Drug diffusion and release from a bioerodible spherical capsule

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Abstract

Controlled release of a drug contained in a spherical polymer capsule is of significant interest in many fields of medicine. There is growing interest in tailoring the erosion properties of the drug to help control and optimize the drug release process. Theoretical understanding of the nature of drug release from a bioerodible capsule is, therefore, important for designing effective drug delivery systems. While drug release from a fixed-radius capsule is relatively easier to model, the shrinking nature of a bioerodible capsule due to surface erosion presents several difficulties in theoretical modeling. This work presents a closed-form solution for the drug concentration distribution and drug delivery characteristics from a spherical capsule undergoing linear surface erosion. This problem is solved by a transformation that converts the moving boundary problem into a fixed-boundary problem. For uniform initial drug distribution, the solution is shown to depend on a single non-dimensional parameter. The theoretical model is used to develop an understanding of the impact of varying the drug diffusion coefficient and rate of erosion on drug

delivery characteristics. It is found that, in general, the nature of drug release in a bioerodible sphere is determined by a delicate balance between two simultaneously occurring processes – erosion and diffusion. This work improves the theoretical understanding of diffusion in drug delivery systems by accounting for the practical erosion phenomena, and may contribute towards the design and optimization of drug delivery systems.

Keywords: Drug Delivery; Mass Transfer; Bioerodible Sphere; Moving Boundary Problem.

CRediT Authorship Contribution Statement

A. Jain – Conceptualization, Methodology, Formal Analysis, Validation, Investigation, Data Curation, Supervision, Project Administration; S. McGinty – Conceptualization, Methodology, Formal Analysis, Validation; G. Pontrelli – Conceptualization, Methodology, Formal Analysis, Validation. All authors contributed towards Writing Original Draft, Review and Editing.

Nomenclature

c	concentration (mol m^{-3})
D	diffusion coefficient (m^2 s^{-1})
A	initial radius (m)
B	rate of erosion of the radius (m s^{-1})
r	radial coordinate (m)
t	time (s)
ψ	cumulative fraction of drug released
$\bar{c}$	non-dimensional concentration, $\bar{c} = c/c_{ref}$
$\bar{r}$	non-dimensional radial coordinate, $\bar{r} = r/A$
$\bar{t}$	non-dimensional time, $\bar{t} = Dt/A^2$
λ	non-dimensional eigenvalue

Subscripts

in	initial
ref	reference

1. Introduction

The incorporation of drug within polymeric capsules is ubiquitous in pharmaceutics. The primary benefit of this approach is the ability to control the release of the drug. In the simplest case, the drug is contained within the core of a spherical capsule, with a polymeric shell providing protection from the external environment, thereby delaying drug release until the capsule has been delivered to the desired location [1,2]. Key performance characteristics of any drug delivery system include the drug release profile, which refers to the mass of drug released into the surrounding medium as a function of time, often expressed relative to the initial mass of the drug in the drug delivery system [3]. A linear (zero order) drug release profile is often desirable [4]. Further, the drug release process is also often characterized by a time constant for the release process, which may be expressed in terms of time taken to release a certain fraction of the total drug [5]. In such cases, the rate of drug release is typically governed by drug dissolution and drug transport properties within the polymeric material.

In recent decades, there has been intense research focused on the development of enhanced capsules with desirable properties that enable finer control of release. For example, multi-layer capsules with layer-dependent material properties can widen the range of possible drug release profiles [6,7], while functional materials such as responsive polymers can trigger drug release in response to certain environmental stimuli such as pH [8]. Another popular approach is the use of bioerodible polymers such as polyanhydrides [9]. These offer the dual benefit of additional flexibility to tailor the drug release and eventually being eliminated within the body. As the name suggests, bioerodible polymers undergo erosion over time due to backbone cleavage and various autocatalytic processes [10]. Two distinct types of erosion have been identified [3] – in bulk

erosion, penetration of water into the polymer matrix causes bulk erosion within the volume of the drug delivery system without appreciable change in overall size. On the other hand, when erosion is limited to the surface, it results in gradual reduction in the physical size of the drug delivery system without much change within the bulk volume. These are two extremes in the spectrum of erosion, and in practice, both bulk and surface erosion likely occur to some degree. Whether erosion is dominated by bulk or surface erosion depends on the relative rates of water imbibition into the polymer matrix and degradation processes such as polymer backbone hydrolysis [11]. Specifically, bulk erosion likely dominates when the diffusion of water into the polymer happens on a quicker time scale than the degradation of polymer bonds, while surface erosion is likely the dominant process when the degradation of the polymer bonds is the faster process [Von Burkersroda et al.]. The degree of hydrophobicity of the polymer plays an important role in determining the relative importance of bulk versus surface erosion: the higher the solubility of the polymer, then the greater is the influence of bulk erosion, provided water imbibition is sufficiently rapid. In general, erosion of the polymeric matrix occurs only in part mechanically, while dissolution plays an important role in initiation and evolution of the process [12]. The rate of erosion in a polymer can be carefully controlled by changing the co-monomer composition in the polymer [13]. There is theoretical [10,14] as well as experimental evidence [15] that the rate of erosion in a surface-erosion dominated system is expected to be linear in nature.

Mathematical modeling of bioerodible capsules is usually based on empirical or phenomenological models [16], although probabilistic models have also been proposed [17]. Most of the past work on mathematical modeling of bioerodible polymers has focused on systems dominated by bulk erosion. Literature on drug release from bulk eroding capsules utilizes diffusion-dissolution modeling [18,19], wherein the dissolution number is an important non-

dimensional parameter [15,18]. The simplest mathematical models for drug delivery systems dominated by surface erosion only account for the physical reduction in size over time [14]. Drug delivery estimates based on a quasi-steady assumption, i.e., linear concentration distribution in a slab have been presented [4,20]. It is clearly important to also account for diffusion, mass transfer boundary conditions at the surface, and the drug dissolution process, if the rate of dissolution is not large enough. Recent work [21] outlined the governing equations for these processes and presented a numerical solution of the equations. However, it is also desirable to derive an analytical solution of such processes. Compared to numerical solutions, analytical solutions are easier to implement, often faster to compute, and provide a much better physical understanding of the problem, for example, the role of various non-dimensional parameters that govern the problem. Moreover, analytical solutions, even those based on simplifying assumptions, may serve to validate numerical simulations for more complicated problems.

Within the context of surface erosion, key physical processes leading to drug release include aqueous imbibition, dissolution of the drug from the polymer matrix and diffusion towards the outer surface [1-3]. The reduction of outer radius of the spherical capsule over time may increase concentration gradients within, and thus increase diffusion towards the surface. The nature of the release medium, in terms of mass transfer conditions at the interface, is also important. In one extreme, the release medium may be considered to be large enough to be represented as an infinite sink for the drug. More generally, a mass transfer coefficient may be specified on the outer surface, represented non-dimensionally by the Sherwood number.

There continues to be a need for robust mathematical modeling of drug release from bioerodible polymers that accounts for considerations such as those discussed above [2,22].

Compared to bulk erosion, there are relatively fewer theoretical studies that consider surface erosion. Such models, when combined with accurate information about properties such as diffusion coefficients, may help down-select candidate materials and system design choices, thereby reducing the cost and complexity of *in vitro* and *in vivo* experiments.

From a modeling perspective, the problem of drug diffusion in a surface-eroding sphere is similar to Stefan problems related to phase change heat transfer [23,24]. Both problems feature a moving boundary – the physical boundary of the sphere in the present problem, and the phase change front in the Stefan problem. However, in the Stefan problem, the rate of propagation of the phase change front is related to the gradient of the temperature distribution, whereas in the present case, the rate of erosion is completely independent of the concentration distribution within the remaining sphere. Inverse Stefan problems [23] often specify a velocity of the phase change front, similar to the present work. However, in inverse Stefan problems, the rate of change of the boundary is directly proportional to the gradient of the field at the boundary [23], whereas in the present problem, the two are completely unrelated to each other, since the boundary erosion in the present problem is being driven by external factors, such as chemical erosion due to the release medium surrounding the capsule, and not by the diffusion processes inside the capsule. A few other, problems that are mathematically similar to present problem, such as heat transfer in an ablating region [25,26] and water pressure in a consolidating layer of clay [27] have been presented, and it may be possible to use the heat and mass transfer analogy to adapt such methods to solve the present drug diffusion problem.

This paper presents an analytical solution for the problem of drug diffusion from a homogeneous sphere undergoing linear surface erosion. The sphere is loaded with an initial drug

concentration distribution and the primary interest is in determining the drug release profile over time. Through an appropriate transformation, this problem is converted into that of diffusion in a fixed-size sphere, which is solved to derive an overall solution of the eroding sphere problem. Under uniform initial loading, the solution of the non-dimensional problem is shown to be based on a single non-dimensional parameter. Consequently, general solution curves for the problem for various values of this parameter are presented. The impact of various problem parameters, such as rate of erosion, diffusion coefficient and the nature of the initial loading on drug delivery characteristics is discussed. The analytical solution derived in this work provides predictive capability and may help design and optimize drug delivery systems based on bioerodible polymers.

2. Problem Definition and Derivation of Solution

The problem considered here is that of drug diffusion from a spherical microcapsule immersed in a large liquid release medium. The radius of the microcapsule reduces linearly over time due to surface erosion by the fluid (Figure 1). By combining mass conservation and kinetics of the erosion process, past theoretical work [10,14] has justified the linear erosion assumption. Comparison of drug release simulations with experimental data [15] also supports the linear erosion assumption [21]. The capsule is originally loaded with an initial distribution of drug, and releases the drug into the release medium due to diffusion and mass transfer at its outer surface. It is of interest to determine the concentration distribution in the capsule at any given time, as well as the drug release rate from the capsule as a function of time due to the combined effect of diffusion and erosion. Convective drug transport within the sphere, which may potentially occur in a porous sphere, is neglected. We assume that drug is immediately available for diffusion, in other words, dissolution of drug is not the rate-limiting process. . Binding reactions within the

capsule are also neglected. Diffusion of drug within the sphere is assumed to be characterized by a constant and uniform diffusion coefficient *D*, which characterizes the microcapsule material and the drug, and remains invariant with the shrinking microcapsule. This assumption is consistent with the understanding of surface erosion of a bioerodible polymer capsule. We note, however, that depending on the rate of water imbibition and the solubility of the drug, an effective diffusion coefficient that depends on the local water saturation level may be more realistic in certain cases.

The outer surface of the sphere is assumed to erodes linearly with time, with the time-dependent radius of the sphere given by $R(t) = A - Bt$, where $A > 0$ is the initial radius, and $B > 0$ is the rate of erosion, which remains unaffected by the diffusion process within the capsule, or by the interactions between the capsule and the ambient medium. The case of negative B would represent an expanding sphere: this is not considered here explicitly, although the model and results would still be valid in this case.

While the moving boundary in this problem makes it similar to phase change heat transfer problems involving a melting/solidification front [24], note that in Stefan phase change problems, the rate of change of the boundary is not fixed, and must be determined based on the physics of the problem and the values of system parameters such as the Stefan number [24].

Mathematically, the present problem may be described by the following conservation equation for the concentration of drug $c(r, t)$:

$$\frac{1}{D}\frac{\partial c}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) \qquad 0 < r < R(t), 0 < t < A/B \tag{1}$$

which is a transient, one-dimensional equation due to assumed circumferential symmetry around the microcapsule. The associated boundary conditions include zero concentration on the outer surface, which represents the infinite sink nature of the release medium, and the requirement of finiteness at the center of the sphere, i.e.,

$$\frac{\partial c}{\partial r} = 0 \qquad at\ r = 0 \tag{2}$$

$$c = 0 \qquad at\ r = R(t) \tag{3}$$

Equation (3) reflects the most common experimental configuration adopted in *in vitro* experiments. This boundary condition is also applicable to the *in vivo* situation when the drug is sufficiently soluble (as per model assumptions above) and the drug transport properties within the surrounding fluid are not significantly slower than within the sphere itself. Finally, an initial condition for the drug concentration field may be written as

$$c = c_{in}(r) \qquad at\ t = 0 \tag{4}$$

In most practical problems, the drug is uniformly loaded in the capsule initially, so that $c_{in}(r)$ is a constant.

While several analytical tools are available for solving drug diffusion problems with fixed boundaries [28,29], this problem presents a key complication in the form of the moving boundary.

In order to solve this problem, non-dimensionalization is first carried out as follows: $\bar{c} = \frac{c}{c_{ref}}$, $\bar{r} = \frac{r}{A}$, $\bar{t} = \frac{Dt}{A^2}$, $\bar{c}_{in} = \frac{c_{in}}{c_{ref}}$. Here, c_{ref} is a reference concentration, which in the usual case of uniform initial loading may be chosen as the value of the initial concentration in the sphere. Note that spatial terms are being non-dimensionalized using the initial radius of the sphere. The governing equations in non-dimensional form are given by:

$$\frac{\partial \bar{c}}{\partial \bar{t}} = \frac{1}{\bar{r}^2}\frac{\partial}{\partial \bar{r}}\left(\bar{r}^2 \frac{\partial \bar{c}}{\partial \bar{r}}\right) \qquad 0 < \bar{r} < 1 - \bar{B}\bar{t},\ 0 < \bar{t} < 1/\bar{B} \tag{5}$$

where $\bar{B} = AB/D$ is the non-dimensional rate of erosion that combines the initial radius, rate of erosion and diffusion coefficient into a single parameter.

The associated boundary conditions are

$$\frac{\partial \bar{c}}{\partial r} = 0 \qquad as\ \bar{r} \to 0 \tag{6}$$

$$\bar{c} = 0 \qquad at\ \bar{r} = 1 - \bar{B}\bar{t} \tag{7}$$

along with the following initial condition:

$$\bar{c} = \bar{c}_{in}(\bar{r}) \qquad \text{at } \bar{t} = 0 \tag{8}$$

Note that for uniform initial loading of the drug, one may choose $c_{ref} = c_{in}$, leading to an initial condition of $\bar{c} = 1$ at $\bar{t} = 0$. In such a case, the only non-dimensional parameter appearing in the problem is the non-dimensional rate of erosion $\bar{B}$.

In order to solve equations (5)-(8), the following transformation is used [25]:

$$\bar{c}(\bar{r},\bar{t}) = (1-\bar{B}\bar{t})^{-3/2}\exp\left(\frac{\bar{r}^2\bar{B}}{4(1-\bar{B}\bar{t})}\right)w(\xi,\tau) \quad (9)$$

Where

$$\xi = \frac{\bar{r}}{1-\bar{B}\bar{t}}\ ;\ \ \tau = \frac{\bar{t}}{1-\bar{B}\bar{t}} \quad (10)$$

This transformation converts the moving boundary problem above into a fixed-boundary problem while preserving the functional form of the governing differential equation and associated boundary conditions [25]. It has been shown [25] that this results in the following differential equation for $w(\xi,\tau)$:

$$\frac{\partial w}{\partial \tau} = \frac{1}{\xi^2}\frac{\partial}{\partial \xi}\left(\xi^2\frac{\partial w}{\partial \xi}\right) \qquad 0<\xi<1 \ (11)$$

with boundary conditions given by $w = 0$ at $\xi = 1$ and finiteness requirement, $\frac{\partial w}{\partial \xi} = 0$ at $\xi = 0$. The initial condition is $w = \theta_{in}(\xi)\exp\left(-\frac{\xi^2\bar{B}}{4}\right)$ at $\tau = 0$. The problem for $w(\xi,\tau)$ is a straightforward problem of diffusion in a sphere of fixed radius. A solution for $w(\xi,\tau)$ can be written as [28]:

$$w(\xi,\tau) = \sum_{n=1}^{\infty} p_n \frac{\sin(\lambda_n \xi)}{\xi} \exp\left(-\lambda_n^2 \tau\right) \tag{12}$$

where, using the outer boundary condition, λ_n are given by roots of $\sin(x) = 0$, i.e., $\lambda_n = n\pi, (n = 1,2,3..\infty)$. Finally, by using the initial condition and principle of orthogonality of eigenfunctions in the spherical coordinate system, the coefficients p_n can be found to be

$$p_n = 2\int_0^1 \xi\theta_{in}(\xi)\sin(\lambda_n \xi)\exp\left(-\frac{\xi^2 \bar{B}}{4}\right)d\xi \tag{13}$$

This completes the solution of the problem. The final solution for the concentration distribution is given by equations (9), (10), (12) and (13).

Based on this solution, an expression for cumulative drug delivery up to any time may be derived. The total mass of drug delivered up to a given time, relative to the initial mass loaded in the capsule is given by

$$\psi(t) = \frac{\int_0^t -D\left(\frac{\partial \bar{c}}{\partial r}\right)_{r=A-Bt^*}(A - Bt^*)^2 dt^*}{\int_0^A r^2 \bar{c}_{in}(r)dr} \tag{14}$$

Assuming uniform initial distribution, this can be written in non-dimensional form as follows:

$$\bar{\psi}(\bar{t}) = 3\int_0^{\bar{t}} -\left(\frac{\partial \bar{c}}{\partial \bar{r}}\right)_{\bar{r}=1-\bar{B}\bar{t}^*} (1-\bar{B}\bar{t}^*)^2 d\bar{t}^* \tag{15}$$

Inserting equation (9) into equation (15) results in the following explicit, but rather complicated, expression for the amount of drug released as a function of time.

$$\bar{\psi}(\bar{t}) = 3\int_0^{\bar{t}} -(1-\bar{B}\bar{t}^*)^{-1/2} \exp\left(\frac{\bar{B}(1-\bar{B}\bar{t}^*)}{4}\right) \sum_{n=1}^{\infty} p_n \lambda_n \cos(\lambda_n)\ \exp\left(\frac{-\lambda_n^2 \bar{t}^*}{(1-\bar{B}\bar{t}^*)}\right) d\bar{t}^* \tag{16}$$

Note that $\bar{\psi}(\bar{t})$ can also be determined by subtracting the amount of drug remaining, obtained by appropriately integrating the drug concentration distribution from the initial drug mass. Based on overall mass conservation, the two approaches are equivalent.

3. Results and Discussion

3.1. Number of eigenvalues needed

Since the analytical solution is derived in the form of an eigenfunction-based infinite series, it is important to examine the convergence of this series, and the number of terms required to be computed to ensure reasonable accuracy. To investigate this further, the concentration distribution is computed for different number of eigenvalues. For a representative problem with $\bar{B} = 1$, Figures 2(a) and 2(b) plot the drug concentration distribution at two different times, and drug concentration as a function of time at $\bar{r} = 0.5$, respectively, for different number of eigenvalues. Figure 2(a) shows convergence in concentration distribution within three eigenvalues. At very early times, within less than 1% of the total time duration of problem, a small discrepancy is seen in the inset

in Figure 2(b) with five eigenvalues. This discrepancy vanishes as the number of eigenvalues considered is increased. Since the eigenvalues for the present problem are quite straightforward, the computational cost of considering a larger number of eigenvalues is quite small.

Figure 3 plots the drug release profile, i.e., $\bar{\psi}$, the drug released expressed as a fraction of initial drug in the capsule as a function of $\bar{t}$ for $\bar{B} = 1$. It is found that the calculated total drug delivered, which at large time should asymptote to 1, is influenced only slightly by the number of eigenvalues. The computed value of $\bar{\psi}$ by the end of the drug release process is found to be within 6%, 3%, 1.5% and 0.5% of the asymptotic value when using 10, 20, 40 and 100 eigenvalues. Since the analytical solution, including determination of the eigenvalues, is not computationally intensive, all further results in this work based on the use of 100 eigenvalues.

3.2. Special case of non-erodible sphere

It is instructive to examine the behavior of the solution derived here for the special case of a static sphere, $\bar{B} = 0$. By inserting $\bar{B} = 0$ in equations (9), (10), (12) and (13), the concentration distribution for this special case reduces to the following:

$$\bar{c}(\bar{r}, \bar{t}) = \sum_{n=1}^{\infty} p_n \frac{\sin(\lambda_n \bar{r})}{\bar{r}} \exp\left(-\lambda_n^2 \bar{t}\right) \tag{17}$$

where, for this case,

$$p_n = 2\int_0^1 \bar{r}\bar{c}_{in}(\bar{r})\sin(\lambda_n \bar{r})\, d\bar{r} \tag{18}$$

and λ_n remain the same as the ones for the general problem.

This is identical to the independently derived solution for the standard problem of diffusion in a static sphere [2,28].

Further, by inserting $\bar{B} = 0$ in the expression for $\bar{\psi}(\bar{t})$ given by equation (16), it can be shown that the drug delivery profile reduces to the following for the special case of a static sphere:

$$\bar{\psi}(\bar{t}) = -3\sum_{n=1}^{\infty} p_n \lambda_n \cos(\lambda_n)\, \frac{1 - \exp\left(-\lambda_n^2 \bar{t}\right)}{\lambda_n^2} \tag{19}$$

which is also identical to the independently-derived expression for a sphere that does not undergo erosion. This shows that the generalized results for an eroding sphere derived in this work correctly reduce to well-known results for the special case of a non-erodible sphere.

Figure 4 plots the impact of the non-dimensional rate of erosion on the concentration distribution in the sphere at a specific time. Curves are presented for multiple values of $\bar{B}$. For reference, the curve for a static sphere, based on equation (17) [28] is also shown. Figure 4 shows that as the non-dimensional rate of erosion in the eroding sphere problem approaches zero, the resulting concentration distribution curve approaches the solution of the static sphere problem. Further, as expected, the concentration distribution is lower for greater values of $\bar{B}$, which is because of greater drug diffusion to the surface when the sphere erodes rapidly.

3.3. Effect of non-dimensional parameter $\bar{B}$

Assuming uniform initial loading of the drug within the sphere, equations (5)-(8) show that only one non-dimensional parameter, $\bar{B}$ appears in the governing equation and boundary/initial conditions. Therefore, it is possible to plot general solution curves that represent the solution for any set of dimensional parameters corresponding to different values of $\bar{B}$. This is shown in Figure 5, where the drug release profile $\bar{\psi}(\bar{t})$ is plotted for different values of $\bar{B}$. Figure 5 can be used to determine the drug release profile of any problem for given initial radius A, rate of erosion B and diffusion coefficient D, all of which are combined into a single non-dimensional parameter $\bar{B}$. Note that the curves for different values of $\bar{B}$ shown in Figure 5 terminate at different times. This is because the total time for the entire sphere to erode is given by $\bar{t}_{full} = \bar{B}^{-1}$. Figure 5 shows that $\bar{\psi}$ rises from a value of 0 to 1 relatively rapidly for small values of $\bar{B}$, since drug release is completed before the sphere has fully eroded at $\bar{t}_{full}$. This is mainly because, for fixed D, small $\bar{B}$ corresponds to low rate of erosion, and therefore, the drug release is primarily governed by diffusion.

Note that the rate of erosion B and diffusion coefficient D represent two key parameters that combine to determine the drug delivery characteristics. Unfortunately, $\bar{B}$ contains both, and, in addition, D also appears in $\bar{t}$. This results in difficulties in interpreting Figure 5 in terms of the impact of B or D on drug delivery characteristics. This is addressed in subsequent Figures through a dimensional analysis where only one of the two parameters is varied at a time.

The effect of the nature of initial loading of the drug is examined in Figure 6. The scenario considered here is that the drug is not uniformly loaded in the initial sphere of radius A, but rather,

only in an inner core of radius ηA, where $\eta \leq 1$. The impact of the radius of the drug core relative to the initial sphere radius, i.e., η, on drug delivery characteristics is presented in Figure 6, which plots $\bar{\psi}$ as a function of non-dimensional time for multiple values of η. All other parameters are fixed in the form of $\bar{B} = 1$. For a reasonable comparison between the various cases, it is assumed that the same total mass of the drug is initially loaded, so that the smaller the value of η, the greater is the concentration of the initial drug loading. The case of $\eta = 1$, corresponding to the drug being loaded uniformly in the entire sphere, is also plotted. Figure 6 shows that for $\eta < 1$, the drug delivery curves are S-shaped. The curves start with an initial zero slope, followed by an inflexion after some time, wherein the drug delivered begins to rise much more rapidly with time, and finally, as one gets close to the erosion process consuming the entire sphere, there is another slowdown in the drug delivery curve. The initial zero slope is explained by a finite amount of time needed initially for the drug to diffuse from the core to the outer surface before appreciable drug delivery to the release medium occurs. As expected, the smaller the value of η, the larger is the initial period of slow drug delivery seen in Figure 6, because a smaller value of η corresponds to a smaller initial drug core, and therefore, a greater distance that the drug must diffuse initially to reach the outer surface. Only when $\eta = 1$, i.e., the drug is initially loaded in the entire sphere, does the drug become immediately available for release from the outer surface to the ambient, which is why, the curve corresponding to $\eta = 1$ in Figure 6 rises sharply beginning at $\bar{t} = 0$.

3.4. Effect of dimensional parameters

While non-dimensional analysis, such as the one presented in sections 3.2 and 3.3, is helpful for theoretical understanding of the problem, practical applications of the theoretical model developed here may necessitate dimensional analysis. Key quantities of interest include the drug

release profile as a function of time, and its dependence on problem parameters including the diffusion coefficient and rate of erosion. In the present problem, the entire sphere vanishes at $t = A/B$, and therefore, the maximum time for completion of drug delivery is fixed, regardless of the diffusion coefficient. However, the rate of drug delivery is still of much interest, and a quantity such as $t_{0.95}$, defined as the time taken to delivery 95% of the total drug mass may help understand the drug delivery characteristics of a specific system. When rapid release of the drug is desired, the system must be designed to offer low $t_{0.95}$. Conversely, when slow and steady drug release is desired over the release period, the design parameters must be chosen to ensure a high value of $t_{0.95}$.

In general, the nature of drug delivery from the sphere is influenced by a combination of two processes – diffusion, governed by the diffusion coefficient D and erosion, governed by the rate of erosion, B. While the non-dimensional problem combines these into a single non-dimensional parameter $\bar{B}$, it is helpful to examine the dimensional problem, so that the influence of diffusion and erosion on drug delivery – and the interplay between the two processes – can be better understood. Some of these considerations that require analysis of dimensional parameters are discussed in the next two Figures.

The effect of diffusion coefficient on drug delivery characteristics is investigated first. Assuming an initial radius of $A = 50\ \mu m$ – a typical size for microcapsules – Figure 7(a) plots the relative amount of drug delivered, $\bar{\psi}$ as a function of time in dimensional form for multiple values of the diffusion coefficient taken from the literature [8,28]. In this and subsequent Figures, the drug is assumed to be initially loaded uniformly throughout the entire sphere. As expected, these plots show rapid delivery of the drug at early times, when there is a strong gradient between the

drug concentration within the sphere and outside, followed by flattening out of the curve at larger times. Particularly at large values of diffusion coefficient, Figure 7(a) shows that it is possible for nearly all the drug to be delivered long before complete erosion of the sphere. In each case, the initial slope of the curves shown in Figure 7(a) is non-zero, which is because the drug, initially loaded throughout the volume of the sphere, is readily available for delivery to the release medium even at $t = 0$. In contrast, if the drug was loaded only within a smaller radius of the initial sphere, the plots in Figure 7(a) would exhibit zero initial slope.

Figure 7(b) plots $t_{0.95}$, the time taken for delivery of 95% of the total drug mass, as a function of the diffusion coefficient for a capsule of $50\ \mu m$ initial radius and for three different values of the rate of erosion. These curves highlight several interesting aspects of the drug delivery process. At any given rate of erosion, $t_{0.95}$ decreases with increasing diffusion coefficient. The reduction is not linear, however. The curve is relatively flat at small values of D, wherein there is minimal change in $t_{0.95}$ with increasing D. This is because when the diffusion coefficient is small enough, the rate of drug delivery is governed primarily by the rate of erosion rather than diffusion, and therefore, changes in D do not result in significant change in $t_{0.95}$, particularly when B is large. In this regime, $t_{0.95}$ is governed primarily by erosion – the larger the rate of erosion, the larger is $t_{0.95}$. This is because the faster the sphere erodes, the greater is the concentration gradient within the sphere, and therefore, the greater is the rate of drug delivered to the release medium. In contrast, at large values of D, $t_{0.95}$ is largely insensitive to the rate of erosion. This is because when the diffusion coefficient is very large, most of the drug diffuses out of the sphere very rapidly, before any significant level of erosion has occurred. The problem in such a case is governed by diffusion rather than erosion. Most of the drug delivery is completed very early, and during further time, the eroding sphere does not have significant drug remaining within. These two regimes of small and

large diffusion coefficients represent two extremes in the dynamics of drug delivery from an eroding sphere, dominated by erosion or diffusion, respectively.

The impact of diffusion and erosion on drug delivery is further investigated in Figure 8. The dependence of the drug delivery profile, $\bar{\psi}$ as a function of time on the rate of erosion is plotted in Figure 8(a). This plot shows that the larger the rate of erosion, the steeper is the drug delivery profile. This is because a large rate of erosion results in large concentration gradient within the sphere, which enhances the rate of mass transfer to the release medium. There is, however, some saturation in this trend at large values of the rate of erosion. Also, note that the curves in Figure 8(a) terminate at different times, at which the sphere has completely eroded, given by $t = A/B$.

Further, $t_{0.95}$ is plotted as a function of rate of erosion in Figure 8(b). Curves are presented for three different diffusion coefficients. In general, $t_{0.95}$ decreases as B increases, which is expected, since a rapidly eroding sphere will release the drug faster. However, when the diffusion coefficient is relatively large, Figure 8(b) shows that $t_{0.95}$ may become largely insensitive to the rate of erosion. This is because when the diffusion coefficient is large, most of the drug diffuses out rapidly, and the drug delivery process becomes independent of the rate at which the sphere erodes. Figure 8(b) also shows that for a given rate of erosion, $t_{0.95}$ is larger for larger diffusion coefficient, which is also as expected. When the diffusion coefficient is large, the problem is diffusion controlled, and $t_{0.95}$ does not change appreciably with changing B, as shown in Figure 8(b).

The curves in Figure 7(a) and 8(a) represent different types of drug delivery characteristics. If the goal is to deliver most of the drug in a short period of time, these curves show that one must

design the capsule with high D and high B. However, if the goal is a steady delivery over a longer period, both D and B must be small.

Finally, Figure 9 investigates the impact of changing the number of capsules to deliver the same mass of drug on drug delivery characteristics in the presence of erosion. In this case, the total mass of drug to be delivered and the total volume of the capsule material is held constant, and a number of cases corresponding to different number of identical capsules, including a single capsule of size $50\ \mu m$, are considered. When the same material volume is divided into a larger number of capsules, each capsule is smaller in size, and therefore, is expected to deliver the drug faster. The theoretical model presented in Section 2 is used to quantify this effect. It is assumed that the release medium is large enough that it can continue to be considered as an infinite sink regardless of the number of capsules. Further, a constant rate of erosion is assumed for each case considered here. Based on these assumptions, the analytical model is used to compute the drug delivery profile, $\bar{\psi}$ as a function of time. Results are plotted in Figure 9(a) for one, two, three and four capsules. Since the total volume is held constant, the radius of individual capsules reduces as the number of capsules increases. For this problem, the specific values are 50, 39.7, 34.7 and 31.5 μm for one, two, three and four capsules, respectively. Figure 9(a) shows that as the drug dosage is split into a larger number of individually smaller capsules, the release curve becomes steeper and steeper, representing a faster rate of initial drug delivery.

The time taken for completion of 95% of drug delivery is plotted as a function of number of capsules in Figure 9(b). This plot shows, as expected, a reduction in $t_{0.95}$ as the number of capsules increases, due to the smaller radius of each capsule. Similar to Figure 9(a), the reduction in release time is primarily because of the reduction of radius of each sphere, while all other

parameters remain the same. The effect is not linear in nature, however. There is a rapid reduction initially, but as the number of capsules increases, the reduction in $t_{0.95}$ flattens out somewhat.

4. Conclusions

This work presents a closed-form analytical solution for the problem of drug diffusion in a bioerodible sphere. This is a challenging problem primarily due to the change in the outer boundary of the sphere over time. This challenge is overcome in the present work by an appropriate variable transformation. By doing so, it is shown that a non-dimensional parameter that combines the initial radius, rate of erosion and diffusion coefficient plays a key role in determining the dynamics of drug release.

The analytical model presented in this work is to be seen as a first step towards complete theoretical characterization of drug release from a surface-erodible capsule. It is important to further extend this model to account for other processes such as drug dissolution that have been partly modeled in past work [21]. Doing so is likely to render this problem not amenable to an analytical solution any more, and a numerical simulation may instead be needed. Further, the modeling of a core-shell composite structure may also be of interest, in order to align with commonly used drug delivery systems.

Finally, comparison of the present work with experimental data is an important direction for future work. In the present work, the key difficulty in comparison with experimental data was in the lack of information on rate of erosion for commonly available diffusion data [15,21]. Comparison of model predictions with experimental datasets with well-known values of parameters such as initial radius, diffusion coefficient and rate of erosion is expected to benefit the design and optimization of bioerodible drug delivery systems.

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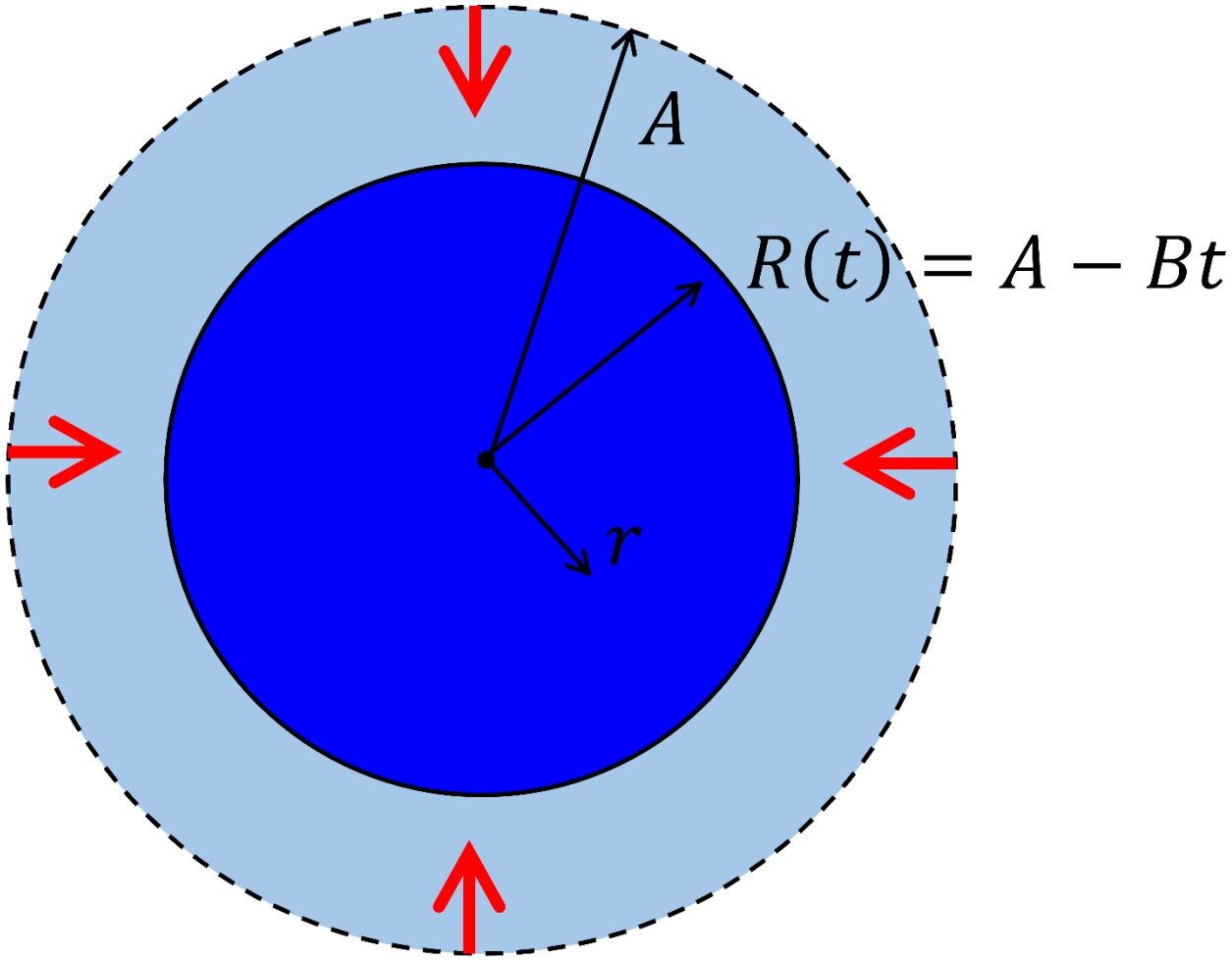

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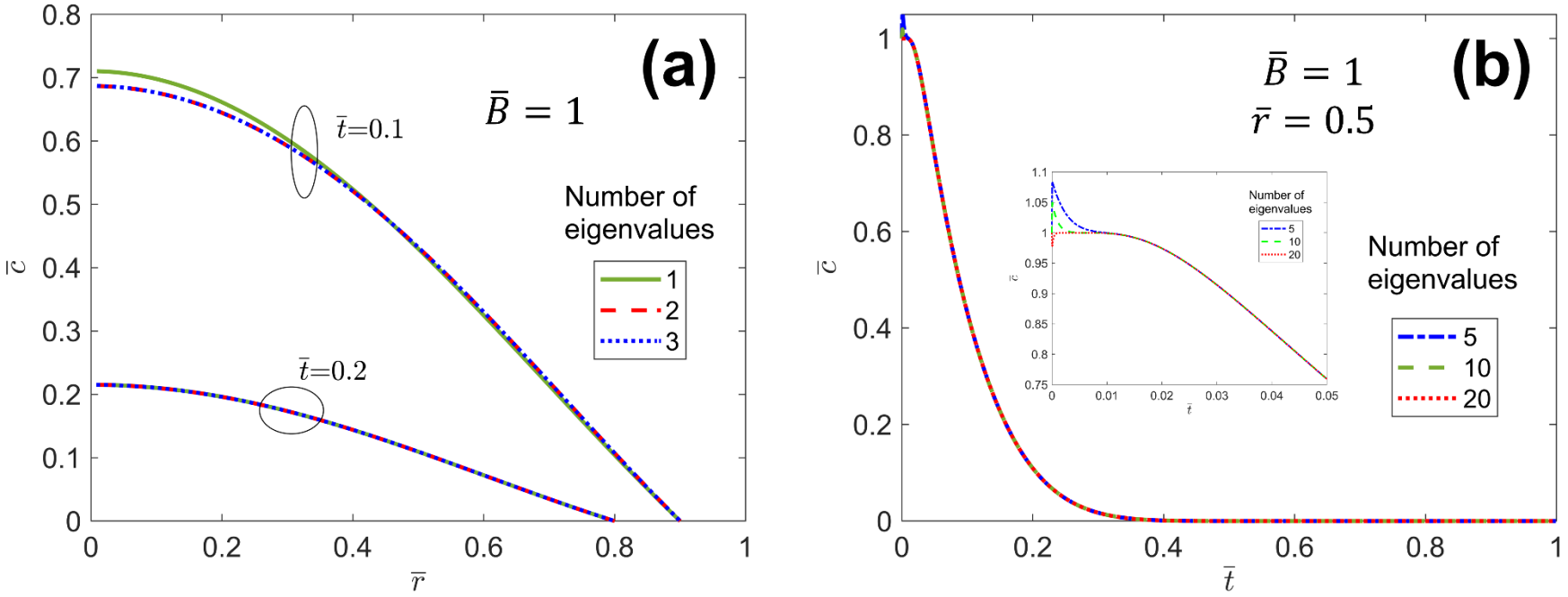

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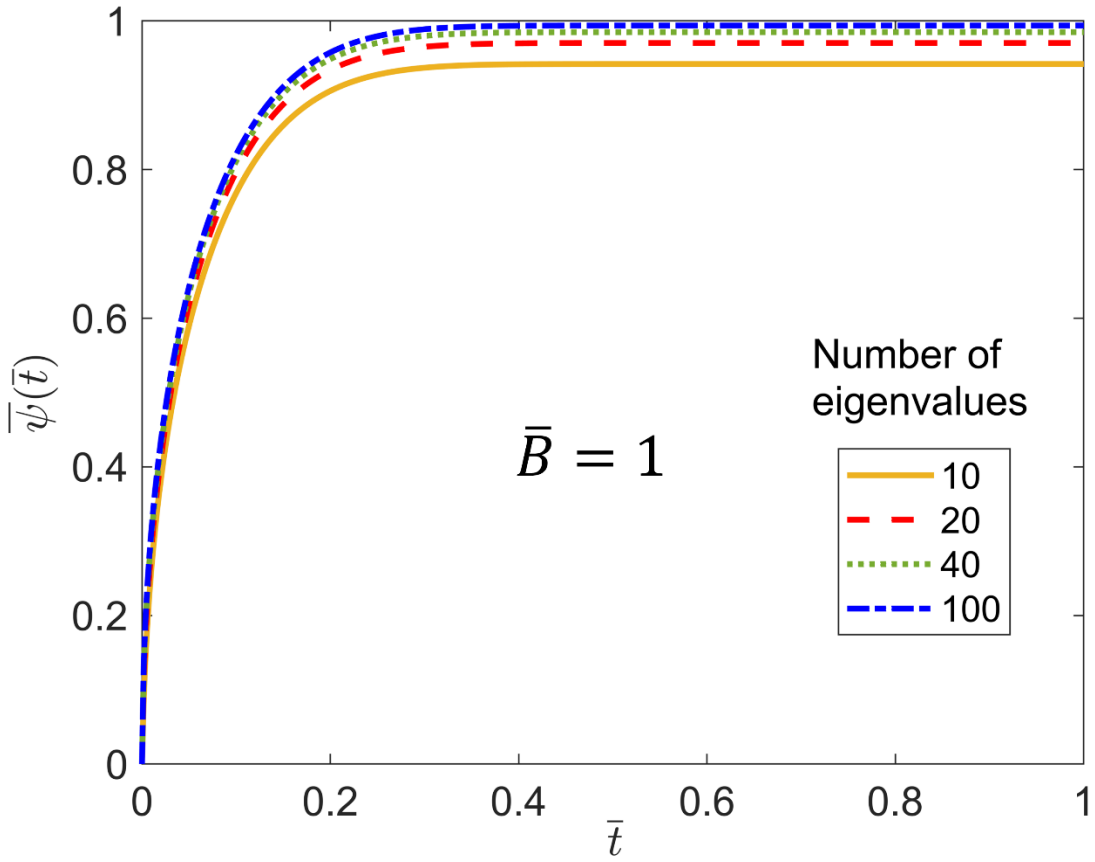

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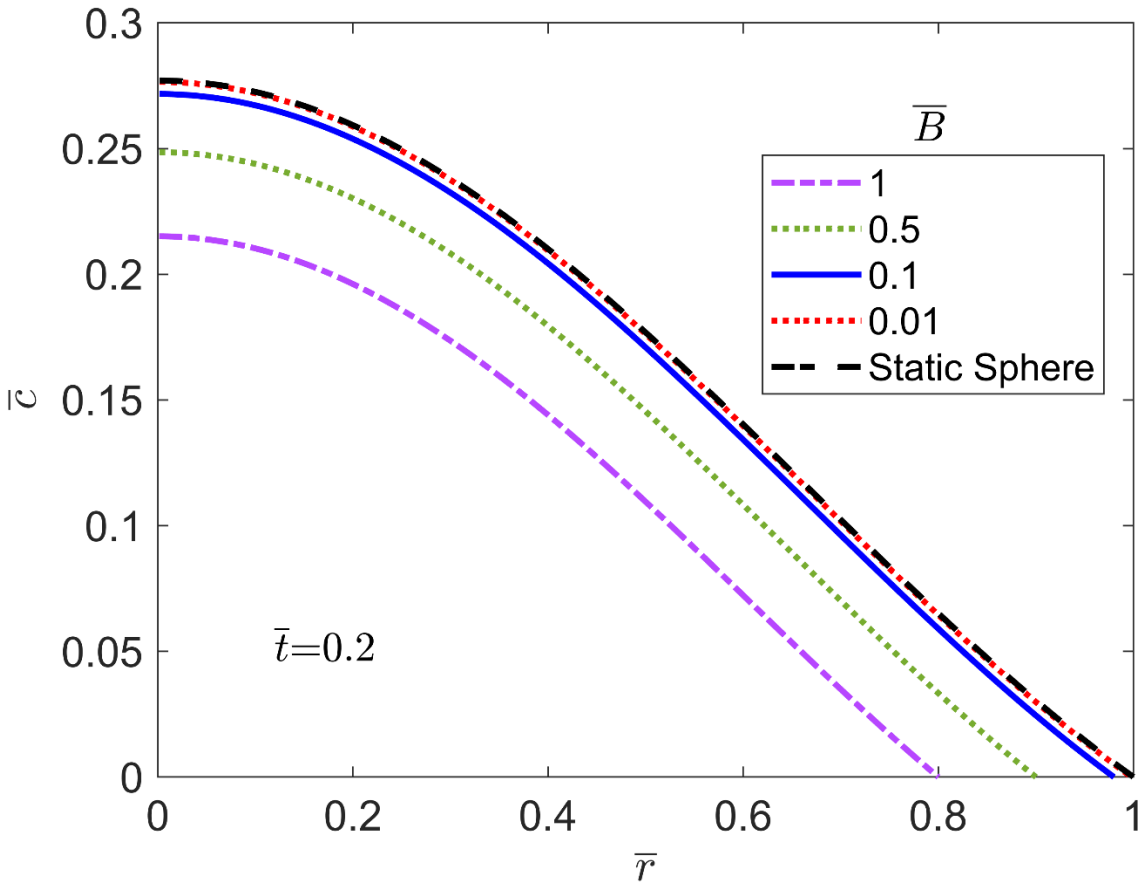

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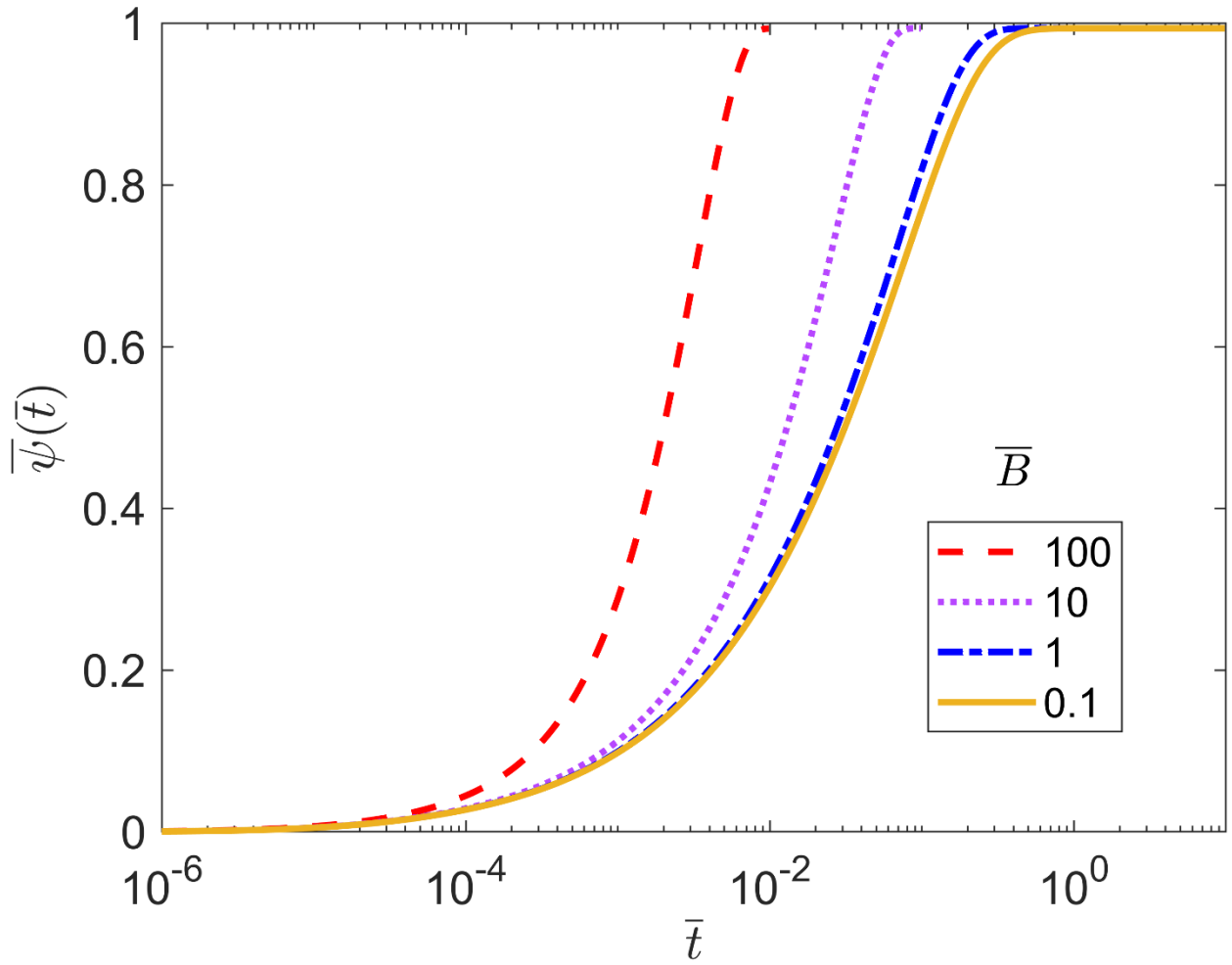

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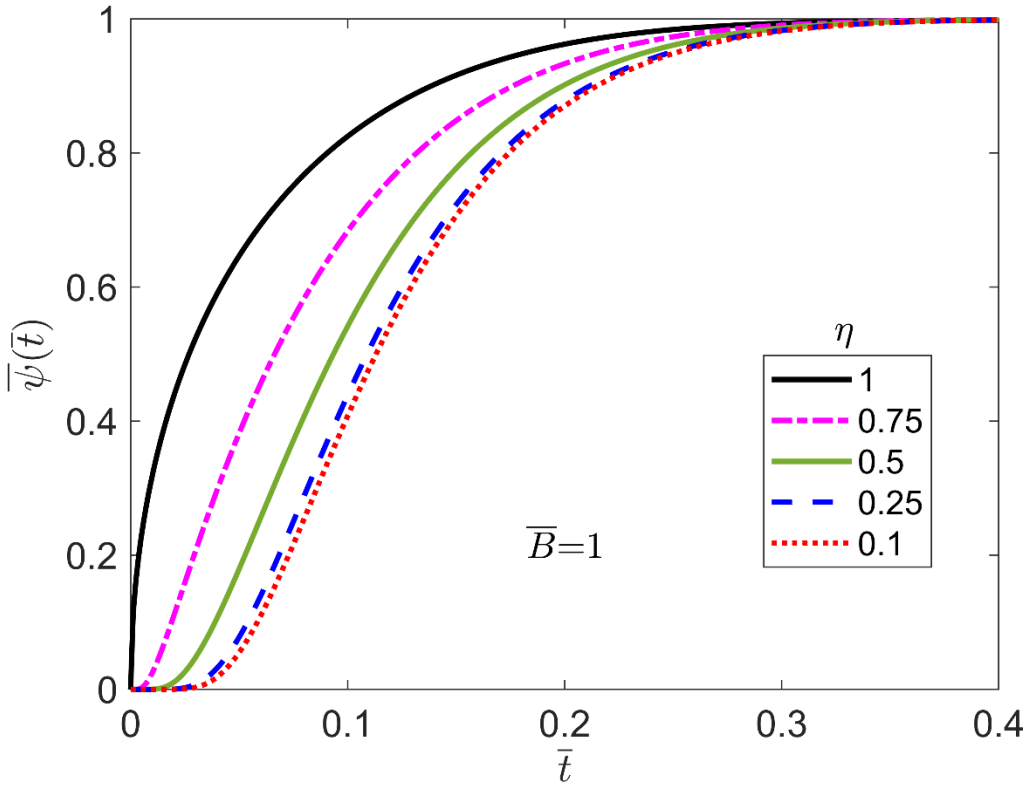

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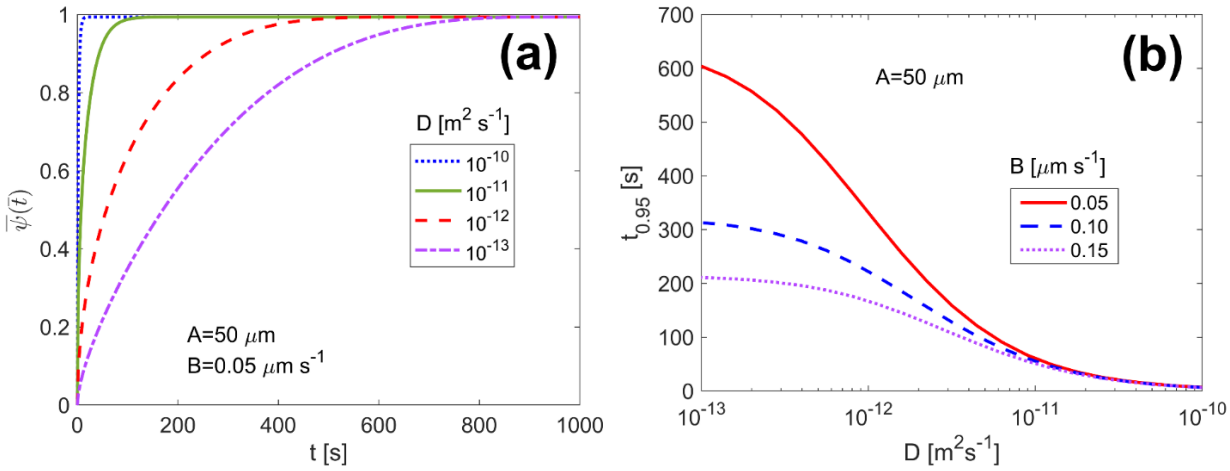

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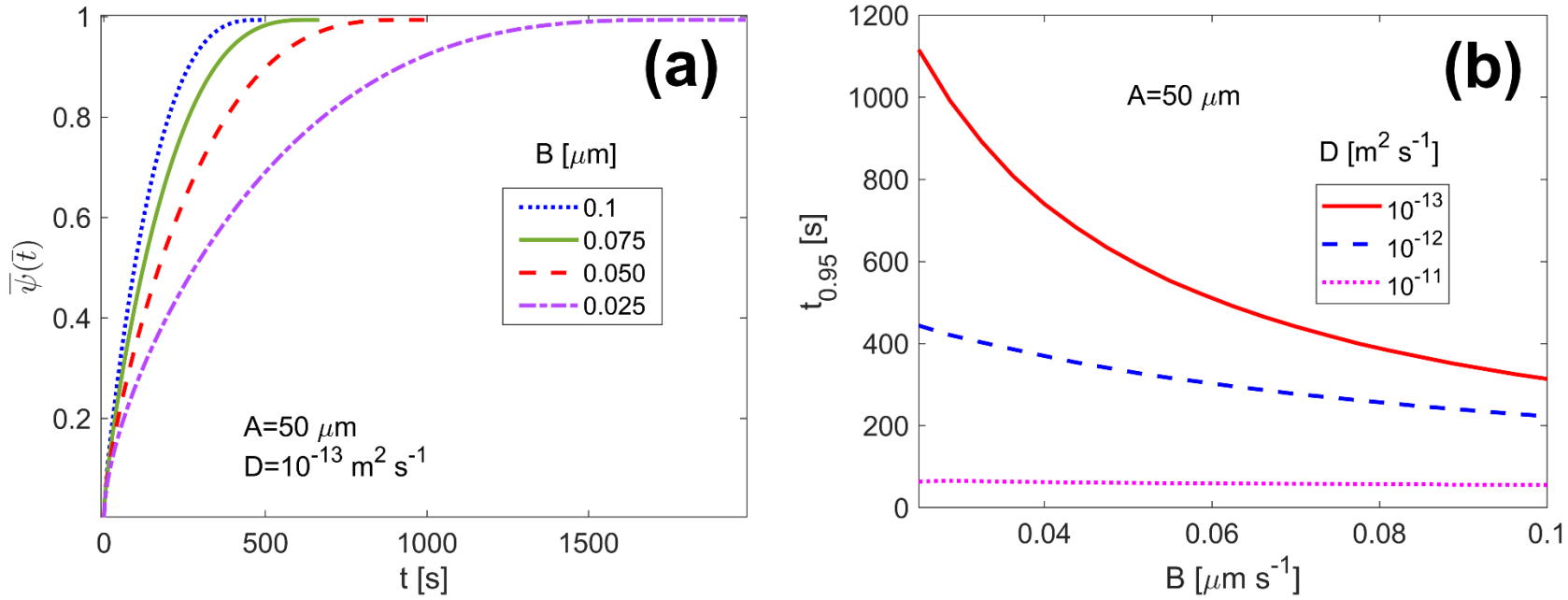

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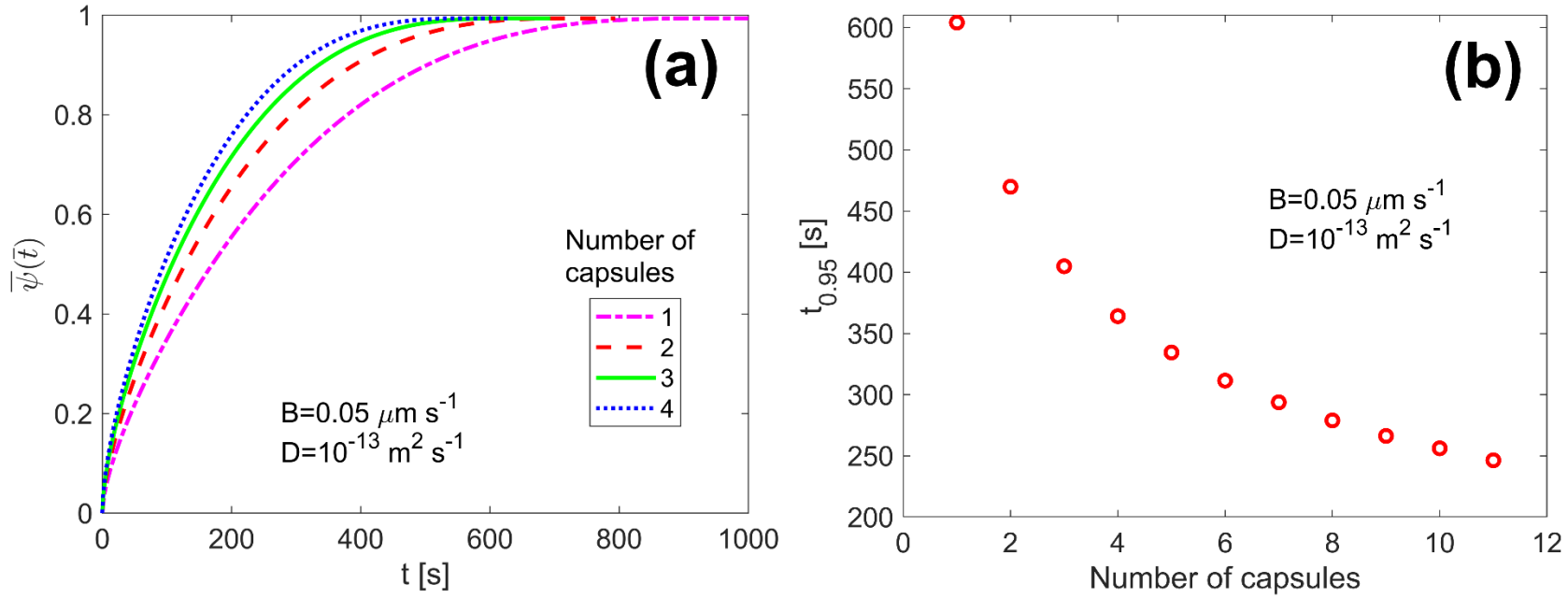

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