International Journal of Pharmaceutics 418 (2011) 78–87

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Anomalous diffusion of drug release from a slab matrix: Fractional diffusion models

Chen Yin [a,*], Xicheng Li [b]

[a] State Key Laboratory for Turbulence and Complex Systems, Department of Mechanics and Aerospace Engineering, College of Engineering, Peking University, Beijing 100871, PR China
[b] Department of Engineering Mechanics, Hohai University, Nanjing 210098, Jiangsu Province, PR China

ARTICLE INFO

Article history:
Received 26 September 2010
Received in revised form 6 December 2010
Accepted 6 December 2010
Available online 14 December 2010

Keywords:
Drug release mechanism
Mathematical models
Anomalous diffusion
Fractional calculus
Moving boundary problem
Exact and approximation solutions

ABSTRACT

Mathematical models for the release of drug from both non-degradable and degradable slab matrices in which the initial drug loading is greater than the solubility are presented in this paper. Taking the anomalous diffusions in the drug release processes into account, the fractional calculus is introduced to model the related phenomena. To describe different kinds of anomalous diffusions, corresponding fractional diffusion equations are adopted. By employing the integral transform methods, similarity solution method and perturbation method, exact and approximation solutions to the models are obtained.

1. Introduction

Controlled release formulations can be used to reduce the amount of drug necessary to cause the same therapeutic effect in patients. Mathematical models predicting the dynamics of solute concentration and mass flux are of interest for biomedical engineers and clinicians, because good models can provide insights concerning mass transport and chemical processes and offer a suggestion for optimizing the design and technology of drug delivery system. Since Higuchi published his remarkable work in the early 1960s (Higuchi, 1961, 1963), many mathematical models have been developed to interpret the kinetics of drug release process. Some exact and approximate solutions were obtained to predict the amount of drug release for designing matrix system.

In controlled drug delivery system, diffusion is the basic mechanism. Most of the models describing drug release from a slab matrix are based on Fick's first and second laws. However, the diffusion processes in complex systems named 'anomalous diffusion' usually no longer follow Gaussian statistics, and Fick's second law fails to describe the related transport behavior (Metzler and Klafter, 2000b). Many mathematical models are used to describe the anomalous diffusions, such as continuous time random walk (CTRW) models, generalized diffusion equations, Langevin equations and so on. Using the CTRW models, the Brownian motion can be generalized to sub-diffusion or dispersive transport, to Lévy flights or to Lévy walks. All of these models can be mapped onto the corresponding fractional equations (Metzler and Klafter, 2004). Although the fractional calculus has been conceptualized since 1695 (Miller and Ross, 1993), its connections with these statistical models have not been formally established until the last 20 years (Mandelbrot, 1983; Podlubny, 1999; Kilbas et al., 2006).

In this paper, some mathematical aspects on diffusion models of drug release process based on integer and fractional derivatives are shown. The review is organized as follows: In Section 2, we show some mathematical models of drug release using integer order operators. The models considering anomalous diffusion in both non-degradable and degradable matrices using fractional derivatives are presented in Section 3. Some results of fractional models are given in Section 4. In Section 5, the conclusions are given.

2. Models based on classical Fick's law

2.1. Pseudo-steady-state assumption

Higuchi (1961) firstly developed a remarkable simple model to simulate the drug release process from ointment in a planar system

* Corresponding author. Tel.: +86 10 6275 4244; fax: +86 10 6275 1812.
E-mail addresses: pkuyinchen@gmail.com (C. Yin), xichengli@hhu.edu.cn (X. Li).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.12.009

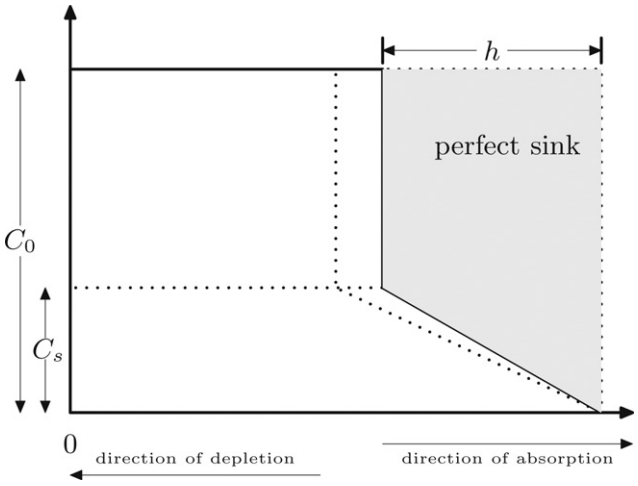

Fig. 1. Profile of concentration in Higuchi's model.

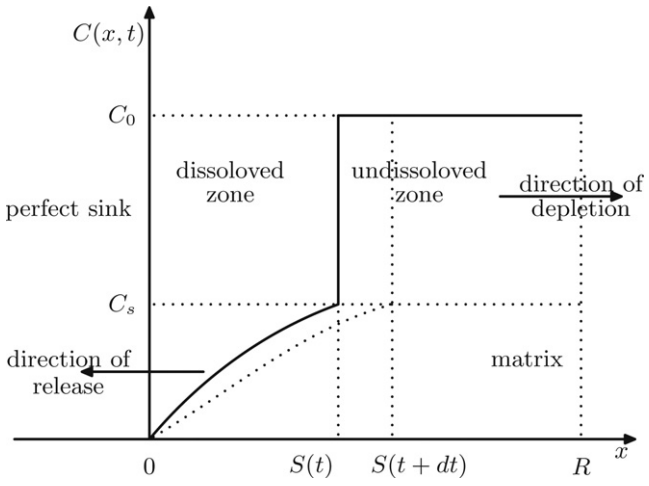

Fig. 2. Profile of concentration of one moving boundary problem.

(Fig. 1). The well-known Higuchi's result is given as

$$Q = \sqrt{(2C_0 - C_s)C_s Dt}, \tag{1}$$

where Q is the amount of drug absorbed at time t per unit area. C_0 is the initial loading of drug. C_s is the solubility of drug and D is the diffusion coefficient of drug.

The model is based on the assumption named 'pseudo-steady-state', which supposes a linear concentration profile in the diffusion region of a planar system. Another important assumption is that the initial drug loading C_0 should be greater than C_s, which implies that the drug release system is diffusion-controlled. Perfect sink condition implies the drug is absorbed or removed immediately after it diffuses out from the ointment.

Higuchi (1963) studied the drug release process from granular matrix in a planar system. The extensive formula is given as

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2C_0 - C_s)C_s t}, \tag{2}$$

where ε is the porosity of matrix system and τ is the tortuosity factor which is introduced to correct the effect of granular matrix. He also studied the drug release mechanism in a spherical system. But the relation between amount of drug release and parameters of a spherical system is not simple as formula (1).

2.2. Moving boundary problem

Formula (1) is convenient to use because only parameters of drug release system and release time are needed and its result coincides with the experimental data when $C_0 \gg C_s$. But in the case $C_0 \to C_s$, deviations from the real mass transport rates become significant. To overcome this shortcoming, Paul and McSpadden (1976) and Paul (1985) generalized the classical Stefan model to the research of drug release process from planar matrix and laminated matrix. Fick's second law

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{3}$$

is applied as the governing equation in diffusion region ($0 < x < S(t)$, Fig. 2) with the initial and boundary conditions

$$C(x,t) = 0, \quad t = 0,$$
$$C(x,t) = 0, \quad x = 0,$$
$$C(x,t) = C_s, \quad x = S(t),$$

and the mass balance equation

$$(C_0 - C_s)\frac{dS(t)}{dt} = D\left.\frac{\partial C}{\partial x}\right|_{x=S(t)}, \tag{4}$$

which is known as 'Stefan condition' mentioned in the book of Crank (1987) is adopted at diffusion interface $S(t)$. The exact solution of the model in planar system (Paul and McSpadden, 1976) is

$$C = C_s\frac{\mathrm{erf}(\delta)}{\mathrm{erf}(\delta^*)} \tag{5}$$

where $\mathrm{erf}(z)$ is the error function and

$$\delta = \frac{x}{2\sqrt{Dt}}, \quad \delta^* = \frac{S(t)}{2\sqrt{Dt}},$$
$$\sqrt{\pi}\delta^* \exp(\delta^{*2})\mathrm{erf}(\delta^*) = \frac{C_s}{C_0 - C_s}.$$

Consequently, the exact amount of drug release to semi-infinity space can be written as

$$M_t = \frac{2C_s}{\mathrm{erf}(\delta^*)}\sqrt{\frac{Dt}{\pi}}. \tag{6}$$

Compared with the exact solution (6), the error of Higuchi's approximation (1) is less than 1% when $C_0/C_s > 10$, while in the case $C_0/C_s \to 1$, it is greater than 11.3%.

Abdekhodaie and Cheng (1997) studied the drug release kinetics of a solute from planar and spherical matrices into a finite external volume by using the combination of variables method. They obtained the exact solutions which have the similar form to formula (5). Their results indicate that fractional release and the maximum fractional release increase as the increase of the external fluid volume, but fractional release decreases as the increase of initial drug loading at external volume.

From the viewpoint of mathematics, the presence of moving diffusion interface leads to the nonlinearity of the system, and only a few exact solutions can be obtained (Crank, 1987). Many approximation methods have been applied to solve the moving boundary problems of integer order, e.g., the refined integral method (Lee, 1980), the perturbation method (Aziz and Na, 1984; Cohen and Erneux, 1988a,b; Lin and Peng, 2005), and so forth (Ozisik, 1993; Crank, 1987).

Lee (1980) successfully applied refined integral method, which has been demonstrated to be effective in phase change problem, to the moving boundary problems in both planar and spherical sys-

tems with perfect sink condition. The approximation amount of drug release in a planar system is given as

$$M_t = \frac{1+H}{\sqrt{3H}} C_s \sqrt{Dt},$$
$$H = 5\left(\frac{C_0}{C_s}\right) - 4 + \sqrt{\left(\frac{C_0}{C_s}\right)^2 - 1}. \quad (7)$$

This expression of M_t is similar to Higuchi's result (1) and the exact expression (6). Compared with formula (1), (7) keeps the simplicity and shows the higher accuracy for any values of the initial drug loadings. The refined integral method is also used to study the kinetics of degradable matrix system with constant degradable velocity (Lee, 1980). The results can be written as

$$\frac{M_t}{M_\infty} = \delta + \left(\frac{Ba}{D}\right)\tau - \delta\frac{C_s}{C_0}\left(\frac{1}{2} + \frac{a_3}{6}\right),$$
$$a_3 = \frac{C_0}{C_s} + \delta h - \sqrt{\left(\frac{C_0}{C_s} + \delta h\right)^2 - (1 + 2\delta h)},$$
$$h = \frac{1}{2}\left(1 - \frac{C_0}{C_s}\right)\left(\frac{Ba}{D}\right),$$

where δ is dimensionless diffusion interface, B is the constant degradable velocity having the dimensions of a, and τ is dimensionless time.

In some pharmaceutical fields, many simple empirical formulae can also be accepted for the prediction of drug release in order to avoid complicated mathematical analysis. Ritger and Peppas (1987a,b) developed a new semi-empirical, exponential expression of fractional release of drug

$$\frac{M_t}{M_\infty} = kt^n, \quad (8)$$

where k is a constant incorporating characteristics of the macromolecular network system, and n is the diffusional exponent which relates to the transport mechanism. The semi-empirical solution can be applied to many areas of drug delivery system.

3. Mathematical models with fractional operators

Anomalous diffusion has been known since the treatise of Richardson (1926) on turbulent diffusion. Over the past few decades, many efforts have been made to provide the physical interpretations of the empirical data in disorder media by the aid of fractional calculus (Dokoumetzidis and Macheras, 2009; Dokoumetzidis et al., 2010a,b; Kytariolos et al., 2010; Liu and Xu, 2009; Metzler and Klafter, 2000b; Tan et al., 2007; Voller, 2010). Due to the heterogeneous character in the complex systems, fractional operators can be introduced as a powerful tool. The advantage of fractional operators is the flexible orders of fractional derivatives and integrals which have a range of applications. Considering the viscoelasticity of the cytoplasm and its complex structures, Tan et al. (2007) developed an anomalous sub-diffusion model for exploring calcium spark formation in cardiac myocytes. The fractional operators were also used to reproduce the experimental results by moderating the order of fractional derivatives. Dokoumetzidis and Macheras (2009) showed that a fractionalized zero-order release give rise to power law kinetics by using fractional calculus and it provided a physical interpretation of the empirically used power law for the description of the entire release curve. Voller (2010) used the fractional differential equation to describe anomalous diffusion behaviors of Stefan melting problem in heat transfer where heterogeneities at all scales are present. Some other applications of fractional calculus on pharmacokinetics have been presented recently (Dokoumetzidis and Macheras, 2009; Fuite et al., 2002; Macheras, 1995, 1996; Marsh and Tuszyski, 2006). Fractional calculus can provide a unified basis to interpret the transport and heterogeneous processes of drug release.

3.1. Fundamentals of fractional calculus

In this section, three kinds of fractional operators and their properties are listed (Kilbas et al., 2006; Podlubny, 1999).

3.1.1. Definitions

Let $[0, t]$ be a finite interval on the real axis $\mathbb{R}$. The Riemann–Liouville fractional integral and derivative operators are defined as

$${}_0D_t^{-\beta} f(t) := \frac{1}{\Gamma(\beta)} \int_0^t \frac{f(\tau)}{(t-\tau)^{1-\beta}} d\tau \quad (\beta > 0), \quad (9)$$

$${}_0D_t^{\alpha} f(t) := \frac{d^n}{dt^n}\left[\frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{f(\tau)}{(t-\tau)^{\alpha+1-n}} d\tau\right] \quad (n-1 < \alpha \le n). \quad (10)$$

The Riemann–Liouville (R–L) fractional operators have played an important role in the development of theory of fractional calculus due to their applications in pure mathematics. However, R–L fractional operators lead to initial conditions containing the limit values of the R–L fractional derivatives at the lower terminal $t = 0$. The Caputo fractional operators are presented because there is no known physical interpretation for the initial conditions caused by the R–L's definition. Caputo's definition with order α $(n-1 < \alpha \le n)$ can be written as

$${}_0^C D_t^{\alpha} f(t) := \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{f^{(n)}(\tau)}{(t-\tau)^{\alpha+1-n}} d\tau. \quad (11)$$

From the definitions of two types of fractional operators, we know that the R–L derivative is constructed as the integer derivative of the fractional integral while the Caputo derivative is the fractional integral of an integer derivative.

An important property used in following sections is

$${}_0^* D_t^{\alpha} t^{\mu} = \frac{\Gamma(1+\mu)}{\Gamma(1+\mu-\alpha)} t^{\mu-\alpha}, \quad (12)$$

where D_t^{α} represents R–L ($\alpha > 0$, $\mu > -1$) or Caputo ($\mu \ge 1 \ge \alpha > 0$, or $0 < \mu \ge \alpha \ge 1$) fractional derivative. In particular, it should be mentioned that the Caputo derivative of a constant is zero, and this is not the case for an R–L derivatives, that is

$${}_0^C D_t^{\alpha} C = 0, \quad (13)$$

$${}_0D_t^{\alpha} C = \frac{1}{\Gamma(1-\alpha)} t^{-\alpha}. \quad (14)$$

3.1.2. Integral transforms

Integral transform methods are the powerful tools to solve fractional differential equations. Fourier transform and Laplace transform are the methods frequently used in solving fractional differential equations. The definitions are given as follows

$$\hat{f}(k) = \mathcal{F}\{f(x); k\} = \int_{-\infty}^{\infty} e^{-ikx} f(x) dx, \quad (15)$$

$$\tilde{f}(p) = \mathcal{L}\{f(t); p\} = \int_0^{\infty} e^{-pt} f(t) dt. \quad (16)$$

Using the Fourier transform, the Riesz fractional derivative can be defined by

$$\mathcal{F}\{\nabla^{\alpha} g(x); k\} = |k|^{\alpha} G(k), \quad (17)$$

where $G(k)$ is the Fourier transform of $g(x)$.

The formula for Laplace transform of Riemman–Liouville derivative is (Podlubny, 1999)

$$\mathcal{L}\{{}_0D_t^{\alpha}f(t);p\} = p^{\alpha}F(p) - \sum_{k=0}^{n-1} p^k[{}_0D_t^{\alpha-k-1}f(t)]_{t=0}, \tag{18}$$

while Laplace transform of Caputo derivative is

$$\mathcal{L}\{{}_0^CD_t^{\alpha}f(t);p\} = p^{\alpha}F(p) - \sum_{k=0}^{n-1} p^{\alpha-k-1}f^{(k)}(0), \tag{19}$$

where $F(p)$ is the Laplace tranform of $f(t)$ and $\alpha \in (n-1, n]$ is the fractional order.

3.2. Fractional anomalous diffusion equation

Due to the nature of heterogeneities (Metzler and Klafter, 2000b; Zhang et al., 2009), the Gaussian statistics may be modified in order to describe the anomalous diffusion in the complex systems. In the drug delivery systems, a range of heterogeneity length scales should be taken into account. If the heterogeneity length scales are much smaller than the scale of system, the Gaussian statistics holds and the transport behavior can be described by standard diffusion relationship which is the mean squared displacement in the course of time, i.e.,

$$\langle x^2(t)\rangle \sim \mathcal{D}t. \tag{20}$$

On the other hand, if the heterogeneities occur across a range of length scales, with the largest approaching the domain scale, the standard diffusion models maybe not suitable for describing the transport phenomena, and anomalous transport behaviors should be taken into account (Voller, 2010). Generally, a signature of anomalous diffusion is that the mean squared displacement in the course of time is a nonlinear power law rather than a linear growth, i.e.,

$$\langle x^2(t)\rangle \sim \mathcal{D}t^{\alpha}. \tag{21}$$

The process is called sub-diffusion if $0 < \alpha < 1$ while it is called super-diffusion if $\alpha > 1$. Fractional diffusion equations are usually obtained from the standard diffusion equation by replacing the second order space derivative by a fractional derivative of order $\beta \in (0, 2]$ or the first order time derivative by a fractional derivative of order $\alpha \in (0, 1]$. The equations can be written as

$${}_0^*D_t^{\alpha}C(x,t) = \mathcal{D}\nabla_x^{\beta}C(x,t), \tag{22}$$

where $C(x, t)$ is the concentration of solvent. ${}_0^*D_t^{\alpha}$ and ∇_x^{β} are the time and space fractional derivatives in R–L, Caputo, Riesz or other senses (Kilbas et al., 2006; Podlubny, 1999), and $\mathcal{D}$ is the generalized diffusion coefficient whose dimension is $[L^{\beta}/T^{\alpha}]$.

Sub-diffusive dynamics is characterized by strong memory effects on the level of the probability density function (PDF) and is classically described in terms of CTRW with a long-tailed waiting time PDF. Mathematically, these assumptions will lead to a time fractional diffusion equation. In contrast, when the jump lengths are distributed according to a β-stable symmetric Lévy law and the survival probability being of Mittag–Leffler type with index α, the macroscopic evolution obeys the space–time fractional diffusion (22).

3.3. Fractional flux

In the standard diffusion case, Fick's first law is

$$F(x,t) = -D\frac{\partial}{\partial x}C(x,t), \tag{23}$$

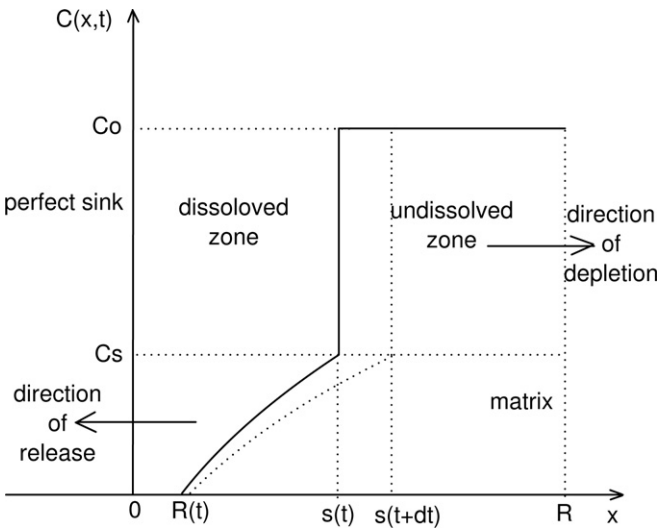

Fig. 3. Profile of concentration of two moving boundary problem.

Due to the non-local property of anomalous diffusion, following Chaves (1998), Zanette (1998) and Paradisi et al. (2001), we use the generalized non-local Fick's law

$$F(x,t) = -\mathcal{D}_0D_t^{1-\alpha}\nabla_x^{\beta-1}C(x,t) \tag{24}$$

to replace (23). Expression (24) can be obtained by combining the continuity equation

$$\nabla \cdot F + \frac{\partial C}{\partial t} = 0 \tag{25}$$

with the fractional diffusion equation (22). As a result, the Stefan condition can be written as

$$(C_0 - C_s)\frac{dS(t)}{dt} = \mathcal{D}_0D_t^{1-\alpha}\nabla_x^{\beta-1}C(x,t). \tag{26}$$

From another point of view, Liu and Xu (2004) used the following Stefan condition

$$(C_0 - C_s){}_0D_t^{\alpha}S(t) = \mathcal{D}\nabla_x^{\beta-1}C(x,t) \tag{27}$$

to keep the balance of the dimensions.

3.4. Mathematical models of controlled drug release devices

To describe anomalous diffusion in the drug release process, Liu and Xu (2004) firstly introduced an mathematical model using time fractional diffusion equation. Li et al. (2007) generalized the time fractional diffusion equation in Liu and Xu's model to a space–time fractional one. Li et al. (2008) also examined the space fractional derivative of both Riemman–Liouville type and Caputo type and obtained the similarity solutions. Yin and Xu (2009) studied the drug release process in slow degradable matrix by using fractional calculus. The profiles of the drug in the matrix can be shown in Fig. 2 or Fig. 3, where $R(t)$ is the outer boundary of the matrix. Actually, Fig. 2 is a special case of Fig. 3 ($R(t) = 0$). All these models can be written as

$${}_0D_t^{\alpha}C(x,t) = \mathcal{D}\nabla_x^{\beta}C(x,t), \quad (0 < \alpha \le 1 < \beta \le 2, \quad R(t) < x < S(t)) \tag{28}$$

$$C(x,t) = 0 \quad (x = R(t)), \tag{29}$$

$$C(x,t) = C_s \quad (x = S(t)), \tag{30}$$

$$(C_0 - C_s)\frac{dS(t)}{dt} = \mathcal{D}_0D_t^{1-\alpha}\nabla_x^{\beta-1}C(x,t), \quad (t > 0), \tag{31}$$

$$(C_0 - C_s)\,{}_0D_t^{\alpha} S(t) = \mathcal{D}\nabla_x^{\beta-1} C(x,t), \quad (t>0), \tag{31*}$$

$$S(t) = 0 \quad (t=0). \tag{32}$$

The models mentioned above can be obtained based on different fractional operators and boundary conditions.

Model-I (Liu and Xu, 2004) $R(t)=0$, $0<\alpha\le 1$, $\beta=2$ and $\nabla_x^{\beta} = \partial^2/\partial x^2$. The boundary condition (31*) is used.
Model-II (Li et al., 2007) $R(t)=0$, $0<\alpha\le 1$, $1<\beta\le 2$ and ∇_x^{β} is the Riesz type derivative. The boundary condition (31) is used.
Model-III (Li et al., 2008) $R(t)=0$, $0<\alpha\le 1$, $1<\beta\le 2$ and ∇_x^{β} is the Caputo type (case I) or the Riemman–Liouville type (case II) derivative. The boundary condition (31) is used.
Model-IV (Yin and Xu, 2009) $R(t)=\zeta t$, $0<\alpha\le 1$, $\beta=2$ and $\nabla_x^{\beta} = \partial^2/\partial x^2$. The boundary condition (31*) is used.

The time fractional derivative ${}_0D_t^{\alpha}$ in model-I is a sequential fractional derivative ${}_0D_t^{\alpha} = {}_0D_t^{\alpha-1}\,{}_0D_t^{1}$ under the assumption ${}_0D_t^{\alpha-1} C(x,t)|_{t=0} = 0$. In other models, the time fractional derivatives are all defined in the Caputo sense.

4. Some results of fractional diffusion models

4.1. non-degradable matrix

The moving boundary problem is a special nonlinear problem which is difficult to get the exact solution (Crank, 1987). Furthermore, many useful properties of integer derivatives are not known to carry over analogously for the case of fractional derivative operator, such as a clear geometric or physical meaning, product rules, and chain rules. In this study, we just give some results of the four models mentioned above.

For model-I, II and III, by using reduced dimensionless variables defined as

$$\xi = \frac{x}{R}, \quad \tau = \left(\frac{\mathcal{D}}{R^{\beta}}\right)^{1/\alpha} t, \quad \theta = \frac{C(x,t)}{C_s}, \quad S(\tau) = \frac{s}{R}, \tag{33}$$

and changing variables of the fractional derivatives similar to the relations presented in Li et al. (2007, Appendix), the governing equation (28) subject to the conditions (29)–(32) can be reduced to the respective dimensionless forms,

$${}_0D_{\tau}^{\alpha}\theta(\xi,\tau) = \nabla_{\xi}^{\beta}\theta(\xi,\tau), \quad (0<\xi<S(\tau)), \tag{34}$$

$$\theta(\xi,\tau) = 0, \quad (\xi=0), \tag{35}$$

$$\theta(\xi,\tau) = 1, \quad (\xi=S(\tau)), \tag{36}$$

$$\eta\frac{dS(\tau)}{d\tau} = -F(\xi,\tau)|_{\xi=S(\tau)}, \tag{37}$$

$$S(0) = 0, \tag{38}$$

where $\eta=(C_0-C_s)/C_s$ and $F(\xi,\tau)={}_0D_{\tau}^{1-\alpha}\nabla^{\beta-1}\theta$ is the non-dimensional flux.

4.1.1. Integral transform method: model-I, II

The Laplace, Fourier and Mellin integral transforms are the most common methods used to solve fractional diffusion equations in certain domain (Metzler and Nonnenmacher, 2002; Metzler and Klafter, 2000a; Mainardi et al., 2001, 2005). Mainardi et al. (2001) discussed Cauchy problem for the space–time fractional diffusion equation. The fundamental solution is obtained by using Mellin transform with respect to the Fourier–Laplace representation of the equation. Gorenflo et al. (2000) used the similarity method and Laplace transform to obtain the scale-invariant solution of time-fractional diffusion-wave equation in terms of Wright function.

Since we only consider the early stage of loss before the diffusion front moves to R, the semi-infinite assumption can be used. As a result, we first consider Eq. (34) in semi-infinite space which satisfies

$$\theta(0,\tau) = 0 \tag{39}$$

and

$$\theta(\xi,0) = q = const. \tag{40}$$

For time fractional diffusion, the above problem has been discussed by Schneider and Wyss (1989) in detail. The solutions of the models I and II can be written as

$$\theta = q\int_0^{\infty} dy\left\{G(|\xi-y|,\tau) - G(|\xi+y|,\tau)\right\}, \tag{41}$$

where $G(\xi,\tau)$ is Green's function (or fundamental solution). It can also be written as

$$\theta(\xi,\tau) = 2q\int_0^{\xi} G(z,\tau)dz. \tag{42}$$

For model-I, Green's function is

$$G(\xi,\tau) = \frac{1}{2}\tau^{-\alpha/2} M\left(|\xi|\tau^{-\alpha/2};\frac{\alpha}{2}\right), \tag{43}$$

The $M(z;\alpha)$ and $W(z;\alpha,\beta)$ are Mainardi and Wright functions defined as (Podlubny, 1999)

$$M(z;\tfrac{\alpha}{2}) = \sum_{k=0}^{\infty}\frac{(-z)^k}{k!\,\Gamma\left[-\frac{\alpha}{2}k+(1-\frac{\alpha}{2})\right]} = W\left(-z;-\frac{\alpha}{2},1-\frac{\alpha}{2}\right). \tag{44}$$

While in the space–time fractional case (model-II), using $G_{\alpha,\beta}(\xi,\tau)$ to denote Green's function of our problem, we have

$$\begin{aligned} G_{\alpha,\beta}(\xi,\tau) &= \frac{1}{\beta\xi}\frac{1}{2\pi i}\int_{r-i\infty}^{r+i\infty}\frac{\Gamma(s/\beta)\Gamma(1-(s/\beta))\Gamma(1-s)}{\Gamma(s/2)\Gamma(1-(s/2))\Gamma(1-(\alpha s/\beta))}\left(\frac{\xi}{\tau^{\gamma}}\right)^{s} ds \\ &= \frac{1}{\beta\xi}H_{3,3}^{2,1}\left[\frac{|\xi|}{\tau^{\gamma}}\middle|\begin{matrix}\left(1,\frac{1}{\beta}\right)\left(1,\frac{\alpha}{\beta}\right)\left(1,\frac{1}{2}\right)\\ \left(1,\frac{1}{\beta}\right)(1,1)\left(1,\frac{1}{2}\right)\end{matrix}\right], \end{aligned} \tag{45}$$

where $\gamma=\alpha/\beta$, $0<r<1$, and $H_{m,n}^{p,q}(z)$ is Fox H function (Mainardi et al., 2005).

After some calculations, the solutions to model-I are obtained as

$$\theta(\xi,\tau) = K\left[1 - W\left(-\frac{\xi}{\tau^{\alpha/2}};-\frac{\alpha}{2},1\right)\right], \tag{46}$$

$$S(\tau) = p\cdot\tau^{\alpha/2}. \tag{47}$$

And K, p are the constants to be determined by the following equations

$$K = \frac{1}{1-W(-p;-(\alpha/2),1)}, \tag{48}$$

$$K = \frac{p\eta\Gamma(1+(\alpha/2))}{\Gamma(1-(\alpha/2))W(-p;-(\alpha/2),1-(\alpha/2))}. \tag{49}$$

Using the Fourier transform of $G_{\alpha,\beta}(\xi,\tau)$ and the integral expression of H function, $\theta(\xi,\tau)$ in model-II can be presented in terms of Fox H function,

$$\theta(\xi,\tau) = \frac{2q}{\beta}H_{4,4}^{2,2}\left[\frac{\xi}{\tau^{\gamma}}\middle|\begin{matrix}\left(1,\frac{1}{\beta}\right)(1,1)\left(1,\frac{\alpha}{\beta}\right)\left(1,\frac{1}{2}\right)\\ \left(1,\frac{1}{\beta}\right)(1,1)(0,1)\left(1,\frac{1}{2}\right)\end{matrix}\right], \tag{50}$$

where q is a constant to be determined. Noting that the boundary condition (36) has to be satisfied for all values of τ, $S(\tau)$ must be proportional to τ^{γ}, i.e.

$$S(\tau) = p\tau^{\gamma}, \tag{51}$$

where p is a constant to be determined.

Substituting solutions (50) and (51) into the boundary conditions (36) and (37), the equations for p and q can be written as

$$\frac{2q}{\beta}H_{4,4}^{2,2}\left[p\left|\begin{matrix}\left(1,\frac{1}{\beta}\right)(1,1)\left(1,\frac{\alpha}{\beta}\right)\left(1,\frac{1}{2}\right)\\ \left(1,\frac{1}{\beta}\right)(1,1)(0,1)\left(1,\frac{1}{2}\right)\end{matrix}\right.\right]=1. \tag{52}$$

$$\eta p\gamma=\frac{2q}{\beta p}H_{3,3}^{2,1}\left[p\left|\begin{matrix}\left(\frac{2}{\beta},\frac{1}{\beta}\right)\left(\frac{2\alpha}{\beta},\frac{\alpha}{\beta}\right)\left(1,\frac{1}{2}\right)\\ \left(\frac{2}{\beta},\frac{1}{\beta}\right)(1,1)\left(1,\frac{1}{2}\right)\end{matrix}\right.\right]. \tag{53}$$

In order to get the value of p and q, we must solve the above two equations. However, computing routine for H function is not available. Fortunately, in some special cases, the H function can be represented by convergent series which can be calculated. Some results are listed in Li et al. (2007).

4.1.2. Similarity solution: model-III

The results of the two cases of model-III can be written as the following theorems.

Theorem 4.1. *The similarity transformations under which Eqs. (34)–(37) are invariant are given by the expressions*

$$z=\xi\tau^{-\alpha/\beta},\quad \theta(\xi,\tau)=f(z)\quad\text{and}\quad S(\tau)=p\tau^{\alpha/\beta}, \tag{54}$$

where p is a constant to be determined.

Theorem 4.2. *The Caputo derivative ${}_0^C D_\tau^\alpha$, $(0<\alpha\le 1)$ of the function $\theta(\xi,\tau)=f(z)$, $z=\xi\tau^{-\alpha/\beta}$ is given by the relation*

$${}_0^C D_\tau^\alpha f(z)=\tau^{-\alpha}\,{}_*P_{\beta/\alpha}^{0,1-\alpha}f(z)=\tau^{-\alpha}K_{\beta/\alpha}^{0,1-\alpha}\left(-\frac{\alpha}{\beta}\frac{d}{dz}f(z)\right), \tag{55}$$

where ${}_*P_{\beta/\alpha}^{0,1-\alpha}$ is the Caputo-type modification of Erdélyi–Kober fractional differential operator

$$K_\delta^{\theta,\alpha}g(y)=\frac{\delta}{\Gamma(\alpha)}y^{\delta\theta}\int_y^\infty(u^\delta-y^\delta)^{\alpha-1}u^{-\delta(\theta+\alpha-1)}g(u)du,\quad \alpha>0. \tag{56}$$

Theorem 4.3. *The reduced form of Eq. (34) is given by*

$${}_*P_{\beta/\alpha}^{0,1-\alpha}f(z)={}_0D_z^\beta f(z), \tag{57}$$

and the conditions become

$$f(0)=0,\quad f(p)=1,\quad \eta p\frac{\Gamma(1+(\alpha/\beta))}{\Gamma(1+(\alpha/\beta)-\alpha)}={}_0D_z^{\beta-1}f(z)|_{z=p}. \tag{58}$$

Theorem 4.4. *As for case 1, the similarity solution of equation (57) is*

$$f(z)=C_1zW_{(-\alpha,1-(\alpha/\beta))(\beta,2)}(z^\beta), \tag{59}$$

where $W_{(\mu,a)(\nu,b)}(z)$ is the generalized Wright function defined by

$$W_{(\mu,a)(\nu,b)}(z)=\sum_{k=0}^\infty\frac{z^k}{\Gamma(a+\mu k)\Gamma(b+\nu k)},\quad \mu,\nu\in R,\quad a,b\in C. \tag{60}$$

In the following analysis, the constraint $-1<\mu<0$, $\nu>0$ is used.

Theorem 4.5. *As for case 2, the similarity solution of equation (57) is given by*

$$f(z)=C_2z^{\beta-1}W_{(-\alpha,1+(\alpha/\beta)-\alpha)(\beta,\beta)}(z^\beta). \tag{61}$$

Theorem 4.6. *As for case 1, we have*

$$\eta p^2\frac{\Gamma(1+(\alpha/\beta))}{\Gamma(1+(\alpha/\beta)-\alpha)}W_{(-\alpha,1-(\alpha/\beta))(\beta,2)}(p^\beta)=p^{2-\beta}W_{(-\alpha,1-(\alpha/\beta))(\beta,3-\beta)}(p^\beta) \tag{62}$$

and

$$C_1=\frac{1}{pW_{(-\alpha,1-(\alpha/\beta))(\beta,2)}(p^\beta)}. \tag{63}$$

With some computation, the value of C_1 and p can be obtained. Correspondingly, as for case 2, we have

$$\eta p^\beta\frac{\Gamma(1+(\alpha/\beta))}{\Gamma(1+(\alpha/\beta)-\alpha)}W_{(-\alpha,1+(\alpha/\beta)-\alpha)(\beta,\beta)}(p^\beta)=W_{(-\alpha,1+(\alpha/\beta)-\alpha)(\beta,1)}(p^\beta) \tag{64}$$

and

$$C_2=\frac{1}{p^{\beta-1}W_{(-\alpha,1+(\alpha/\beta)-\alpha)(\beta,\beta)}(p^\beta)}. \tag{65}$$

4.1.3. Discussions on solutions

The dimensionless diffusion interface $S(\tau)$ versus dimensionless time τ at various solute loading levels is shown in Fig. 4. Curves 1–3 correspond to space fractional diffusion models, 4 corresponds to the ordinary diffusion model, 5–6 correspond to time fractional diffusion models. It is obvious that the time fractional diffusion model and the space fractional one describe sub-diffusion and super-diffusion, respectively. It is consistent with the conclusion of Metzler and Klafter (2000b, 2004). As for the same curve, by comparing the four pictures in Fig. 4, we can see that the higher initial solute loading level is, the longer the time to reach R for the diffusion interface $S(\tau)$ needs. These conclusions show the fact that the models are well consistent with the truth.

For model-I, the amount of released drug per unit area of dimensional variables given by Liu and Xu (2004) is

$$M_t=\int_0^t\mathcal{D}\frac{\partial C}{\partial x}|_{x=0}dt=\frac{K\lambda t^{1-\alpha/2}}{\Gamma(2-\alpha/2)} \tag{66}$$

where $\lambda^2=\mathcal{D}$.

But K is included in transcendental equations (48) and (49), and the exact solution is difficult to apply. An approximate solution of M_t

$$M_t\approx\frac{\lambda t^{1-\alpha/2}}{\Gamma(2-\alpha/2)}\left\{\frac{1}{2}\nu C_s+\left[\frac{\delta C_s(C_0-C_s)\Gamma(1+\alpha/2)}{\Gamma(1-\alpha/2)}+\frac{(4\gamma+\nu^2)C_s^2}{4}\right]^{1/2}\right\} \tag{67}$$

where

$$\nu=2a_1b_0^{-1}-a_0b_0^{-2}b_1,\quad \delta=a_0^2b_0^{-1},$$

$$\gamma=2a_0a_2b_0^{-2}+a_0^2b_0^{-4}b_1^2-a_1^2b_0^{-2}-a_0^2b_0^{-3}b_2-a_0a_1b_0^{-3}b_1,$$

$$a_0=\Gamma(1-\alpha/2),\quad a_n=a_0\sum_{j=1}^n\frac{(-1)^{j+1}}{j!\Gamma(-\alpha/2+1-\alpha/2)}a_{n-j},$$

$$b_n=\sum_{j=0}^n\frac{(-1)^{n-j}a_j}{(n-j+1)!\,\Gamma[-\alpha(n-j)/2+1-\alpha/2]},$$

is provided.

When $0<\alpha\le 1$, Eq. (67) becomes

$$M_t\propto t^{1-\alpha/2}=t^n,\quad n\in[\frac{1}{2},1). \tag{68}$$

Formula (68) coincides with well known semi-empirical formula (8), which is mentioned that $n\in[0.5,1)$ is the non-Fickian process by Ritger and Peppas (1987a).

The amount of drug released per unit area at time t can also be obtained by using the following formula (Abdekhodaie and Cheng, 1996, 1997),

$$M_t=C_0s(t)-\int_0^{s(t)}C(x,t)dx, \tag{69}$$

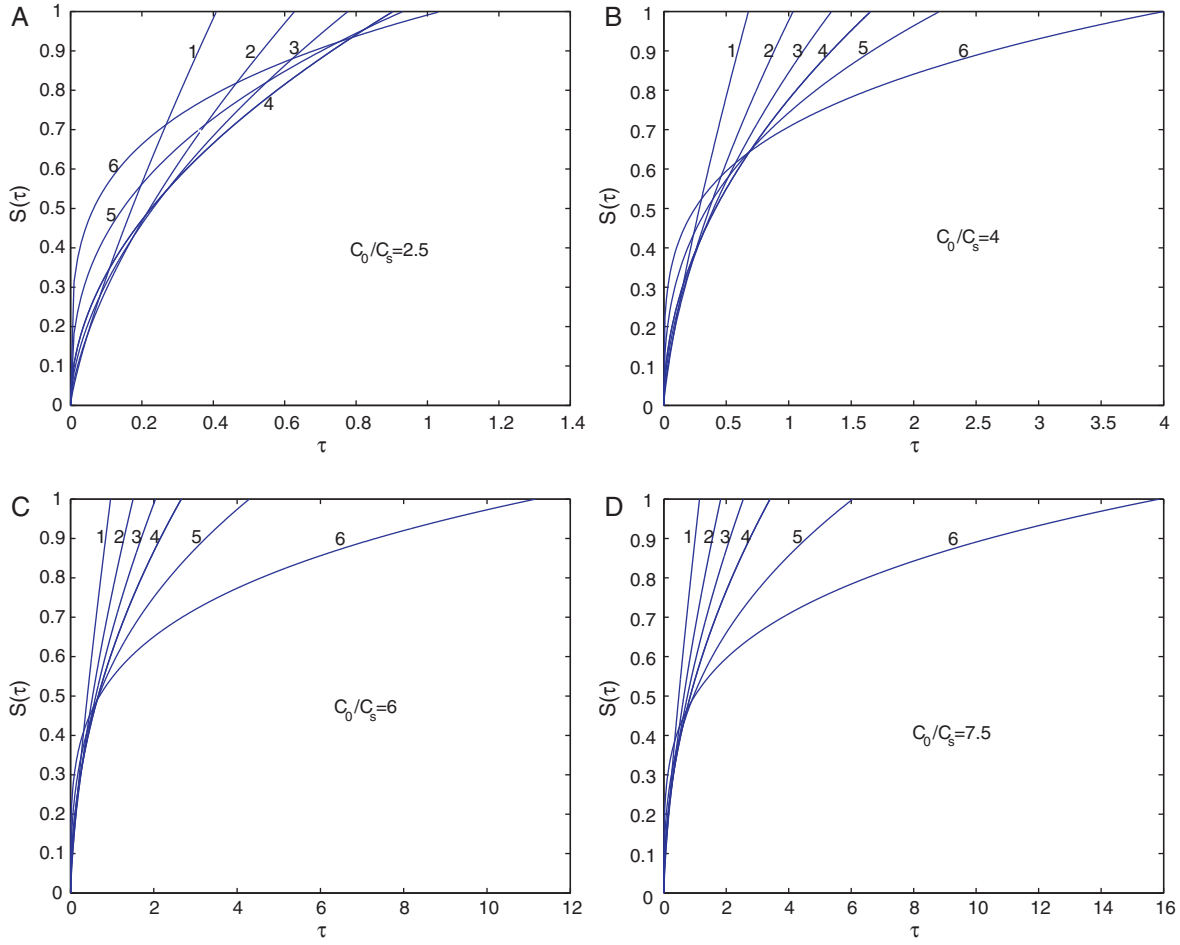

Fig. 4. Dimensionless diffusion interface $S(\tau)$ versus dimensionless time at various solute loading levels. Curves 1–6 correspond to the cases that (α, β) equals to (1, 1.25), (1, 1.5), (1, 1.75), (1, 2), (0.75, 2) and (0.5, 2), respectively.

while the total amount of drug per unit area is given by $M_\infty = C_0 R$. Using the variables in Eq. (33), we can get the fractional release in a dimensionless form

$$\frac{M_t}{M_\infty} = S(\tau) - \int_0^{S(\tau)} \frac{C_S}{C_0}\theta(\xi, \tau)d\xi. \tag{70}$$

From solution (50) and formula (70), we obtain

$$\frac{M_t}{M_\infty} = \left[p - \frac{C_s}{C_0}\frac{2pq}{\beta}H^{2,2}_{4,4}\left[p\left|\begin{matrix}\left(1,\frac{1}{\beta}\right)(1,1)\left(1,\frac{\alpha}{\beta}\right)\left(1,\frac{1}{2}\right)\\ \left(1,\frac{1}{\beta}\right)(1,1)(-1,1)\left(1,\frac{1}{2}\right)\end{matrix}\right.\right]\right]\tau^\gamma. \tag{71}$$

Similarly, the fractional release can be obtained easily by using the series forms of solution (59) and (61). The results are

$$\frac{M_t}{M_\infty} = \left[p - \frac{C_s}{C_0}C_1 p^2 W_{(-\alpha,1-\alpha/\beta)(\beta,3)}(p^\beta)\right]\tau^\gamma, \tag{72}$$

and

$$\frac{M_t}{M_\infty} = \left[p - \frac{C_s}{C_0}C_2 p^\beta W_{(-\alpha,1+\alpha/\beta-\alpha)(\beta,\beta+1)}(p^\beta)\right]\tau^\gamma. \tag{73}$$

The dimensionless fractional releases for the two cases of model-III when $\eta = 3.5$ versus to the dimensionless time τ are shown in Fig. 5. Apparently, for every set of parameters, case 1 needs less time for the diffusion interface to reach R. To show the effects of the initial drug loading, the fractional releases of case 2 of model-III in the case $\alpha = 0.75$, $\beta = 1.75$ are shown in Fig. 6. It is obvious that the maximum fractional release increases as the increase of the initial drug loading.

4.2. Degradable matrix: model-IV

Most researches in drug release were based on one moving boundary model, which only considered the diffusion process in non-degradable matrix. The shortcoming of non-degradable system is that the matrix needs to be removed from patients. In many cases, using biodegradable materials as matrices is an important

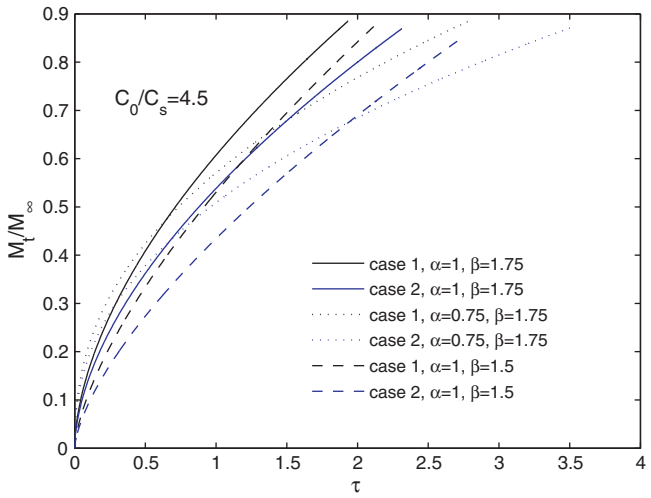

Fig. 5. Results of M_t/M_∞ versus to τ.

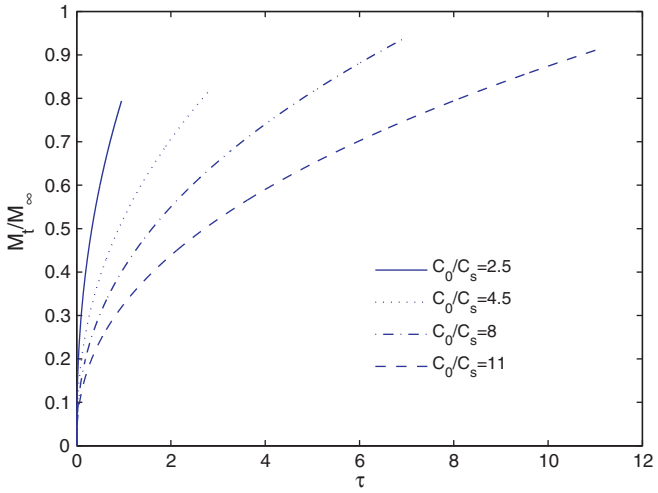

Fig. 6. Results of M_t/M_∞ versus to τ for case 1 of model-III. $\alpha = 0.75$, $\beta = 1.75$.

advantage without patient's second surgery for taking matrix out. Furthermore, the additional degradable boundary can also moderate drug release rate.

4.2.1. Two-parameter regular perturbation method: model-IV

In particular, taking into account of the effect of degradable matrix, the mathematical analysis on drug release kinetics becomes more complicated with the presence of a second moving boundary, namely degradable interface (shown in Fig. 3). Especially, the approximation methods with some numerical computation should be applied to moving boundary problems. The perturbation method is a powerful tool to solve the nonlinear equations. Cohen and Erneux (1988a,b) introduced the perturbation method to investigate the diffusion process in planar glassy polymers. Lin and Peng (2005) also applied perturbation method to the research of drug release in a spherical swelling polymer. Then, the perturbation method was introduced by Yin and Xu (2009) to get an approximation analytic solution of drug release in slow degradable matrix.

Some assumptions in Yin and Xu (2009) are listed as follows: (1) The polymer as a slab matrix should be degraded very slowly. (2) A perfect sink condition at degradable interface is assumed. (3) The diffusivity $\mathcal{D}$ of drug in matrix system is constant. (4) The initial loading concentration C_0 of drug is much greater than the solubility C_s of drug, i.e. $C_0 \gg C_s$. By introducing the following dimensionless variables

$$\theta(x,t) = \frac{C(x,t)}{C_s}, \quad t^* = \left(\frac{\mathcal{D}}{R^2}\right)^{1/\alpha} t, \quad \varepsilon = \frac{C_s}{C_0},$$

$$R^*(t^*) = \frac{R(t)}{R}, \quad S^*(t^*) = \frac{S(t)}{R}, \quad x^* = \frac{x}{R},$$

where $\varepsilon \sim o(1)$ from the fourth assumption is ratio of initial concentration C_s and solubility C_0 and R is the scale of length, the dimensionless equations are obtained while omitting the '*' for brevity in the following paper:

$${}_0^C D_t^\alpha \theta(x,t) = \frac{\partial^2 \theta}{\partial x^2} \quad (R(t) < x < S(t)), \tag{74}$$

$$\theta(x,t) = 0 \quad (x = R(t)), \tag{75}$$

$$\theta(x,t) = 1 \quad (x = S(t)), \tag{76}$$

$$(\varepsilon^{-1} - 1)\,{}_0^C D_t^\alpha S(t) = \left.\frac{\partial \theta}{\partial x}\right|_{x=S(t)} \quad (t > 0), \tag{77}$$

$$R(t) = S(t) = 0 \quad (t = 0). \tag{78}$$

The new dimensionless space–time variables are introduced

$$y = x - R(t), \tag{79}$$

$$X(t) = S(t) - R(t). \tag{80}$$

From the first assumption, we have

$$R(t) = \zeta t, \quad \zeta \sim o(1), \tag{81}$$

where ζ represents the dimensionless moving velocity of degradable interface. And dimensionless parameters ζ and ε are smaller than one.

Two-parameter regular perturbation method is introduced to solve the nonlinear equations. and the solutions of the equations can be assumed as

$$\theta(y,t;\zeta,\varepsilon) = \theta_0(y,t) + \theta_1(y,t)\zeta + \theta_2(y,t)\varepsilon + \cdots, \tag{82}$$

$$X(t;\zeta,\varepsilon) = X_0(t) + X_1(t)\zeta + X_2(t)\varepsilon + \cdots. \tag{83}$$

Substituting Eqs. (79)–(83) into Eqs. (74)–(78) and equating the terms with identical powers of ζ and ε, the equations of zero, one and two orders can be solved.

Using Fourier and Laplace integral transforms, the solutions of concentrations can be written as

$$\theta_0(y,t) = H_0\left[1 - W\left(-\frac{y}{t^{\alpha/2}}; -\frac{\alpha}{2}, 1\right)\right], \tag{84}$$

$$\theta_1(y,t) = \frac{\pi H_0}{2} y t^{1-\alpha} W\left(\frac{-y}{t^{\alpha/2}}; -\frac{\alpha}{2}, 2-\alpha\right) + \frac{\pi H_0}{2} t^{1-\alpha/2} W\left(\frac{-y}{t^{\alpha/2}}; -\frac{\alpha}{2}, 2-\frac{\alpha}{2}\right), \tag{85}$$

$$\theta_2(y,t) = H_1\left[1 - W\left(-\frac{y}{t^{\alpha/2}}; -\frac{\alpha}{2}, 1\right)\right] \tag{86}$$

and the solutions of diffusion moving boundaries are

$$X_0(t) = 0, \tag{87}$$

$$X_1(t) = -t, \tag{88}$$

$$X_2(t) = \frac{H_0 t^{\alpha/2}}{\Gamma(1+\alpha/2)}, \tag{89}$$

where H_0, H_1 are integral constants to be determined from Stefan conditions.

4.2.2. Discussions on solutions

Considering the special case ($\zeta = 0$), two moving boundaries problem can be simplified to one moving boundary problem discussed by Liu and Xu (2004). Figs. 7 and 8 show that how velocity of diffusion interface varies with different parameters α and ε. From Fig. 7, the diffusion interface runs faster when α increases. From Fig. 8, the diffusion interface runs faster when ε increases. The parameter α can be controlled by using different polymer matrices, while the parameter ε can be controlled by using different loading drug. We can vary the two parameters to control the rate of drug release.

Fig. 9 shows the comparison between exact solution and approximation solution. When ε is determined, approximation solution curve runs faster than exact solution curve. But the difference between exact solution and approximation solution becomes smaller when the ε decreases.

Considering the degradable boundary condition, two moving boundaries are obtained as

$$R(t) = \zeta t, \tag{90}$$

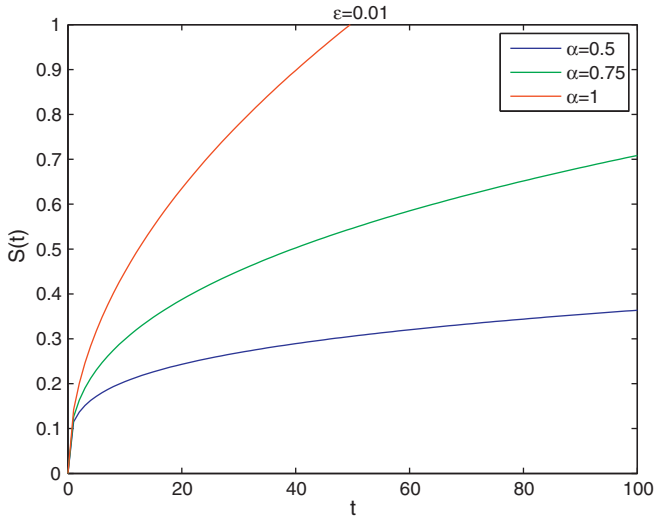

Fig. 7. The dimensionless diffusion interface $S(t)$ versus dimensionless time t with different α.

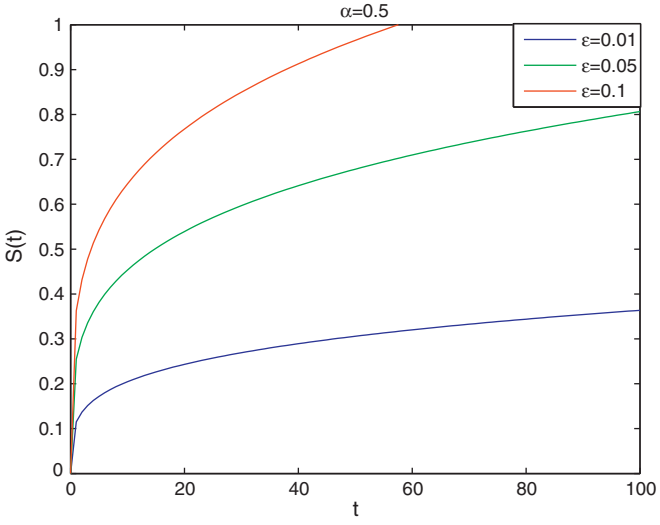

Fig. 8. The dimensionless diffusion interface $S(t)$ versus dimensionless time t with different ε.

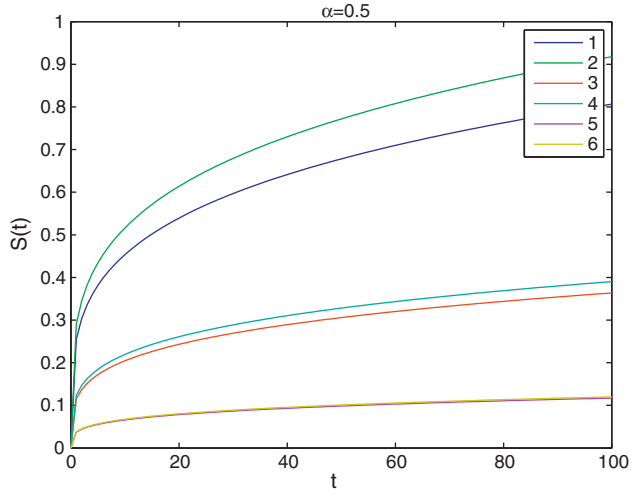

Fig. 9. The comparison between exact solution and approximation solution (when $\alpha = 0.5$). Curves 1,3,5 correspond to exact solution when $\varepsilon = (0.05, 0.01, 0.001)$, Curves 2, 4, 6 correspond to approximation solution when $\varepsilon = (0.05, 0.01, 0.001)$, respectively.

$$\begin{aligned} S(t) &= X(t) + R(t) \\ &= X_0(t) + X_1(t)\zeta + X_2(t)\varepsilon + \zeta t + \cdots \\ &= \frac{H_0 t^{\alpha/2}}{\Gamma(1+\alpha/2)}\varepsilon + \cdots. \end{aligned} \tag{91}$$

Because the degradable velocity is very slow, it can not influence the diffusion interface evidently and rate of diffusion interface would be the main factor of drug release. Although smaller ε can make approximation solution get closer to exact solution, smaller ε also results that the diffusion interface runs slower. If degradable interface runs faster than diffusion interface, degradable velocity of matrix would be the main factor of drug release and the mechanism of system would change.

5. Conclusions

Since the remarkable work of Higuchi (1961) was published, the mathematical model and simulation of drug release process have been developed by many scientists (Arifin et al., 2006). The theoretical researches on predicting mechanism of drug delivery system have developed into an important component as well as experimental studies. Most of previous studies in this field focused on the ordinary diffusion process. In the past few decades, fractional calculus has attracted a good deal of attention due to its applications in the modeling of complex systems. Fractional anomalous diffusion equation is one of most studied subjects. Fractional calculus provides a scientific basis for the analysis of diverse and heterogeneous process of drug release.

Replacing the diffusion equations by fractional ones in classical models for drug release process, four fractional models are introduced to describe anomalous diffusions. Some methods and results of fractional diffusion equations are presented in this review.

Until now, only some simple cases of fractional diffusion equation in drug release process are investigated. Mathematical models considering more factors like matrix of other geometric shapes or swelling matrix will be focused on in the future. With the help of fractional calculus, we believe the mechanism of anomalous diffusion would be investigated more deeply and can be used into practical application flexibly.

Acknowledgements

The authors express their gratitude to the referees of the paper for their fruitful advice and comments. This work is supported by the National Natural Science Foundation of China (Grant Nos. 10825208, 10632010 and 11002049), Jiangsu Planned Projects for Postdoctoral Research Funds (0902099C) and Science Funds of Hohai University (2009427311).

References

Abdekhodaie, M.J., Cheng, Y.L., 1996. Diffusional release of a dispersed solute from a spherical polymer matrix. J. Membr. Sci. 115, 171–178.
Abdekhodaie, M.J., Cheng, Y.L., 1997. Diffusional release of a dispersed solute from planar and spherical matrices into finite external volume. J. Control. Release 43, 175–182.
Arifin, D.Y., Lee, L.Y., Wang, C.-H., 2006. Mathematical modeling and simulation of drug release from microspheres: Implications to drug delivery systems. Adv. Drug Deliv. Rev. 58, 1274–1325.
Aziz, A., Na, T., 1984. Perturbation Methods in Heat Transfer. Hemisphere, Washington, DC.
Chaves, A.S., 1998. A fractional diffusion equation to describe Lévy flights. Phys. Lett. A 239, 13–16.
Cohen, D.S., Erneux, T., 1988a. Free boundary problems in controlled release pharmaceuticals. I. Diffusion in glassy polymers. SIAM J. Appl. Math. 48, 1451–1465.
Cohen, D.S., Erneux, T., 1988b. Free boundary problems in controlled release pharmaceuticals. II. Swelling-controlled release. SIAM J. Appl. Math. 48, 1466–1474.
Crank, J., 1987. Free and Moving Boundary Problems. Clarendon Press, Oxford.
Dokoumetzidis, A., Macheras, P., 2009. Fractional kinetics in drug absorption and disposition processes. J. Pharmacokinet. Pharmacodynam. 36, 165–178.

Dokoumetzidis, A., Magin, R., Macheras, P., 2010a. A commentary on fractionalization of multi-compartmental models. J. Pharmacokinet. Pharmacodynam. 37, 203–207.
Dokoumetzidis, A., Magin, R., Macheras, P., 2010b. Fractional kinetics in multi-compartmental systems. J. Pharmacokinet. Pharmacodynam. 37, 507–524.
Fuite, J., Marsh, R., Tuszyński, J., 2002. Fractal pharmacokinetics of the drug mibefradil in the liver. Phys. Rev. E 66, 021904.
Gorenflo, R., Luchko, Y., Mainardi, F., 2000. Wright functions as scale-invariant solutions of the diffusion-wave equation. J. Comput. Appl. Math. 118, 175–191.
Higuchi, T., 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. 50, 874–875.
Higuchi, T., 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.
Kilbas, A.A., Srivastava, H.M., Trujillo, J.J., 2006. Theory and Applications of Fractional Differential Equations. Elsevier, Amsterdam.
Kytariolos, J., Dokoumetzidis, A., Macheras, P., 2010. Power law IVIVC: an application of fractional kinetics for drug release and absorption. Eur. J. Pharm. Sci. 41, 299–304.
Lee, P., 1980. Diffusional release of a solute from a polymeric matrix-approximate analytical solutions. J. Membr. Sci. 7, 255–275.
Li, X., Xu, M., Wang, S., 2007. Analytical solutions to the moving boundary problems with space–time-fractional derivatives in drug release devices. J. Phys. A: Math. Theor. 40, 12131.
Li, X., Xu, M., Wang, S., 2008. Scale-invariant solutions to partial differential equations of fractional order with a moving boundary condition. J. Phys. A: Math. Theor. 41, 155202.
Lin, J.-S., Peng, Y.-L., 2005. Swelling controlled release of drug in spherical polymer-penetrant systems. Int. J. Heat Mass Transfer 48, 1186–1194.
Liu, J., Xu, M., 2004. An exact solution to the moving boundary problem with fractional anomalous diffusion in drug release devices. Z. Angew. Math. Mech. 84, 22–28.
Liu, J., Xu, M., 2009. Some exact solutions to Stefan problems with fractional differential equations. J. Math. Anal. Appl. 351, 536–542.
Macheras, P., 1995. Carrier-mediated transport can obey fractal kinetics. Pharm. Res. 12, 541–548.
Macheras, P., 1996. A fractal approach to heterogeneous drug distribution: calcium pharmacokinetics. Pharm. Res. 13, 663–670.
Mainardi, F., Luchko, Y., Pagnini, G., 2001. The fundamental solution of the space–time fractional diffusion equation. Fractional Calc. Appl. Anal. 4, 153–192.
Mainardi, F., Pagnini, G., Saxena, R., 2005. Fox *H* functions in fractional diffusion. J. Comput. Appl. Math. 178, 321–331.
Mandelbrot, B.B., 1983. The Fractal Geometry of Nature, 1st ed. W.H. Freeman.
Marsh, R., Tuszyski, J., 2006. Fractal Michaelis–Menten kinetics under steady state conditions: application to mibefradil. Pharm. Res. 23, 2760–2767.
Metzler, R., Klafter, J., 2000a. Boundary value problems for fractional diffusion equations. Phys. A: Stat. Mech. Appl. 278, 107–125.
Metzler, R., Klafter, J., 2000b. The random walk's guide to anomalous diffusion: a fractional dynamics approach. Phys. Rep. 339, 1–77.
Metzler, R., Klafter, J., 2004. The restaurant at the end of the random walk: recent developments in the description of anomalous transport by fractional dynamics. J. Phys. A: Math. Gen. 37, R161.
Metzler, R., Nonnenmacher, T.F., 2002. Space- and time-fractional diffusion and wave equations, fractional Fokker–Planck equations, and physical motivation. Chem. Phys. 284, 67–90.
Miller, K.S., Ross, B., 1993. An Introduction to the Fractional Calculus and Fractional Differential Equations, 1st ed. John Wiley & Sons.
Ozisik, M.N., 1993. Heat Conduction, 2nd ed. Wiley-Interscience.
Paradisi, P., Cesari, R., Mainardi, F., Tampieri, F., 2001. The fractional Fick's law for non-local transport processes. Phys. A: Stat. Mech. Appl. 293, 130–142.
Paul, D., 1985. Modeling of solute release from laminated matrices. J. Membr. Sci. 23, 221–235.
Paul, D., McSpadden, S., 1976. Diffusional release of a solute from a polymer matrix. J. Membr. Sci., 33–48.
Podlubny, I., 1999. Fractional Differential Equations. Academic Press, New York.
Richardson, L.F., 1926. Atmospheric Diffusion shown on a distance-neighbour graph. Proc. R Soc. London. Ser. A 110, 709–737.
Ritger, P.L., Peppas, N.A., 1987a. A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Control. Release 5, 23–36.
Ritger, P.L., Peppas, N.A., 1987b. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. J. Control. Release 5, 37–42.
Schneider, W.R., Wyss, W., 1989. Fractional diffusion and wave equations. J. Math. Phys. 30, 134–144.
Tan, W., Fu, C., Fu, C., Xie, W., Cheng, H., 2007. An anomalous subdiffusion model for calcium spark in cardiac myocytes. Appl. Phys. Lett. 91, 183901.
Voller, V., 2010. An exact solution of a limit case stefan problem governed by a fractional diffusion equation. Int. J. Heat Mass Transfer 53, 5622–5625.
Yin, C., Xu, M., 2009. An asymptotic analytical solution to the problem of two moving boundaries with fractional diffusion in one-dimensional drug release devices. J. Phys. A: Math. Theor. 42, 115210.
Zanette, D.H., 1998. Macroscopic current in fractional anomalous diffusion. Phys. A: Stat. Theor. Phys. 252, 159–164.
Zhang, Y., Benson, D.A., Reeves, D.M., 2009. Time and space nonlocalities underlying fractional-derivative models: distinction and literature review of field applications. Adv. Water Resour. 32, 561–581.