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Review Article

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In-vitro Modeling of the Release Kinetics of Micron and Nano-Sized Polymer Drug Carriers

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Abstract

This article reviews in-vitro modeling of the release kinetics of hydrophobic drugs encapsulated by polymeric materials. Major continuum models along with their assumptions and limitations for micron-sized systems will be considered. The dependence on the swelling and degradation for such systems will also be discussed. As polymer micelles have gained popularity in the past decades, applications and limitations of continuum models to such nano-sized systems will be examined. A different approach based on molecular dynamics simulation will be introduced.

Keywords: Diffusion, Continuum models, Swelling, Degradation, Micelles, Molecular dynamics simulation

Introduction

Polymers have been used as drug carrier systems for several decades.All polymers used in practice are biodegradable[1-5]. This is because non-degradable polymers cannot be easily eliminated from the patient's body upon the consumption of the drugs. Therefore, such polymers are not used in practice. However, polymers that exhibit long degradation time (longer than the time scale of the drug release) are usually considered as "non-degradable" from the drug kinetics perspective as the molecular weights of such polymers do not change during the release process. Figure 1 and Figure 2 show a few "non-biodegradable" and biodegradable polymer structures that are commonly used as drug delivery systems. Figure 3 (a) and (b) show the drug carrier systems in which the drug is encapsulated by polymer in a spherical geometry. Different geometries (e.g., cylindrical) can be used but they exhibit different release kinetics even though the same polymer is used. The effect of the device geometry on drug release kinetics will be discussed later. Since such systems are usually micron-sized, continuum models are found suitable for describing the corresponding kinetics. Figure 3 (c) shows a carrier system that is made up of polymeric micelles. In fact, this type of carrier system has become quite popular in recent years as such nanometer-size systems offer longer circulation times[6-9]. Such micelles are formed from individual amphiphilic polymer chains that spontaneously form nano-sized aggregates in selective solvents (water in the case of drug delivery systems) above a threshold concentration called the critical micelle concentration (CMC). This is due to the good solubility of one and poor solubility of the other block of the copolymer in the selected solvent [10]. These polymeric micelles are usually tens of nanometers in size. They are characterized by their unique core-shell structure, in which the core is composed of hydrophobic blocks that are surrounded by a palisade of hydrophilic blocks. Generally, the hydrophobic core acts as a micro reservoir for the solubilization of hydrophobic drugs while the hydrophilic shell provides stealth properties. However, their release kinetics differs significantly from that of the micron-sized carriers and it is conceivable that continuum models may not be applicable.

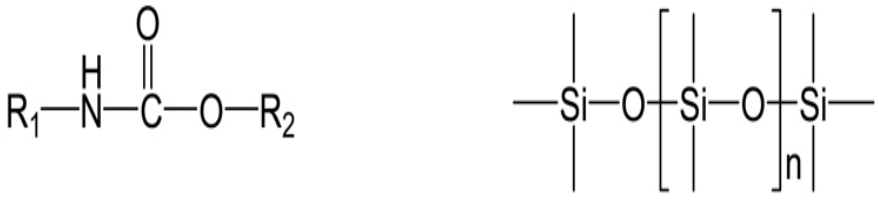
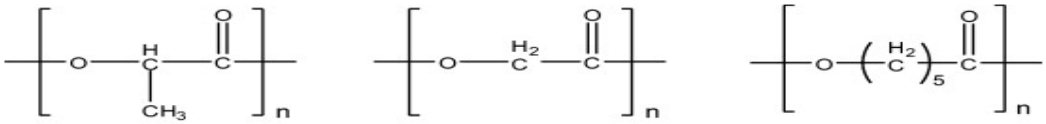


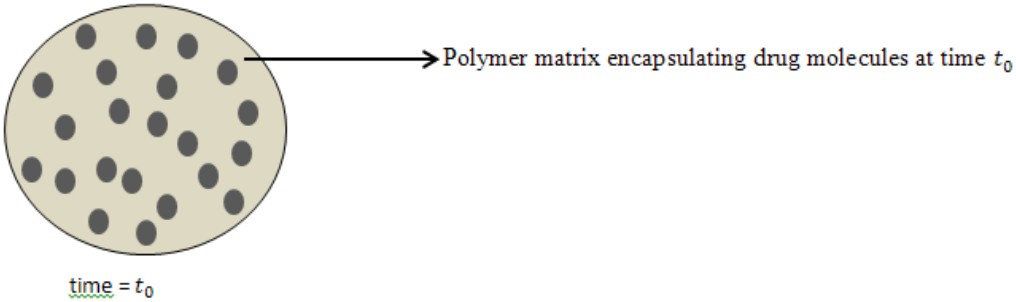
Figure 1. Chemical structures of "non-biodegradable" polymers used for drug delivery. The first structure from the left is urethane links and the second structure is polydimethylsiloxane.



a b c

Figure 2. Chemical structures of biodegradable polyesters: (a) poly(lactide), (b) poly(glycolide) and (c) poly(-caprolactone).

a)



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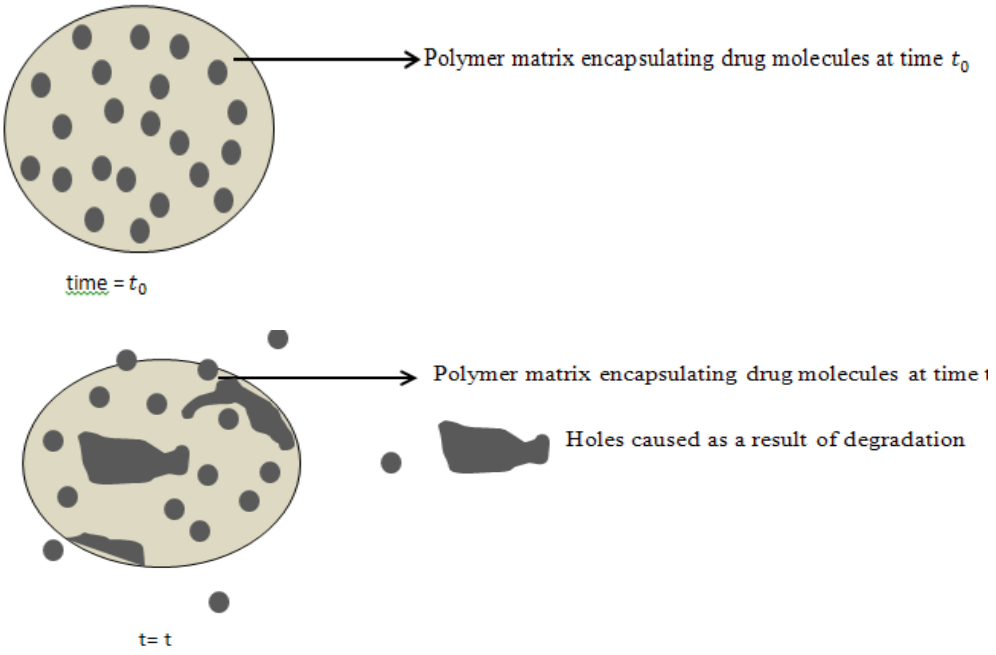

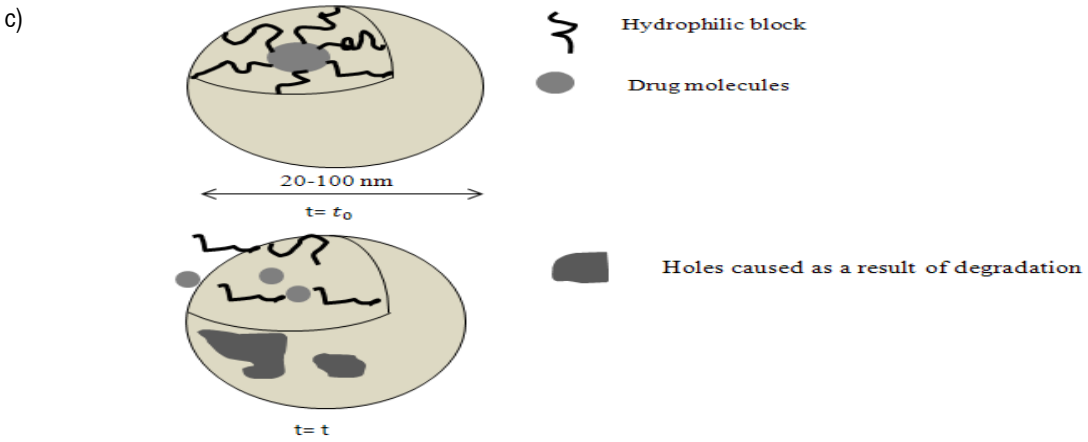

Figure 3. Schematic representation of a) micron-sized non-biodegradable polymer, b) micron-sized biodegradable polymer and c) nano-sized polymeric micelle system.

Obviously, the chemical structure of the polymer used in the aforementioned carriers will play a significant role in determining the total amount of drug released over a given period of time (i.e., release profile) which will in turn affect the *in vivo* pharmacokinetics parameters (e.g., clearance, half-life, etc.).All of the aforementioned polymer carrier systems can be administered via oral or intravenously. Recently, a great deal of attention has focused on the development of controlled release drug delivery systems that are administrated intravenously. It is desirable to have the total concentration of drug last longer in the bloodstream so that multiple dosages for patients are not required. When comparing single dose to multiple dose administration of drugs, a single dose has been proven to be a more cost-effective alternative so far.

It is worth noting that the decrease in drug concentration in blood is attributed to two factors: distribution of the drug to targeted and non-targeted tissues and elimination of the drug by kidney or metabolism. The distribution of the drug to the tissues occurs at a much faster rate compared to its elimination process. Figure 4 shows a typical drug concentration vs. time curve from a pharmacokinetic experiment on micron-sized polymer drug carriers. During the distribution process, the concentration of the drug in bloodstream decreases considerably because a high percentage of the drug distributes to different tissues. Later, equilibrium in the drug concentration will then be established between the tissues and the blood stream.

The elimination process occurs to micron-sized carriers. However, if the polymer carrier systems have sizes in the range of 10nm – 400nm, the elimination rate can be significantly decreased[6-9].Obviously, the most ideal situation is that the carriers are only distributed to the target tissues and there is no elimination. Regardless micron-sized or nano-sized carriers, it is obvious that drugs exhibiting required diffusivity in the polymer are most desirable. The intent of this review paper is to discuss different in-vitro mathematical models as well as their usages and limitations.

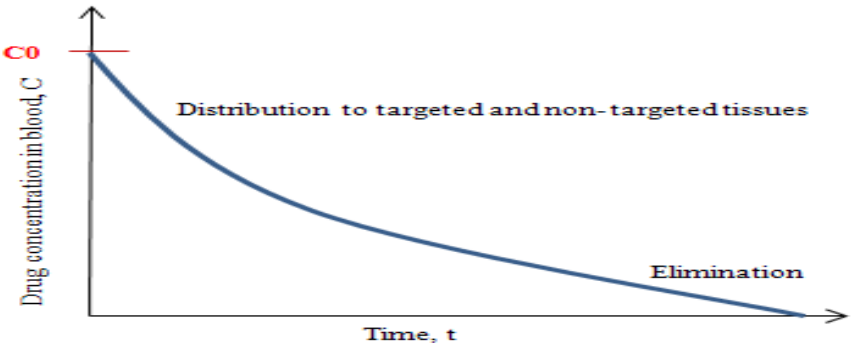

Figure 4.A typical drug concentration profile in blood after intravenous administration of drug. The drug concentration is at the highest level shortly after the intravenous injection at t~0 (C_0) and decreases during the distribution and elimination phases. The distribution phase includes distribution of drug to targeted and non-targeted tissues.

Continuum Models for Micron-Sized Carriers

Continuum models were first developed to describe the release kinetics of drug encapsulated in a micron-sized polymer film. Such models are essentially developed for in vitro environment by including various effects such as concentration gradient, swelling, and degradation of polymer. Later, researchers developed micron-sized continuum models to describe kinetics of drug encapsulated in devices with different geometries such as thin films, spheres and cylinders. Three types of micron-sized drug carriers will be discussed and they are non-biodegradable, swollen, and biodegradable polymers.

The advantages and disadvantages of micron-sized continuum models used to describe drug delivery kinetics will be discussed respectively for thin films, spheres and cylinder geometries for each drug delivery device in the following sections.

Non-Biodegradable Polymeric Carriers

As mentioned, mathematical models developed for this type of polymers are essentially used for biodegradable polymers exhibiting long times for complete degradation. In other words, the degree of degradation is negligible relative to the release time scale. With these types of polymers, water molecules tend to diffuse into these systems causing swelling which results in diffusion of drug molecules out through the swollen polymer matrix. Five decades ago, Professor Higuchi was the first one to lay the foundation for quantitative analysis of drug release from polymer matrices. He proposed a simple thin film model based on a pseudo-steady state assumption for the release of drug from an ointment using simple mass balance concept and Fick's laws.

Higuchi Model for Non-Reservoir Polymeric Carriers

Higuchi treated the drug release problem as a steady state, one dimensional diffusion process. Based upon Fick's first law [11], the rate of diffusion of drug R_t (mole/s)for a non-biodegradable and non-swelling polymer matrices[12]is given by the following expression:

$$R_t = -SD\frac{dC}{dx} \quad (1)$$

S is the cross sectional area (m2); D is the diffusion coefficient of the drug in the polymer matrix (m^2/s); C is the concentration of the drug and x is the distance from solvent-matrix interface (Figure 5).

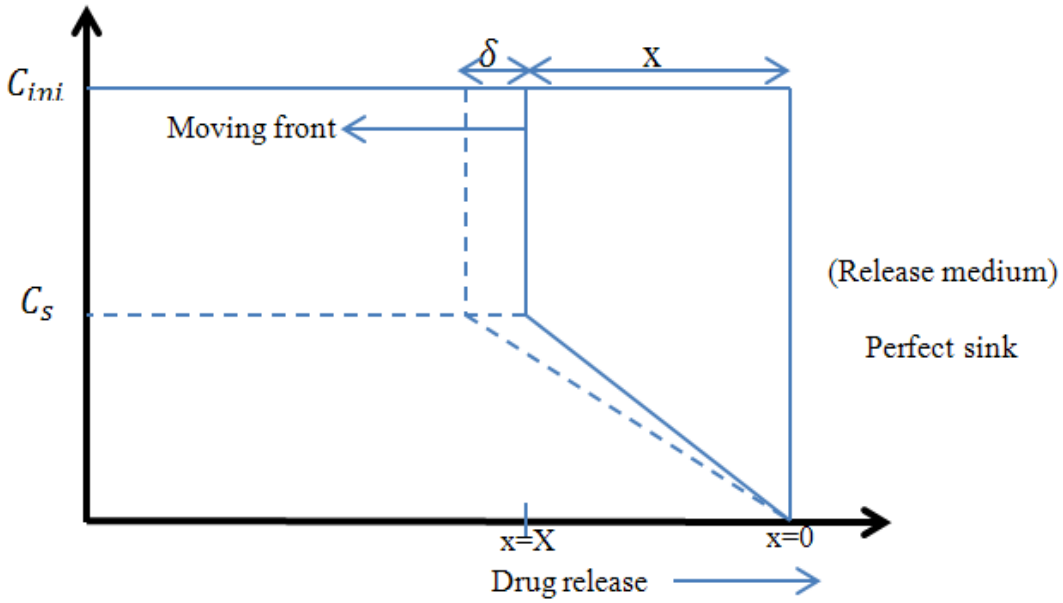

Figure 5. Schematic presentation of the drug concentration-distance-profile after exposure to perfect sink conditions.$\boldsymbol{C_{ini}(C_0)}$ is the initial drug concentration in the polymer matrix which is much higher than $\boldsymbol{C_s}$ the solubility concentration of the drug in the matrix. X represents the distance from the matrix-medium interface, $\boldsymbol{\delta}$ is the thickness of the thin film.

The boundary conditions are:

$C=C_bK$ at $x=0$ (2)

$C=C_s$ at $x= X$(3)

$C_b$is the drug concentration in the release media and C_s is the solubility concentration of the drug in the matrix. C is the drug concentration in the polymer matrix. Perfect sink condition is assumed which implies that the concentration of drug in the polymer matrix is much higher than the drug concentration at the

matrix-medium interface (C_bK). K is the matrix-to-medium partition coefficient. The initial drug concentration inside the polymer matrix is much higher than its solubility concentration (by a factor of 10 or more). According to this assumption is takes a very long time for the excess amount of the drug concentration to dissolve at a distance x from the films surface. Therefore, the drug concentration at a distance "x" from the film at any time remains almost constant which results in pseudo steady state condition. In order to solve Fick's law to obtain the diffusion coefficient we must know how the concentration profile of the drug looks like.One solution is to assume a linear concentration profile for the drug. Therefore we have:

$$R_t = SD\frac{(C_S - C_bK)}{X(t)} \quad (4)$$

In order to solve the above equation we have:

$$R_t = \frac{dM_t}{dt} = \frac{d}{dt}\left\{\left[C_0 - \frac{1}{2(C_s + C_bK)}\right] SX(t)\right\} \quad (5)$$

where$C_0(C_{ini})$is the total drug concentration. After substituting R_t in equation (5) with equation (4) and the followed by a series of integration, the final equation is written as:

$$M_t = S[D(C_s - C_bK)(2C_0 - C_s - C_bK)t]^{1/2} \quad (6)$$

It is assumed that the initial drug concentration is higher than its solubility concentration in the polymer matrix. Also, under sink conditions it is assumed that the drug concentration in the release medium is almost zero which means that: $C_b \sim 0$. When $C_s \ll C_0$:

$$M_t = S[2DC_sC_0t]^{1/2} \quad (7)$$

The above equation can also be further simplified to the following form:

$$M_t = k\sqrt{t}, \qquad \text{where } k = S\sqrt{2DC_sC_0} \quad (8)$$

It is obvious that total mass of drug released follows "square root of time" dependence.

In all the above equations K is the partition function of the drug between the membrane and the reservoir.

For the non-core-shell carriers with different geometries as shown in Figure 6, the mass of drug released shows much more complicated time dependence. Roseman and Higuchi proposed the following implicit equations. Here, the term implicit signifies that Mt cannot be isolated on the left hand side of the equation[13, 14].

For spherical carriers:

$$\frac{M_t}{M_\infty} - \frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{\frac{2}{3}}\right] = -\frac{3D}{R^2}\cdot\frac{C_s}{C_0}\cdot t \quad (13)$$

For cylindrical carriers:

$$\frac{M_t}{M_\infty} + \left(1 - \frac{M_t}{M_\infty}\right)\ln\left(1 - \frac{M_t}{M_\infty}\right) = \frac{4D}{R^2}\cdot\frac{C_s}{C_0}\cdot t \quad (14)$$

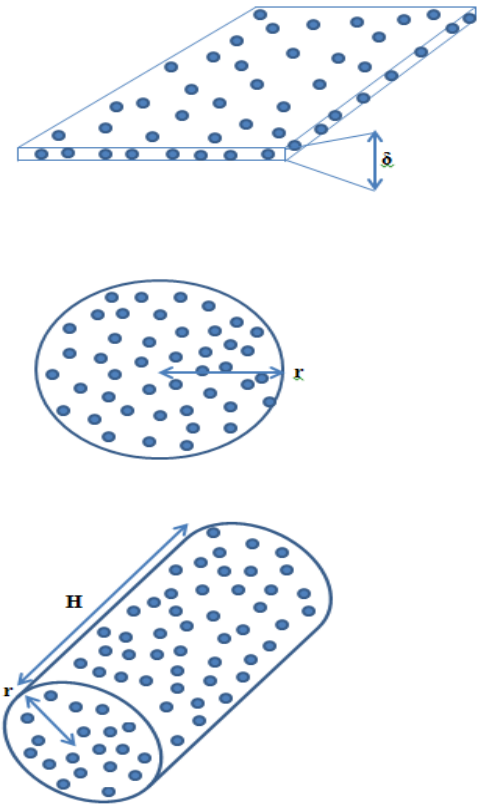

Figure 6. Thin film, spherical and cylindrical geometries used to model drug release from non-reservoir devices (devices without a core-shell structure).

If the initial concentration of the drug in the polymer matrix is homogeneously distributed at a value below the solubility concentration of the drug (C_0), and the perfect sink conditions are still applied at the surface of the thin film, the drug concentration at a distance "x" from the surface of the thin film cannot be considered constant anymore and will vary with respect to time. In this case, Fick's second law for one dimensional isothermal drug transport should be solved[15]:

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

The solution to Fick's second law with the above assumptions for thin film is [16, 17]:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\delta^2}\right)^{\frac{1}{2}}\left\{\pi^{-\frac{1}{2}} + 2\sum_{n=1}^{\infty}(-1)^n \text{ierfc}\frac{n\delta}{2\sqrt{Dt}}\right\} \quad (9)$$

The second term in brackets vanishes at small times therefore:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\delta^2\pi}\right)^{\frac{1}{2}} \quad (10)$$

The above equation is accurate for $\frac{M_t}{M} \leq 0.6\ (\text{short time release})$. According to Equation (10) which is obtained by using a pure "Fickian diffusion" approach; the release of drug again shows $t^{1/2}$dependence. The same relation between fractional drug release and time was obtained according to Higuchi's approach discussed earlier. Therefore, the principal result is a square root time dependence of the drug transport. For thin films at long times, we have:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\exp\left(-\frac{\pi^2 Dt}{L^2}\right), L = \delta \quad (11)$$

In another study, the release rate of an anti-Parkinson drug from degrading polymer (PLGA matrix) was studied. During the time of the experiment, which was exactly 4 days, the changes in the volume of the polymer matrix was negligible; therefore, the polymer microspheres were considered as non-biodegradable implants. In their study, their experimental results showed a good fit with the following solution of Fick's second law of diffusion:

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{n^2\pi^2}{R^2}Dt\right) \quad (12)$$

where $M_t$and $M_\infty$are the cumulative amounts of drug at time t and infinity; R is the radius of the sphere and D is the diffusion coefficient [18]. This model assumes perfect sink condition, the polymer matrix is considered to be a sphere and that the drug is distributed homogeneously initially. From the above equation, it is obvious that the amount of drug released at any time does not depend on polymer molecular weight and volume during the course of experiment.

For spheres at short times after solving the above equation we have [19]:

$$\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{\pi r^2}\right)^{\frac{1}{2}} - \frac{3Dt}{r^2}, \quad \frac{M_t}{M_\infty} < 0.4 \quad (16)$$

For spheres at long times,

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\exp\left(-\frac{\pi^2 Dt}{r^2}\right), \quad \frac{M_t}{M_\infty} > 0.6 \quad (17)$$

For cylinders at short times,

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi r^2}\right)^{\frac{1}{2}} - \frac{Dt}{r^2}, \quad \frac{M_t}{M_\infty} \leq 0.4 \quad (18)$$

For cylinder at long times,

$$\frac{M_t}{M_\infty} = 1 - \frac{4}{(2.405)^2}\exp\left(-\frac{(2.405)^2 Dt}{r^2}\right), \quad \frac{M_t}{M_\infty} > 0.6 \quad (19)$$

Here, only radial diffusion is considered.

Higuchi's Model for Reservoir Polymer Carriers

The reservoir(or core-shell) structure is one that the drug molecules are in the core of the structure and are surrounded by a layer of polymer. This structure can also be prepared in different geometries as shown in Figure 7.

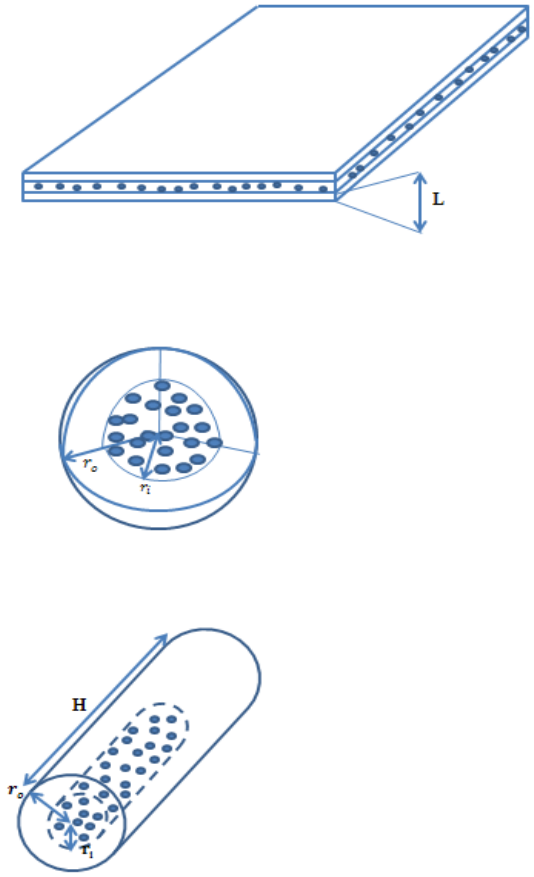

Figure 7. Common reservoir (core-shell type) structures encapsulating drug molecules for drug delivery.

Higuchi's assumption is used again here; the released drug in the shell is rapidly replaced by the excess amount of drug available in the core of the reservoir. This is in line with Higuchi's assumption that initial drug concentration is much higher than the solubility concentration of the drug in the polymer which means the drug concentration will not change as a function of time within the shell of the reservoir. Assuming perfect sink conditions, equations to describe the kinetics of drug release have been obtained for different geometries shown in Figure 7[19].

For thin films,

$$M_t = \frac{SDKC_s}{L}.t$$

For spheres,

$$M_t = \frac{4\pi DKC_s r_o r_i}{r_o - r_i}.t \quad (21)$$

For cylinders,

$$\frac{M_t}{} = \frac{2\pi HDKC_s}{\ln(\frac{r_o}{r_i})}.t \quad (22)$$

Perfect sink conditions are again provided in the surrounding bulk fluid. In the following models, $C_0 \ll C_s$. Furthermore, there is no drug excess in the core which means that the released drug molecules are not replaced and the drug concentration at the inner membrane's surface decreases with time. For thin film

$$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{ADKt}{VL}\right) \quad (23)$$

For spheres,

$$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{3r_0DKt}{(r_i)^2r_0 - (r_i)^3}\right) \quad (24)$$

For cylinders,

$$\frac{M_t}{M_\infty} = 1 - \quad (25)$$

Applications of the above mentioned models for both non-reservoir and reservoir types drug delivery devices to analyze experimental data have been reported by Siepmann et al.[19].

Analytical Solutions

Higuchi's model does have some limitations that are mainly due to the initial assumptions made to simplify the mathematical description of the systems. For example, the initial concentration of the drug should be at least 10 times higher than the solubility concentration of the drug in the matrix to ensure that the pseudo steady state condition applies. This assumption is not possible for drugs with high aqueous solubility which leads to the failure of Higuchi's model with an error more than 11% compared to the exact solution for the system [15]. In this case in practice we will not have a linear concentration profile anymore and the drug concentration at a distance "x" from the thin film surface will change with respect to time and will dissolve in the medium; therefore, Fick's second law will apply and the concentration profile of drug is a Gaussian function (normal probability distribution) which could be obtained by solving Fick's one dimensional law of diffusion for unsteady-state conditions:

$$\frac{\partial f}{\partial t} = D\frac{\partial^2 f}{\partial x^2} \qquad -\infty < x < +\infty, t > 0 \quad (26)$$

The only assumption here is that the diffusion coefficient is not a function of the drug concentration. Initial condition is specified as: f(x, t=0) = $f_0(x)$. The function "f" is "concentration" as a function of x and t.

The solution for the above equation is:

$$f(x,t) = \int_{-\infty}^{+\infty} f_0(x')\{\frac{1}{\sqrt{4\pi Dt}}e^{-\frac{(x'-x)^2}{4Dt}}\}dx'$$

If we use the "Dirac Delta" function for f_0 we obtain:

$$f(\Delta x, \Delta t) = \frac{1}{\sqrt{4\pi D\Delta t}}e^{-\frac{(\Delta x)^2}{4D\Delta t}}$$

Where $\Delta x = x - x_0$.

As we can see in the above equation, the concentration profile of such a case is a Gaussian function that is not linear at all.

Swelling Non-Reservoir Polymeric Carriers

One major assumption of all of the aforementioned models is that the polymer matrix does not swell. However, in reality, swelling does take place in many polymer carriers. Almost all oral drug delivery carriers are non-reservoir, non-biodegradable but swell. These carriers are usually prepared by compressing a powder mixture of a hydrophilic polymer and drug into tablets.

Power Law Model

Peppas et al. modified Higuchi's model in order to consider the polymer swelling kinetics. According to equation (10), the first 60% of the fractional drug release can be explained by multiplying a constant by the square root of time. A simple and comprehensive equation can be used to model such drug release process which is called the power law[20]:

$$\frac{M_t}{M_\infty} = at^n \quad (29)$$

In the above equation "a" is a constant which incorporates the structural and geometric characteristics of the drug delivery device and "n" is the release exponent which is indicative of the drug delivery mechanism. The power law is a very useful equation that was developed by "Peppas" at 1985. This model is not derived from solutions of Fick's laws and is recognized as a semi-empirical equation.

Case I and Case II drug release extremes have been studied by Alfrey et al [21]. Here, Case I refers to a Fickian diffusion process where the penetrant mobility is much slower than the segmental relaxation rate while Case II refers to a case where the penetrant mobility is much higher than the segmental relaxation rate. Case II applies to polymer matrices that swell. When the exponent is between 0.5 and 1 for a thin film, the process is called anomalous transport. In order to better understand the different mechanisms of

drug transport through polymer matrices during swelling, the swelling interface number has been used to describe the balance between drug release and solvent (water) penetration into the polymer matrix:

$$S_W = \frac{\vartheta \delta_t}{D} \quad (30)$$

Where ϑ is the velocity of the polymer-moving front which depends on the solvent (water) diffusivity, D is the drug diffusion coefficient and δ_t is the thickness of the swollen gel layer.

According to the above equation if the drug diffusion coefficient is much lower than that of the solvent (water) ($S_W \gg 1$), solvent penetration will control the release pattern (i.e., swelling controlled transport). If the drug diffusion coefficient is much higher than the solvent (water) mobility ($S_W \ll 1$), drug diffusion will control the release pattern.

In the power law equation, we can see that if the exponent is 0.5 for a thin film the process is Fickian or Case I transport as mentioned before. On the other hand, if the exponent is 1, for a thin film the process, it is Case II transport that involves swelling of the polymer matrix and water uptake. For other geometries different exponent values corresponding to different drug release mechanisms and they can be found in literature [22, 23]. A list of different values for "n" is shown in Table 1for different geometries. One should be cautious about using the values in Table 1 because there are several assumptions used in the power law such as: perfect sink conditions and drug release at short time (60% of the drug is released).

Table 1. Values of the exponent "n" for the power law equation

Geometry	Casel, Fickian diffusion	Anomalous transport	Case II, swelling controlled transport
Thin film	n =0.5	$0.5< n < 1.0$	n =1.0
cylinder	n =0.45	$0.45 < n < 0.89$	n =0.89
sphere	n =0.43	$0.43 < n < 0.89$	n =0.83

The well-known power law expression was used in a study to describe the drug release from simple swellable and erosion matrix systems in which degradation is confined to a thin surface layer of the polymer matrix[24]. In their study, the exponent (n) was used for the interpretation of the release mechanism from polymeric controlled drug release systems[25].

Swelling and degradation of polymer matrices were studied in chitosan-polycarbophil complexes and hydrxypropylmethylcellulose containing a simple mixture of chitosan and polycarbophil powders [26]. The drugs used in this study were hydrochlorothiazide and ketoprofen. According to this study, the chitosan–polycarbophil complex showed good swelling with low degradation and slower drug release compared to the other matrices containing different polymer material. The segment mobility in different polymer types affected the drug release kinetics during swelling. The power law was used to explain the drug release kinetics and different values for the exponent (n) were obtained.

Obviously, the power law has its own limitations:

The power law model still requires the model system to be in the perfect sink conditions. When a large volume of fluid surrounds a drug carrier, this assumption holds. Otherwise, the bulk concentration of drug would not be negligible.

Although different values for "n" are specified here. For different geometries, the power law still lacks the ability to model pharmaceutically relevant geometries. As mentioned before, different parameters in the power law are used for thin films, spheres and cylinders which are usually not the exact geometries used for drug delivery devices in experiments.

An insight to the underlying mechanism for drug release cannot be obtained by using the power law equation.

Only one dimensional diffusion behavior is considered in the power law model.

Other Swelling Models

Mathematical modeling of swelling controlled polymeric systems presented by Lee[27]suggested that both swelling and mass erosion could be modeled using the same type of diffusion equations. Lee [28]considered time-dependent diffusion coefficients defined as:

$$D_t = D_i + (D_\infty - D_i)[1 - \exp(-kt)] \quad (31)$$

D_i = initial drug diffusion coefficient.

D_∞= drug diffusion coefficient in the swollen polymer after long time.

The model equation was solved for a Non-reservoir type system where Higuchi' assumption fails; C_0 Cs:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\{-(n+0.5)^2\pi^2(\frac{D_\infty t}{l^2} + \frac{D_\infty}{kl^2}[1 - \exp(-kt)])\} \quad (32)$$

The analytical solution when Higuchi's assumption holds;C_0> Cs:

$$\frac{M_t}{M_\infty} = \frac{1}{(\frac{C_0}{C_s})\mathrm{erf}(\gamma)} \frac{2}{\pi^{1/2}} [\frac{D_\infty t}{l^2} - \left(1 - \frac{D_i}{D_\infty}\right)\frac{D_\infty}{kl^2}[1 - \exp(-kt)]]^{\frac{1}{2}} \quad (33)$$

where

$$\pi^{1/2}\gamma \exp(\gamma^2)\,\mathrm{erf}(\gamma) = \frac{C_s}{C_0 - C_s} \quad (34)$$

Siepmann and coworkers[29-32] developed a mathematical model to describe drug release from dissolving HPMC matrices. The "sequential layer" model considers diffusion, swelling, and polymer dissolution simultaneously. In the model, they considered transport both in the radial and the axial directions. The drug and water diffusion is based on Fick's second law for cylindrical devices with concentration dependent diffusivities:

$$= \frac{\partial}{\partial r}\left(D_k \frac{\partial C_k}{\partial r}\right) + \frac{DK}{r}\frac{\partial C_k}{\partial r} + \frac{\partial}{\partial z}\left(DK\frac{\partial C_k}{\partial z}\right) \quad (35)$$

whereC_k is the concentration of the diffusion speciesD_k is the diffusion coefficient of the diffusion species. The diffusion coefficients of water and drug are estimated according to the free volume theory:

$$D_1 = D_{1eq}\exp\left(-\beta_1\left(1 - \frac{C_1}{C_{1eq}}\right)\right) \quad (36)$$

$$D_2 = D_{2eq}\exp\left(-\beta_2\left(1 - \frac{C_2}{C_{2eq}}\right)\right) \quad (37)$$

where$D_{1eq}$and D_{2eq} are the diffusion coefficient of water and drug in the equilibrium swollen state of the system, $\beta_1$and $\beta_2$are dimensionless constants and $C_{1eq}$is the water concentration in the equilibrium-swollen state of the system.

The reptation model is used to explain polymer dissolution[33, 34]. In this model, a dissolution rate constant is considered (k_{diss}) which quantitatively characterizes a constant dissolution velocity per unit area:

$$M_{Pt} = M_{P0} - k_{diss}A_t t \quad (38)$$

whereM_{Pt} and M_{P0} are the dry matrix masses at times t=t and t=0. $A_t$is the system surface area at time t.Other models accounting for polymer dissolution have been summarized in a review article by Narasimhan[35].

Figure 8 shows the important parameters one needs to consider before developing a mathematical model for in-vitro drug release kinetics.

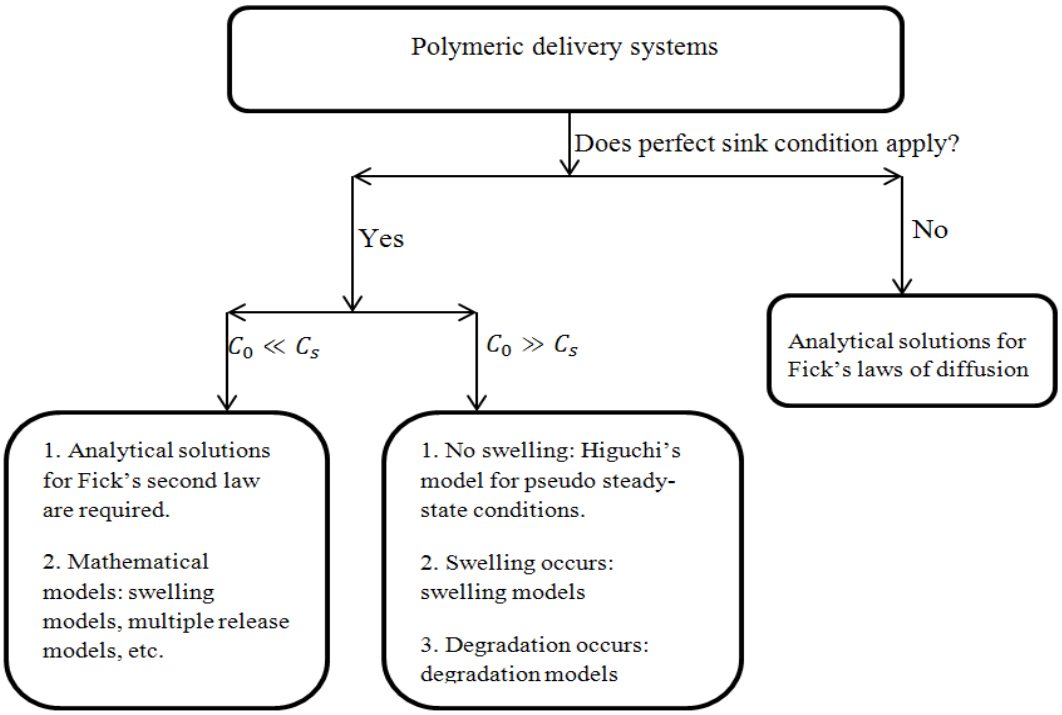

Figure 8. Important steps thatare needed to consider before using or developing mathematical models to describe in-vitro drug release kinetics.

Biodegradable Non-Reservoir Polymeric Carriers

Modeling degradation processes is obviously more challenging than all of the models described in the previous sections simply because such degradation models need to take the hydrolysis reaction into account as such reactions change the polymer structure, molecular weight and properties. The penetration of water molecules into the polymer matrices triggers hydrolysis reaction. As a result, degradation occurs which leads to the formation of monomers and oligomers that create pores or holes in the bulk structure of polymers. Depending on the type of polymer, two types of erosion behavior can happen: surface erosion and bulk erosion. If degradation occurs at a much longer time after diffusion of water molecules into the polymer matrices, all the polymer segments tend to degrade homogeneously resulting in bulk degradation. On the contrary, if polymer segments contain a considerable number of functional groups that can be hydrolyzed, the polymer will have a tendency to degrade really fast, this may cause degradation happen at a much faster rate than water diffusion resulting in surface degradation. Figure 9 illustrates both bulk and surface erosions.

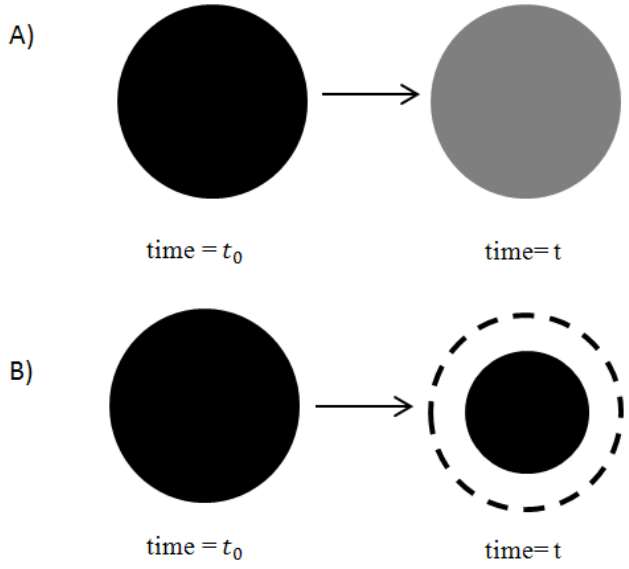

Figure 9 Illustration of bulk eroding matrix polymer (A) and surface eroding matrix polymer (B)

Models

In the following paragraphs we will introduce the major mechanistic models developed for drug release from degrading polymer matrices. In these models, the underlying mechanism of drug release is not clear. However, empirical models have been also developed to describe drug release from degrading polymer matrices based upon the assumption that the drug release process obeys zero order kinetics. Such models somewhat similar to the power law model lack the ability to give the drug release mechanisms.

Hopfenberg [36]developed an empirical model from drug release from eroding polymers by assuming that the overall release process is controlled by a single zero order process. This overall process considers a combination of dissolution, swelling, and polymer chain scission. A general mathematical equation was derived, which is valid for thin films, cylinders, and spheres:

$$\frac{M_t}{M_\infty} = 1 - [1 - \frac{K_0 t}{C_0 a}]^n \qquad (39)$$

where n = 3, 2 and 1 for spheres, cylinders and thin films, respectively. Here, *a* is the radius of the sphere or cylinder or half thickness of thin film. $C_0$is the initial drug concentration in the system. K_0 is the equilibrium rate constant which has the units of concentration per time for a zero order kinetic process. This constant depends on the solution temperature, ionic strength and surface area of the matrix. Since in this model the drug release kinetics controls the overall kinetics, this model cannot be used for bulk eroding surfaces. This model can only be applied to surface eroding systems.

During the course of degradation, the polymer molecular weight and mass change as a function of time that in turn causes the drug diffusivity as well. Therefore, in this process, the drug diffusion coefficient can no longer be considered as constant. For this purpose, equation (40) was used to determine the diffusion coefficient. In equation (40), *Mw* at a given time is calculated using equation (41).

$$D_{Mw} = D_0 + \frac{k}{Mw} \qquad (40)$$

If the degradation kinetics is described by a first order process (e.g., PLGA), *Mw* of the polymer at a given time is approximated by:

$$M_{w,t} = M_{w,0}\exp(-k_{deg}t) \qquad (41)$$

where$M_{w,0}$is the initial polymer molecular weight, $k_{deg}$is the first order degradation rate constant.

By incorporating the time dependence of molecular weight into Crank's[17]diffusion model (equation 42)and Koizumi's[37] model (equation 43), one yields the following kinetics equation:

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\left(\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{Dn^2\pi^2 t}{r^2}\right)\right) \qquad (42)$$

The above model can also be used when the drug initial concentration is smaller than its solubility concentration in the system.

For Koizumi's model:

$$Q = 4\pi a^2 \left[\sqrt{2(C_0 - C_s)C_s Dt} + \frac{4C_s}{9a}\left\{\frac{C_s}{(2C_0 - C_s)} - 3\right\}Dt\right] \quad (43)$$

where a is the radius of a spherical particle.

Equations (42) and (43) can only be used for bulk degradation cases because the degradation kinetics controls the overall kinetics. As mentioned before, surface erosion is considered when the drug diffusion controls the overall kinetics of the release process.

One assumption in the models described in the "non-biodegradable polymers" sections is that the polymer matrix loaded with drug molecules is considered to be homogeneous. When degradation occurs to the polymer matrix, the matrix will become heterogeneous in terms of the distribution of the molecular weight of the polymer chains and pores created on the surface of matrices. This obviously will affect the diffusivity of drug. If we consider other species such as water and acid being released during the course of polymer degradation, this adds complexity tothe required mathematical models. In particular, the diffusion coefficient of drug becomes a function of time and position in the matrix as well. These models are called "models of multiple release mechanisms" which were studied by Himmelstein and co-workers [38, 39].Joshi et al.[40-42] developed a model for thin film geometries to describe the drug release from surface erodible polymer matrices. Their model assumes perfect sink conditions and no changes in the total volume of the matrix. The following expression is used to describe this model:

$$\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial x}\left[D_i(x,t)\frac{\partial C_i}{\partial x}\right] + \vartheta_i \quad i = A, B, C, E \quad (44)$$

C_i and $D_i$are the concentration and the diffusivity of species i, and ϑ_i is the net sum of the degradation and synthesis of species i, and x is the space variable. In order to consider the effect of the degradation process on the diffusion coefficient, the diffusivity of all species is related to the extent of polymer hydrolysis according to the following expression:

$$D_i = D_{i,0}\exp\left[\frac{\mu(C_{D,0} - C_D)}{C_{D,0}}\right], \quad A, B, C, E \quad (45)$$

$D_{i,0}$is the diffusion coefficient of species i when the polymer is not hydrolyzed, $C_{D,0}$ and C_D are the concentration of species i at time zero and t respectively, and μ is a constant.

Charlier et al.[43]also developed a model for bulk eroding PLGA films. Assuming first-order polymer chain cleavage kinetics,

$$\frac{dM}{dt} = -kM \quad (46)$$

$$M = M_0 e^{-kt} \quad (47)$$

where$M_0$is the initial polymer molecular weight, k is the degradation rate constant.

With:

$$\frac{D}{D_0} = \frac{M_0}{M}$$

$$D = D_0 e^{-kt} \quad (49)$$

whereD_0 is the drug diffusion coefficient before degradation.

Finally, an expression for drug release is obtained:

$$Q = S\sqrt{\frac{2C_0 C_s D_0 (e^{kt} - 1)}{k}} \quad (50)$$

whereC_0 is the initial drug concentration, C_s is the drug solubility in the matrix, S is the surface area of the film exposed to the medium.

At short times, the above equation becomes Higuchi's equation:

$$Q = S\sqrt{C_0 C_s D_0 t} \quad (51)$$

In other words, at short times, drug release is diffusion based and at long times, the drug release is affected by polymer degradation.

Heller and Baker[44]developed a model that applies to bulk eroding polymers that undergo hydrolysis and are solubilized by conversion to small, water-soluble molecules. The Higuchi model was used as a basis:

$$\frac{dM_t}{dt} = \frac{A}{2}\left(\frac{2PC_0}{t}\right)^{\frac{1}{2}} \quad (52)$$

where P is the permeability of the polymer to the drug, A is the surface area for both sides of the film and $C_0$is the initial drug concentration in the polymer. According to Higuchi's model, the drug permeability was assumed to be constant but during degradation the drug permeability changes with respect to time:

$$\frac{P}{P_0} = \frac{\text{Initial number of bonds}}{\text{Number of remaining bonds}} = \frac{N}{N - Z} \quad (53)$$

The bond cleavage order was assumed to be first order as shown in the following equation:

$$\frac{dZ}{dt} = K(N - Z) \quad (54)$$

where K is the first order rate constant.

After integration and substituting back into Higuchi's equation, it yields:

$$\frac{dM_t}{dt} = \frac{A}{2}\left[\frac{2P_0 \exp(Kt)\, C_0}{t}\right]^{\frac{1}{2}} \quad (55)$$

It should be noted that factors such as polymer crystallinity, pH of the release medium, and physical size of the matrixalso affect hydrolysis reactions[45, 46].

Nano-Sized Polymeric Carriers

In general, nano-scale (10–200 nm)polymer drug carriers are in the form of micelle. And they tend to be stable (no degradation and/or dissolution in blood stream) relative to the time scale associated with the drug release process. From a modeling perspective, micelles made up of block copolymers can be modeled as non-biodegradable systems even though they are biodegradable. In fact, many studies of micellar carriers showed that drug encapsulated by micelles releases completely before the block copolymers degrades [47].

Owing to the length scale of the micelles, continuum models obviously lack the ability to describe the kinetics of drug release as the concentration of the drug in the micelle fluctuate significantly and it is not appropriate to assign a concentration profile (as what is done for continuum models) to such systems. Nevertheless, there are a few authors who have made the attempt to describe drug release from micelles using continuum models discussed before. For example, E. Khodaverdi et al.[48] have carried out an experimental in vitro release of naltrexone hydrochloride from block copolymer micelles at 37 C under perfect sink conditions. They observed that the amount of drug released is related to the square root of time. Higuchi's diffusion model was used to describe the release process. Sutton et al., [49]have applied the technique of continuum model to study the whole micelle. In particular, the authors treated the micelle as a sphere (see Figure10) and applied the Higuchi model for two time regimes: the first mathematical model, equation (58), is the Higuchi model for short time releases from the micelle (less than 75 hours) and the second model, equation (59), is the Higuchi model for long time release kinetics(more than 100 hours).

$$S\frac{dQ}{dt} = -4\pi a^2 D\frac{dc}{da} \quad (56)$$

where
S: surface area
D: diffusion constant of drug in polymer matrix.
C: concentration of drug in radial distance.
A: distance from the center of the sphere.
Assuming that the release process is pseudo-steady state, they obtained:

$$C_0(a_0^3 + 2a'^3 - 3a_0a'^2) + C_s\left(4a'^2a_0 + a_0^3 ln\frac{a_0}{a'} - a_0^3 - a_0^2a' - 2a'^3\right) = 6DC_sa_0t \quad (57)$$

whereC_s is the solubility of the drug in the permeating fluid:
a_0:radius of the spherical core of the micelle.
a':distance of moving front from the center of the core at time t.
C_0:drug loading concentration.

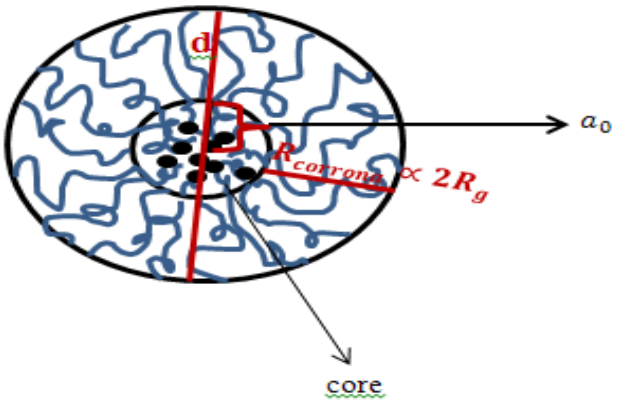

Figure10 .Schematic illustration of DOX loaded in a diblock copolymer micelle with the same corona block PEG and two different core blocks poly (D,L-lactide) or poly(e-caprolactone). d, hydrodynamic diameter of the micelle; 2Rg, PEG, thickness of corona.

The fractional drug release is given by:

$$\frac{M(t)}{M_\infty} = 1 - [(\frac{a'}{a_0})^3 + 1/2\frac{C_s}{C_0}((\frac{a'}{a_0}) + (\frac{a'}{a_0})^2 - 2\left(\frac{a'}{a_0}\right)^3)] \quad (58)$$

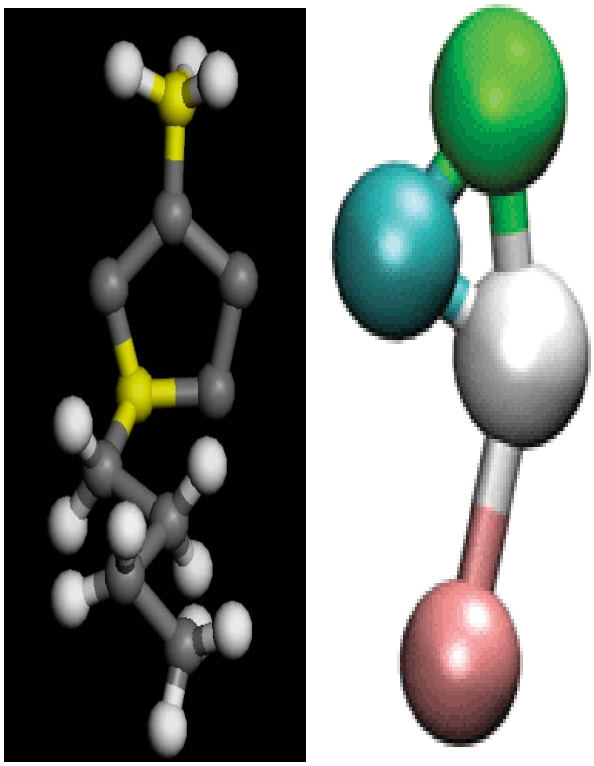

Figure 11.Schematic presentation of an "all atom" model on the left and a coarse-grained model on the right. According to the figure on the right, each sphere color represents a specific monomer inside the blocks of a block copolymer. These spheres represent larger

groups of atoms. In the "all atom" model each atom is presented with the same gray color

where

M (t): Mass of drug released at time t.

M_∞ = Mass of drug released as the time approaches infinity.

$a_0 = \frac{d}{2} - R_{corrona}$

In the above equation,a' is a function of time, t. The dynamic light scattering technique was used to measure d, and radius of gyration was used to find $R_{corrona}$. After calculating a_0 and knowing the ratio of $\frac{C_S}{C_0}$,the value of a'can beestimated by fitting the experimental data (fractions of drug released at each time) into equation (58). The diffusion coefficient was obtained by substituting the value for a'into equation (57). As mentioned earlier, the above equations are valid for short time drug release from micelles. At long times, polymer degradation happens which causes the rest of the drug molecules to be released from the micelle as well. For long time release, the following Higuchi model is used:

$$\frac{M(t)}{M(\infty)} = P\left(1 - \frac{6}{\pi^2}\exp\left(\frac{-\pi^2 Dt}{a_0^2}\right)\right) \quad (59)$$

Where *P* is the fraction of drug released at infinite time which was obtained by the extrapolation of the fraction of drugs released at the longest times of the measurements.

If one examines critically what has been done to model the release kinetics from micelles, it seems that some important aspects are not included. As mentioned, the first Higuchi model is used for kinetics of short time release from the micelle. According to the assumption of the Higuchi model (steady-state release), the concentration profile for the drug was assumed to change linearly with the distance from the solvent-polymer interface. Due to the very small size of the micelles (10 – 200 nm in diameter) one cannot easily establish a concentration profile across the micelle. Another major assumption is that the diffusion takes place under pseudo-steady state conditions. This means that the initial concentration of the drug loaded into the core of the micelle is much higher than the solubility concentration of the drug in solvent. Given the size of the micelle core which is very small, the concentration of the drug loaded in the core cannot be much higher that the drug solubility in the solvent. In other words, an excess amount of drug in the polymer core does not exist. Therefore, the pseudo-steady state assumption fails.

Finally, another assumption here is that the micelle is "spherical". However, other geometries do exist(e.g., rod-like micelles). Therefore, Higuchi's model for sphere would not be valid.

Molecular Modeling

As mentioned, use of continuum models for micelles is not suitable. In this regard, molecular dynamics (MD) simulation is probably the most suitable approach for studying the dynamics of the drug release process. The essence of MD simulation is that every atom in a molecular system is treated as a classical particle and the Newton's equation of motion is solved under certain conditions (e.g., constant temperature, constant pressure, etc.).Analysis of the resultant trajectory (e.g., positions and velocities of the atoms as a function of time) will yield thermodynamic and transport properties of interest. Since MD is a relatively mature simulation technique, there exist many excellent references on the topic [50-51]. In the context of drug release studies, MD can be used for two purposes. One is to simulate the micelle environment and calculate the corresponding flux of the drug molecules while the other is to calculate the diffusion coefficients of drug molecules diffusing in micron thick polymer films. In terms of simulating micelles at the atomistic level, it is very expensive simply because a micelle normally contains more than 100,000 atoms (it contains tens of block copolymers, tens of drug molecules and tens of thousands water molecules). Therefore, certain level of coarse graining is needed to reduce the number of atoms in the system, thereby reducing computational costs (**Figure 11**).For example,[52-54] have developed a coarse-grain (CG) model for simulating phospholipids. Phospholipids have a hydrophilic head due to negatively charged phosphate groups and maybe other groups and their tail is hydrophobic due to lipids. Therefore, they have a high tendency to aggregate and form micelles in water, somewhat similar to the behavior of block copolymers in water. According to Klein and coworkers' method, one way to simulate the micelles is to represent each monomer in a block copolymer as a single spherical unit.

By using this representation, both non-bonded and bonded interaction potentials are defined slightly different from all-atom simulations[55,56].The Harmonic potential used to describe the bonds between monomers is defined as:

$$U_{bond}(r_{ij}) = (k_b/2)(r_{ij} - r_0)^2 \quad (60)$$

wherer_0 is the equilibrium bond distance. Another bonded potential is defined as:

$$U_{bend}(\theta_{ijk}) = k_\theta[1 - \cos(\pi - \theta_{ijk})] \quad (61)$$

where$k_\theta$is adjusted until the bond angle is correct (comparable with all-atom simulation parameters).Regarding the non-bonded interaction potential, the approach is slightly different. Obviously, one cannot use the same non-bonded interaction parameters obtained from the all-atom models to model interactions between larger groups of atoms. The Lennard-Jones potential functions differ from those of various atom pairs with wider potential wells in the case of the CG method. And such CG non-bonded interaction potentials are usually tested by comparing the computed density using such potentials with the corresponding experimental values. In addition, the radial distribution function of the block copolymer obtained from the all-atom method could be used as a reference. The non-bonded parameters σ and $\in$ are adjusted to reproduce

the first peak position and height of the radial distribution function. The non-bonded interaction potential function for CG atom pairs is described as follows:

$$U(r_{ij}) = \left(\frac{15}{4}\right) \in [(\frac{\sigma}{r_{ij}})^9 - (\frac{\sigma}{r_{ij}})^6] \quad (62)$$

Water molecules present in the micelles are considered to be a spherical and symmetric site called "W" which has LJ(6-4) interactions with each other and is made of "three" water molecules:

$$U(r_{ij}) = \left(\frac{15}{4}\right) \in [(\frac{\sigma}{r_{ij}})^6 - (\frac{\sigma}{r_{ij}})^4] \quad (63)$$

To determine the diffusivity of drug molecules through the micelle, one method is to the Einstein relation. For this purpose, one needs to obtain the mean square displacement (MSD) of the center-of-mass of individual drug molecules from the MD trajectory[52]. In the long time limit of normal diffusion, where the slope of the logarithmic plot of mean square displacement versus time (Figure)becomes constant, the center of mass diffusion coefficients is calculated from the Einstein relation [57]:

$$D = \frac{1}{6}\lim_{t\to\infty}\frac{d}{dt}\langle|R(t) - R(0)|^2\rangle \quad (64)$$

where R(t) and R(0) are vectors of displacement at time t and t=0.

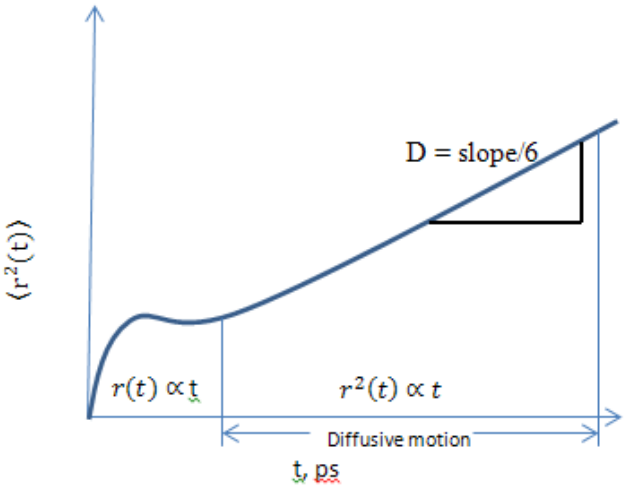

Figure 12. A schematic plot of mean square displacement against time. The slope of the plot at long times is related to the diffusion coefficient according to Einstein's relation.

Molecular dynamics simulation can also be used to calculate the drug diffusivity in micron thick polymer films. This is useful, as the drug release profile requires knowledge of the drug diffusivity. This is true for all the continuum models previously discussed. The challenge here is to obtain reliable diffusivity. The situation becomes more complicated when the polymer matrix degrades. This is because when degradation takes place, the diffusion at short times is considered to be Fickian diffusion and at long times, it is time dependent.

Recently, Berhane et al.,[58]applied the MD technique to calculate diffusion coefficient of a drug namely 5-aminosalicyclic acid in a polymer thin film and found that the resultant value ($5.7\times 10^{-6} cm^2/s$) yielded an accurate prediction of the drug release from the delivery system (root mean square error of 5%). The release profile was validated using experimental data from in vitro dissolution experiments. One noteworthy point here is that the computation only used 3 hours of computational times. In another study, the diffusion coefficient of Nifedipinein phospholipid bilayer was calculated using an all atom molecular dynamics simulation[59]. In addition to the diffusion coefficient, the authors were able to gain insight into the detailed interactions between the drug molecule and the membrane. Experimental permeability values and computed diffusion coefficients were compared in literature [60]to investigate the diffusion coefficient of Theophylline and Aspirin molecules in PVA membranes. Both experimental and simulation data showed that Aspirin exhibited lower diffusivity than Theophylline due to stronger intermolecular interactions between Aspirin and PVA membrane. Many researchers have emphasized on the advantages of using molecular dynamics simulations to avoid experimental estimation of diffusivity that is usually time-consuming and expensive. For example, to design a gel for a specific drug delivery application, Dutta et al.,[61] used molecular dynamics simulations to calculate the cross-linking density of polymers which affect swelling and release of drug molecules. The authors specifically emphasized the advantage of molecular dynamics simulation over continuum modeling and experimental methods as molecular dynamics directly addresses the intermolecular interactions between drug and polymers which are crucial for designing the gels of interest.

Summary

Continuum in vitro drug release models such as Higuchi's model, various variations of it and other complex mathematical models were discussed. When the initial drug concentration in a polymer carrier is lower than its solubility concentration, Higuchi's model tends to fail with an error of about 11% compared to the exact solution of the diffusion equations. This occurs when drug is highly soluble in the aqueous solution. Although the power law is a more comprehensive model for describing drug release kinetics, it still has its own limitations and one of them is not able to provide the release mechanism.

Improvements to the continuum models in fact have been very useful for obtaining the fractional drug release profile vs. time that is commonly done in experimental studies. These models are

normally used to investigate a proper "fit" for the experimental measurements of drug release. In all the major in vitro drug release models, knowledge of the drug diffusivity in the polymer carrier is important to determine the fractional drug release profile. In this regard, molecular dynamics simulation is a powerful tool for estimating the required diffusivity. The molecular level simulation can provide information about the underlying mechanism for drug release from polymer matrices.

If drug release occurs in a nano-sized micelle, none of the discussed continuum models could describe the kinetics of drug release accurately. For such small systems, molecular dynamics simulation is a suitable tool to study the motion of molecules under certain conditions of temperature, pressure and system size. Measurement of drug diffusivity in the micelle environment is obviously not a trivial task. However, diffusivity of drug molecules can be readily calculated using Einstein's equation.

Acknowledgements

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