, the highest concentration of dissolved drug that is measured after a dose is

$$c_{\max} = d\big|_{x=x_{\max}} = \left[\gamma - \frac{3}{2}x_{\max}e^{k}\right]e^{x_{\max}/D} - \gamma, \qquad (54)$$

and the amount of time $T_{\max}$ required for d to reach the highest level $c_{\max}$, when $\nu = -1$, is

$$T_{\max} = \frac{2\gamma e^{-k}}{3} - D \qquad (55)$$

which decreases with k.

On the other hand, considering (55), we can see that the wave front in Case 4 will reach a peak more slowly for larger porosity ε or larger saturation constant c_s, since $\gamma = \varepsilon c_S$. The increase in the diffusivity D in contrast accelerates the drug concentration to attain $c_{\max}$.

In addition, curves in Fig. 5 are plotted with

$$3e^{k}D > \varepsilon c_s \qquad (56)$$

while the plots shown in Fig. 6 are for the case where

$$3e^{k}D < \varepsilon c_s \qquad (57)$$

We see that there is a noticeable time lag initially, before the concentration of d rises sharply. This is because the curve is concave up for a short interval of x in Fig. 5 if dilution rate and dissolution rate are large enough for the quantity on the left of (56) surpasses the product of the porosity and saturation constant on the right of (56).

Such considerations discussed above are of great relevance to the development of targeted drug delivery systems. If the intention is to maintain the drug concentration at a high level, then the physician could consider increasing the frequency of drug regimen so that the next wave arrives in time to prevent the drop in the drug concentration below a desirable level. On the other hand, there is also a level MADL (maximum allowable dose level) below which the drug must be maintained to prevent side effects to the patients such as toxicity, or the inability of the body to remove the access drug, or development of drug resistance.

According to [20], the drug fails to affect a desirable therapeutic response if its concentration falls below the effective level, the minimum acceptable delivered dose (MADD), and can instigate adverse reactions when it rises above the toxic level MADL. The plasma drug concentration between these two limits is termed the "therapeutic concentration range" or "therapeutic window" [20].

Our analyses thus provide important information for the design and manufacture of controlled drug release forms which take into account the above considerations, in order to minimize the side effects of drugs and improve a patient's compliance.

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REFERENCES

[1] V. Kumar, S. K. Prajapati, G. C. Soni, M. Singh, N., "Kumar, Sustained Release Matrix Type Drug Delivery System: A Review," *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 1, no. 3, 2012, pp. 934-960.

[2] J. E. Mockel, B. C. Lippold, "Zero Order Drug Release from Hydrocolloid Matrices, *Pharmaceutical Research*," vol. 10, 1993, pp. 1066-1070.

[3] J. Heller, "Biodegradable Polymers in Controlled Drug Delivery," *Crit. Reviews in Therapeutic Drug Carrier Syst*ems, vol. 1, no. 1, 1984, pp. 39-90.

[4] Transforming the way FDA-regulated products are developed, evaluated, manufactured, and used, Projects Receiving Critical Path Support, Fiscal Year 2008, April 2009, http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative.

[5] J. Crank, The Mathematics of Diffusion, Oxford University Press, London, 1975.

[6] 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," *Journal of Pharmaceutical Sciences*, vol. 87, 1995, pp. 991-997.

[7] T. Higuchi, "Rate of Release of Medicaments from Ointment Bases Containing Drugs in Suspension," *Journal of Pharmaceutical. Sciences*, vol. 50, 1961, pp. 874-875.

[8] T. J. Roseman, W. Higuchi, "Release of Medroxyprogesterone Acetate from a Silicone Polymer," *Journal of Pharmaceutical. Sciences*, vol. 59, 1970, pp. 353-357.

[9] D. R. Paul, S. K. McSpadden, "Diffusional Release of a Solute from a Polymeric Matrix," *Journal of. Membrane Science*, vol. 1, 1976, pp. 33-48.

[10] P. I. Lee, "Diffusional Release of a Solute from a Polymeric Matrix-Approximate Analytical Solutions," *Journal of. Membrane Science*, vol. 7, 1980, pp. 255-275.

[11] A. L. Bunge, "Release Rates from Topical Formulations Containing Drugs in Suspension," *Journal of Controlled Release*, vol. 52, 1998, pp. 141-148.

[12] Y. Zhou, X. Y. Wu, "Theoretical Analyses of Dispersed-Drug Release from Planar Matrices with Boundary Layer in a Finite Medium," *Journal of Controlled Release*, vol. 84, 2002, pp. 1-13.

[13] G. Frenning, M. Strømme, "Drug Release Modeled by Dissolution, Diffusion, and Immobilization," *International Journal of Pharmacology*, vol. 250, 2003, pp. 137-145.

[14] G. Frenning, "Theoretical Investigation of Drug Release from Planar Matrix Systems: Effect of a Finite Dissolution Rate," *Journal of Controlled Release*, vol. 92, 2003, pp. 331-339.

[15] C. Rattanakul, Y. Lenbury, "Stability Analysis and Analytical Solution of a Nonlinear Model for Controlled Drug Release: Travelling Wave Fronts," *International Journal of Mathematics and Computers in Simulation*, vol. 6, no. 3, 2012, pp. 351-359.

[16] C. Rattanakul, Y. Lenbury, "Different Travelling Wave Solutions for Controlled Drug Release Model in Planar Geometry," WSEAS Conference Proceedings, *12th WSEAS International Conference on System Science and Simulation in Engineering*, Morioka City, Iwate, Japan, April 23-25, 2013.

[17] S.-P. Tang, "An Exploratory Research on the Nanovectors for Drug Delivery and for Gene Therapy," *WSEAS Transactions on Biology and Biomedicine*, vol. 5, no. 12, 2008, pp. 313-321.

[18] 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.

[19] 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 Biomedicine*, vol. 4, no. 10, 2007, pp. 145-148.

[20] S. Sangeetha, "Introduction to Pharmacokinetics," www.srmuniv.ac.in/sites/default/files/files/PharmacokineticsBasicConsiderations.pdf, accessed March 15, 2013.