

Expert Opinion

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Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems

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Importance of the field: The advancement in material design and engineering has led to the rapid development of new materials with increasing complexity and functions. Both non-degradable and degradable polymers have found wide applications in the controlled delivery field. Studies on drug release kinetics provide important information into the function of material systems. To elucidate the detailed transport mechanism and the structure-function relationship of a material system, it is critical to bridge the gap between the macroscopic data and the transport behavior at the molecular level.

Areas covered in this review: The structure and function information of selected non-degradable and degradable polymers have been collected and summarized from literature published after the 1990s. The release kinetics of selected drug compounds from various material systems is discussed in case studies. Recent progress in the mathematical models based on different transport mechanisms is highlighted.

What the reader will gain: This article aims to provide an overview of structure-function relationships of selected non-degradable and degradable polymers as drug delivery matrices.

Take home message: Understanding the structure-function relationship of the material system is key to the successful design of a delivery system for a particular application. Moreover, developing complex polymeric matrices requires more robust mathematical models to elucidate the solute transport mechanisms.

Keywords: degradable polymer, mathematical model, non-degradable polymer, release kinetics

Expert Opin. Drug Deliv. (2010) 7(4):429-444

1. Introduction

Drug release has been an important topic in the field of drug delivery for decades. With advances in material design and engineering, new materials with increasing complexity and more functions have been introduced into the development of drug delivery devices and systems. Both naturally derived and synthetic macromolecules are used extensively in controlled drug release to maximize bioefficacy, facilitate clinical applicability and improve quality of life, to name a few. 'Drug release' refers to the process in which drug solutes migrate from the initial position in the polymeric system to the polymer's outer surface and then to the release medium [1]. This seemingly simple process is affected by multiple complex factors, such as the physicochemical properties of the solutes, the structural characteristics of the material system, the release environment, and the possible interactions between these factors. A detailed summary of these driving factors is shown in Figure 1.

Article highlights.

- Release kinetics of solutes from polymeric material systems is affected by multiple factors, and the paper approaches the issue from the point of the material structure–function relationship.
- Non-degradable polymers can be fabricated into matrix- and reservoir-type devices. The solute transport from such delivery devices is mainly diffusion driven.
- Solute transport from biodegradable polymeric delivery systems is driven primarily by diffusion, erosion and swelling.
- Mathematical models provide a potential way to gain insights into the mechanisms of solute transport from polymeric material systems. However, the established models seem to be material specific, drug specific and formulation specific.
- Understanding the structure–function relationship of the material system is critical to the design and development of controlled delivery systems.

This box summarizes key points contained in the article.

Material matrix	Release medium	Drug compounds
• Composition • Structure • Swelling • Degradation	• pH • Temperature • Ionic strength • Enzymes	• Solubility • Stability • Charges • Interaction with matrix

Figure 1. Factors influencing drug release kinetics.

In general, solute diffusion, polymeric matrix swelling and material degradation are suggested to be the main driving forces for solute transport from drug containing polymeric matrices [2]. Specifically, Fick's law of diffusion provides the fundament for the description of solute transport from polymeric matrices. Fickian diffusion refers to the solute transport process in which the polymer relaxation time (t_r) is much greater than the characteristic solvent diffusion time (t_d). When $t_r \approx t_d$, the macroscopic drug release becomes anomalous or non-Fickian [3]. The purpose of mathematical modeling is to simplify the complex release process and to gain insight into the release mechanisms of a specific material system. Thus, a mathematical model focuses mainly on one or two dominant driving forces. In the literature, well-established models have been developed to describe solute transport based on each of the aforementioned mechanisms. However, disconnects exist between theories and experimental data because there are multiple driving forces involved in a single transport process. Moreover, the existing mathematical models may be insufficient in describing more complex material systems, for example, delivery systems integrating multiple material components, or stimuli-triggered delivery systems in which the interaction with complex

physiological condition is involved. In the following sections, the structure–function relationship of the representative material systems is discussed. Recent developments in release kinetics and mathematical modeling of selected non-degradable and biodegradable polymer systems are highlighted.

2. Release kinetics from non-degradable polymeric matrices

Non-degradable polymers have been widely applied in the fabrication of peroral dosage forms, transdermal films and implant devices [4]. These polymers include polyurethanes, silicone rubber, poly(ethylene vinyl acetate), to name a few. Non-degradable polymers used in drug delivery are characterized by tissue/blood compatibility, durability, robust structure and mechanical strength during *in vivo* application. Materials for long-term use, such as orthopedic and dental implants, have water-repellent surfaces to avoid degradation or erosion processes [5]. Solute transport from non-degradable polymeric systems is mainly considered as diffusion driven. Non-degradable polymers can be fabricated into 'reservoir'- and 'matrix'-type devices (Figure 2) [6]. By definition, reservoir-type devices refer to those having an inert coating material, which functions as a rate-controlling membrane. The release rate remains relatively constant and is not affected by concentration gradient, but most probably is related to the thickness and permeability of polymeric membrane. By contrast, for matrix-type devices, drug release is more likely to be Fickian diffusion driven, which is associated with concentration gradient, diffusion distance and the degree of swelling [7,8]. In this section, three representative non-degradable polymers are discussed and the release kinetics of selected solutes is reviewed.

2.1 Polyurethanes

Formed by means of step-growth polymerization, polyurethanes are characterized by urethane linkages in the backbone (Figure 3). Polyurethane copolymers of $(AB)_n$ type consist of alternating 'soft segments' and 'hard segments', and the unique physical and mechanical properties of polyurethanes are largely determined by such two-phase domain structures [9]. The phenomenon of phase separation is a result of the strong hydrogen bonding between urethane and urea-type hard segments and/or hard segment crystallization [10].

As a class of polymer for drug delivery devices, base polyurethanes are considered non-degradable owing to the long time for complete degradation, and the degree of degradation is negligible relative to the entire release timescale. Base polyurethanes have been demonstrated to be biocompatible and stable *in vivo* and therefore have been used in biomedical devices such as insulators for cardiac pacing leads, ventricular assist devices, vascular prostheses, drug delivery implants, tissue adhesives, skin wound dressings, and so on [11–14]. For example, Sureskin® II Silver (EuroMed, NY) is an FDA-approved dressing for wounds consisting of polyurethane foam that delivers

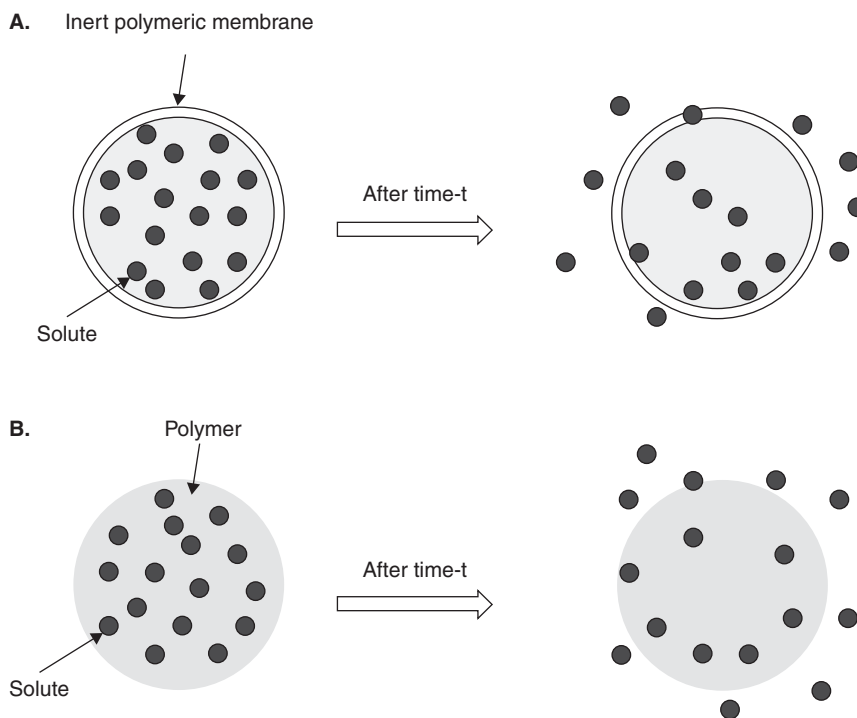


Figure 2. Schematic representation of (A) reservoir- and (B) matrix-type controlled drug delivery devices.

Adapted with permission from [6].

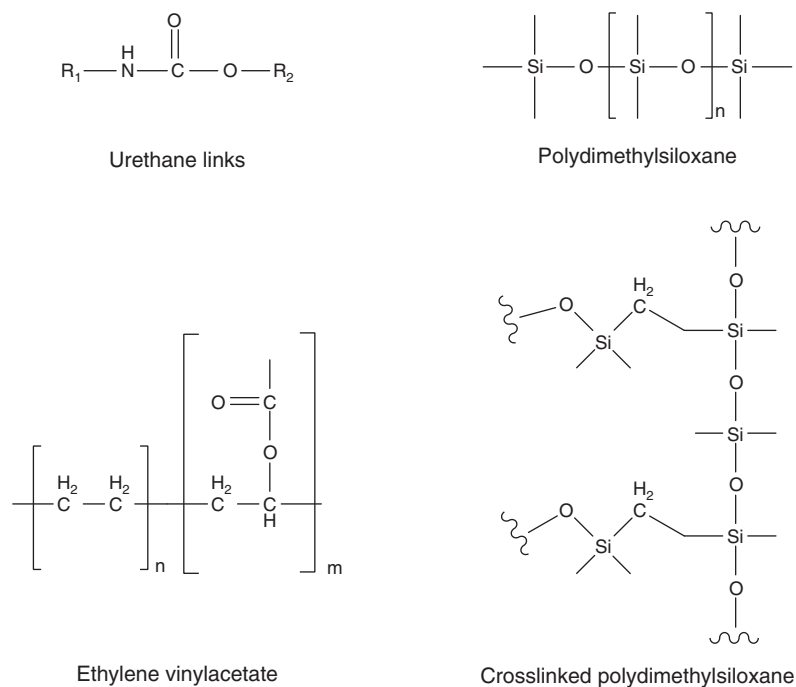


Figure 3. Structures of representative non-degradable pharmaceutically related polymer.

silver-containing agents for treating dermal ulcers, postoperative wounds, superficial wounds and abrasions [15]. Drug loading into polyurethane-based devices can be conducted either before polymerization or by means of equilibrium absorption after polymerization. For polymerization in the presence of drug molecules, mild conditions are generally used to ensure drug stability, such as relatively low temperature and the addition of stabilizing excipients such as heparin to protect protein drugs [16]. Despite the different geometries of the devices, a near linear release profile has been observed after the initial burst release, and diffusion has been suggested to be the main driving force (Table 1). Thus, polyurethanes have been widely used in medical implants and other devices *in vivo* because of the favorable physical mechanical properties and biocompatibility. However, the 'non-degradability' also seems to limit the application of polyurethanes in controlled drug delivery, because second interventions are sometimes necessary to remove the device after the treatment. Recently, biodegradable polyurethane derivatives have become the focus of several studies in the field of controlled drug delivery [17-19].

2.2 Polydimethylsiloxane

Polydimethylsiloxane (PDMS) is different from most other biomedical polymers in that the backbone consists of inorganic Si-O-Si units instead of hydrocarbon chains (Figure 3). Polysiloxanes are very flexible owing to large bond angles and bond lengths when compared with those found in more basic polymers such as polyethylene [20]. In the development of three-dimensional structures, vinyl-terminated polydimethylsiloxanes are crosslinked by branched polydimethylsiloxanes with reactive SiH- groups under the catalysis of platinum [21]. Owing to the hydrophobic nature of crosslinked PDMS (Figure 3), hydrophobic drugs are commonly loaded in PDMS-based delivery devices to achieve prolonged release profiles. As shown in Table 1, drug release from PDMS-based delivery devices can be sustained to over a month. Similar to polyurethanes, PDMS can also be fabricated into reservoir- and matrix-type devices (Figure 2). For matrix-type devices, drug release is mainly controlled by diffusion, as detailed in Table 1, and the cumulative release is linear with respect to the square root of time ($t^{1/2}$). As for crosslinked PDMS network, the network density is described by the average molecular mass M_n (number average) of the crosslinked units [21]. In addition to crosslink density, water uptake is another important impact factor that may affect the degree of swelling and solute transport within the PDMS network. Riggs *et al.* studied the water uptake kinetics of silicone elastomers using ^3He ion-beam analysis and their study demonstrated that water uptake was initially linear with time and then linear with $t^{1/2}$, which indicated a Fickian profile [22]. Malcolm *et al.* investigated the metronidazole release kinetics from crosslinked silicone elastomers, and all of the silicone systems evaluated were shown to obey simple matrix-type $t^{1/2}$ kinetics owing to the fact that most of the drug within the systems existed in the solid-state [23].

Thus, there seems to be a correlation between water uptake and release kinetics for the matrix-type PDMS devices.

In addition, a zero-order release pattern can be achieved by fabricating PDMS into reservoir-type devices. For example, Maeda *et al.* designed a covered-rod formulation with a silicone inner matrix containing active ingredient and a silicone outer layer functioning as the rate-controlling membrane. In contrast to the typical first-order release profile with matrix-type devices, near zero-order release of ivermectin (IVM) from a PDMS reservoir-type device was observed. With the addition of poly (ethylene glycol) (PEG4000) in the matrix, a fourfold increase in IVM release velocity was observed while the zero-order profile was maintained [24], which was mainly a result of the effect of PEG as a solubility-enhancing agent. Studies on PDMS-based intravaginal rings (reservoir-type, IVR) for the delivery of a hydrophobic drug TMC120 also displayed a near zero-order release profile with a short initial burst phase [25,26]. The initial burst was attributed to the enhanced dissolution of the active drugs within the core of the ring, and the incorporation of hydrophilic lactose greatly decreased the burst effect while increasing the release rate in a concentration-dependent manner [25].

2.3 Poly(ethylene vinyl acetate)

Poly(ethylene vinyl acetate) (PEVA) is the copolymer of ethylene and vinyl acetate (VA) (Figure 1). In biomedical engineering, PEVA has been used in the development of medical and controlled drug delivery devices by using casting and freeze-drying methods. PEVA-based devices are designed to release drug compounds slowly over a relatively long period of time [27]. Subcutaneous implantation of ethylene-vinyl acetate copolymer films in Sprague-Dawley rats confirmed that the base polymer did not provoke any inflammatory responses and the polymer had good tissue compatibility [28]. Moreover, PEVA is readily available with a variety of VA contents, ranging from 0 to 40%. The permeability of these copolymer films changes substantially with varying VA content and thus it is possible to tailor the release rate to a desired value by slightly changing the membrane compositions [29]. An increase in crystallinity would also reduce the diffusivity of polymer [30]. Similarly, PEVA is also a diffusion-controlled polymer, and it has been formulated into either microporous films to achieve zero-order release or matrix-type devices to sustain drug release over time (Table 1).

3. Biodegradable polymeric matrices

3.1 Overview

Biodegradable polymers are widely used in the development of controlled delivery systems that can dramatically improve patient compliance and reduce side effects through extended dosing and targeting [31]. Several pharmaceutical products based on biodegradable delivery systems have been approved by the FDA, including hormones, antitumor drugs and antibiotics [32]. In general, biodegradable polymers contain labile bonds such as ester, amide and anhydride bonds that are prone to

Table 1. Summary of release kinetics and transport mechanisms of non-degradable polymer-based delivery devices.

Type of material	Type of device	Loaded drug	Burst release	Release kinetics	Transport mechanism	Ref.
Segmented PU (Cardiomat 610)	Drug-eluting stent	1,3-Dipropyl-8-cyclopentyl xanthine	1 d	Near linear release (~ 20 d)	Non-Fickian diffusion	[81]
Elast-Eon™ (AorTech, Australia)	Drug-eluting stent	Dexamethasone acetate	w/	Biphasic pattern	Fickian diffusion	[82]
Polyurethane (Walopor®; Epurex Films, Germany)	Disk-shaped matrices	Flucloxacillin-Na Fosfomycin	1 d	Near linear (2 ~ 5 d)	Matrix-controlled	[83]
Poly(urea-urethane)	Microcapsule	Gentamicin-base Auramine (Oil-soluble dye)	w/o	Near linear (~ 20 min)	Non-Fickian diffusion	[84]
PEG-modified polyurethane	Dermal patch	Thiamazole, diclofenac sodium, ibuprofen	12 h	Biphasic pattern (~ 48 h)	–	[85]
PDMS	Rod (matrix versus reservoir)	Ivermectin	w/o	Matrix: first order, 50 d; Reservoir: zero order, 84 d	Matrix: diffusion	[24]
PDMS	Intravaginal ring (reservoir)	TMC120	1 – 2 d	Biphasic; near zero-order release for 30 d	Reservoir: case II transport	[25]
PDMS	Intravaginal ring (core-type)	TMC120	w/o	Zero order, 71 d	Case II transport	[26]
PDMS	Strip (10–20 mm)	Metronidazole	w/	Higuchi (linear versus $t^{1/2}$)	Fickian diffusion	[23]
PEVA (VA content, 40%)	Membrane	Quinupramine	w/	Higuchi (linear versus $t^{1/2}$)	Fickian diffusion	[86]
PEVA	Thin film	Acyclovir	w/o	Near zero order (~ 8 d)	Non-Fickian diffusion	[87]
PEVA	Drug-eluting stent coating	Chlorhexidine diacetate	w/	Biphasic pattern (~ 20 d)	Fickian diffusion	[88]
PEVA	Disk-shape film	5-Fluorouracil	w/	Near zero order (~ 7 d)	Non-Fickian diffusion	[89]
PEVA (VA content, 40%)	Membrane	Furosemide	w/	Higuchi (linear versus $t^{1/2}$)	Fickian diffusion	[90]
PEVA (VA content, 40%)	Microcapsule	Insulin	w/	Biphasic pattern (~ 12 h)	Fickian diffusion	[91]
Dextran sulfate	Hydrogel Tablet	Vitamin E Difunisal	~ 3 h w/o	Biphasic Zero order for non-soluble β -CD First order for soluble β -CD	Swelling Non-Fickian diffusion	[92] [93]

w/: With; w/o: Without.

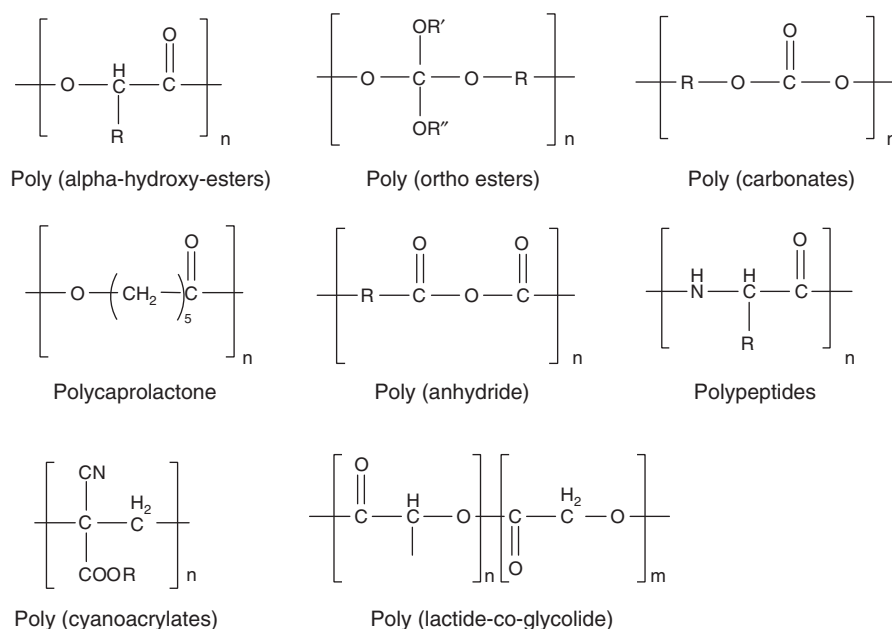


Figure 4. Representative functional groups of biodegradable polymers.

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hydrolysis or enzymatic degradation (Figure 4). Surface degradation and bulk degradation are two typical modes of degradation. In a surface-degrading polymer, degradation is confined to the outer surface of the device [33,34]. In a bulk-degrading polymer, however, degradation occurs homogeneously throughout the material [35]. Water is an important factor during hydrolysis and thus water intrusion into the device is of significant importance for the study of degradation kinetics as well as release kinetics. The degradation of semicrystalline polymers occurs in two stages: i) the first stage consists of water infusion into the amorphous regions with random hydrolytic scission of labile bonds, such as ester bonds; and ii) the second stage starts when most of the amorphous regions are degraded [36]. As degradation results in the scission of polymer chain, the change in the average molecular mass of the polymer could be used to quantify the degradation process over time. Using gel permeation chromatography (GPC), the degradation process is usually characterized by plotting the average molecular mass of the degraded material versus time. The following two equations are widely used to describe the degradation kinetics:

$$\text{Zero - order: } M_{r(t)} = M_{r0} - k_{\text{deg}} t \quad (1)$$

$$\text{Pseudo - first order: } M_{r(t)} = M_{r0} \exp(-k_{\text{deg}} t) \quad (2)$$

where $M_{r(t)}$ and M_{r0} are the average polymer molecular mass at time t and time zero. k_{deg} denotes the apparent degradation rate constant of the polymer. Equation 2 was applied successfully to the degradation data of PLGA microparticles [37,38].

Polymer degradation has been defined by Siepmann and Göpferich as the chain scission process by which polymer

chains are cleaved into oligomers and monomers, whereas bioerosion refers to the loss of material from bulk or surface in contact with a biological system [39]. By virtue of these definitions, the two concepts are not mutually exclusive but are interrelated. In this section, representative polymers that undergo a chain scission process and/or mass loss are discussed.

3.2 Polyesters

Polyester is a class of polymers characterized by ester linkages in the backbone, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactide-co-glycolide) (PLGA), and so on. PLGA is one of the most commonly used biodegradable polymers in developing particulate drug delivery systems [40]. PLGA is synthesized by ring-opening copolymerization of two different monomers, the cyclic dimers (1,4-dioxane-2,5-diones) of glycolic acid and lactic acid [41]. PLGA degrades by means of hydrolysis of its ester linkages in the presence of water. Owing to the hydrophobic nature of PLGA, PLGA nano/microparticles with core-shell structures are prepared through various emulsification processes and hydrophilic drugs could be encapsulated in the hydrophilic core of the particles [42], whereas hydrophobic drugs tend to distribute in the hydrophobic shell [43]. The typical release profile for PLGA particulate delivery systems is the initial burst phase followed by a near-zero-order phase [44]. Various intramuscular or subcutaneous controlled delivery systems in the form of implants or microparticles have been developed using biodegradable polyesters such as PLA and PLGA [45]. An *in vitro* release study of diltiazem hydrochloride and buserelin acetate from *in situ* forming delivery systems (ISM, PLA or PLGA solution

Table 2. Summary of release kinetics and transport mechanisms of degradable polymer-based delivery devices.

Type of material	Type of device	Loaded drug	Burst release	Release kinetics	Transport mechanism	Ref.
PLGA/PLA	Microparticle	Diltiazem hydrochloride	2 h	Triphasic pattern	Diffusion and erosion	[46]
PLGA	Nanoparticle	Estradiol	w/o	Zero order up to 31 ~ 54 d	Diffusion-cum-degradation	[43]
PLGA	Microcapsule	Insulin	20%, 24 h	Triphasic pattern	Diffusion and erosion	[50]
p(FAD-SA) 50:50	Implantable disk	Cefazolin sodium	w/o	100%, 14 d	Diffusion	[51]
		Bupivacaine free base	w/o	90%, 35 d	Diffusion and degradation	
		Taxol	w/o	15%, 77d	Degradation	
PEG hydrogel with degradable crosslinks	Disk	Bovine serum albumin	w/o	Zero order in the presence of human neutrophil elastase	Triggered degradation	[54]
Poly(ortho ester amide) copolymer	NA	FITC-dextran	w/o	Near zero order	Erosion	[55]
HPMC	Tablet	Adinazolam mesylate	w/	Near zero order, 10 h	Swelling and dissolution	[59]

NA: Not available; w/: With; w/o: Without.

dispersed in an external oil phase) displayed a triphasic release pattern (Table 2) [46]. The initial burst was most probably due to the rapid release of surface-associated drug molecules, the second phase was probably due to material degradation via chain scission, and the third phase was mainly the result of polymer erosion, which led to the loss of bulk materials [47]. Although PLA and PLGA are bulk erosion-type biodegradable materials, studies showed that release kinetics of selected solutes from such biodegradable polymeric matrices are not simply driven by degradation [48,49]. In the early stage, the concentration gradient and the shape of the device seem to have a more profound impact on the release rate, whereas in the later stage, degradation becomes the dominant driving force and thus the release profile corresponded to the degradation kinetics of the material [49]. In addition to the property and the structure of the material, the physicochemical properties of the drug compounds also influence the release behavior. For example, the *in vitro* release of a hydrophobic drug, estradiol, from PLGA nanoparticles displayed zero-order release for 31 – 54 days, and the linear release pattern was observed with all formulation groups, which has been found to occur through a diffusion-cum-degradation-mediated process (Table 2) [43]. In comparison, the release of a hydrophilic drug, insulin, from PLGA microcapsules displayed a triphasic pattern with ~ 20% of the insulin released within 24 h, 40% released after 10 days and ~ 50% after 30 days (Table 2) [50].

3.3 Polyanhydrides

Polyanhydrides are a group of surface erosion-dominated biodegradable materials. A release study on a polyanhydride (poly(fatty acid dimer-sebacic acid), p(FAD-SA), 50:50 w/w)-based implant for local drug delivery revealed that the release kinetics was related to the drug solubility and the intrinsic dissolution rate [51]. Three model drugs of different aqueous solubilities, which included cefazolin sodium (350 mg/ml), bupivacaine free base (0.56 – 0.7 mg/ml) and taxol (0.042 mg/ml), have been investigated. Cefazolin sodium achieved 100% release in 14 days whereas 90% bupivacaine free base was released in 35 days. However, only 15% taxol was released in 77 days (Table 2) [51]. Therefore, the hydrophilic and hydrophobic nature of the drugs may potentially affect release rate and cumulative release percentage from the surface erosion-type devices. In the case of taxol, the degradation of polyanhydride might be the main driving force for taxol release, whereas for cefazolin sodium, the concentration gradient between the devices and the release medium would be dominant for solute transport [51]. Manoharan and Singh investigated poly-1,3-bis-(*p*-carboxyphenoxy)propane-*co*-sebacic acid (p(CPP:SA)) microspheres for controlled delivery of basal insulin. Insulin was released within 3 days from SA-only microspheres, whereas a significant amount of insulin was not released from CPP-only microspheres over a month owing to the slow degradation in CPP polymers. By tailoring the CPP:SA ratios of the copolymer, initial burst could be reduced and insulin release

was prolonged over a month with 67% cumulative release at day 35 [52].

3.4 Stimuli-triggered biodegradable polymer

Environmentally sensitive polymeric delivery systems are designed to achieve targeted delivery and controlled release *in vivo* on specific stimuli, such as pH, ionic strength, enzyme substrate, magnetic, thermal, electrical, ultrasound, and so on [53]. Drug release from pH- and enzyme-sensitive polymeric delivery systems is mainly attributed to stimuli-triggered degradation. Aimetti and co-workers developed a poly(ethylene glycol) hydrogel platform with human neutrophil elastase-sensitive peptide crosslinks. The crosslinked hydrogel was formed using thiolene photopolymerization, rendering the gel degradable at sites of inflammation. A zero-order release of bovine serum albumin (BSA) in the presence of human neutrophil elastase was observed, and the release was arrested in the absence of human neutrophil elastase, indicating enzyme-triggered degradation was the driving force for BSA release from this gel matrix (Table 2) [54]. Another example is poly(ortho ester amides) copolymer, the degradation of which is triggered by acids. Both the mass loss kinetics of poly(ortho ester amides) in physiological aqueous buffers and the release of fluorescently labeled dextran followed the near zero-order pattern, suggesting the release was driven predominantly by surface-restricted polymer erosion (Table 2). Moreover, the rates of polymer erosion and drug release were much faster at pH 5.0 than at pH 7.4 [55].

3.5 Polymer for dissolution-controlled drug delivery

Dissolution of polymers in solvents, an important phenomenon in polymer science, has been applied extensively in areas such as microlithography, controlled drug release, membrane science, and so on [56]. In general, polymer dissolution involves two transport processes, that is, solvent diffusion and chain disentanglement [57]. Although polymer dissolution does not result in the scission of polymer chains, it does lead to the loss of bulk material. One example is polysaccharides, a class of hydrophilic macromolecules that are widely used in pharmaceutical industry owing to low toxicity, biocompatibility, availability and abundance. Polysaccharides such as hydroxypropyl methylcellulose (HPMC), cyclodextrin, dextran and gellan gum remain stable under physiological pH and temperature, but will undergo hydrolysis at extreme pH and temperatures. More importantly, polysaccharides undergo dissolution in the aqueous medium owing to the solvent penetration effect, swelling, and polymer chain disentanglement and relaxation [58]. Thus, solute transport from polysaccharides-based material systems could be driven by diffusion and/or dissolution. For example, the fractional release of adinazolam mesylate from tablets consisting of HPMC matrices corresponded well with the fractional release of HPMC, indicating drug release is driven primarily by dissolution (Table 2) [59].

4. Mathematical models for drug release kinetics from polymeric systems

Mathematical modeling of drug release kinetics provides a basis for the study of mass transport mechanisms that are involved in the control of drug release [60]. There have been several nicely written reviews on mathematical modeling for bioerodible polymeric delivery systems [39], dissolution-controlled drug delivery systems [56], microsphere delivery systems [2] and hydrogel networks [61]. In general, diffusion, erosion and degradation are the most important mechanisms for solute transport from polymeric matrices. Mathematical models based on each aforementioned mechanism are summarized here. In addition, models for materials with more complex compositions and structures are also discussed.

4.1 Empirical models

Several commonly used power law equations for modeling release kinetics are summarized (Table 3). These models are easy to use and the established empirical rules may help explain transport mechanism(s). However, these models do not provide further insights into a more complex transport mechanism. Furthermore, these models might fail whenever there is a need for taking into account specific physicochemical processes [39]. For example, Ritger-Peppas and Peppas-Sahlin's equations (see Table 3) have been applied to describe the release of sodium salicylate from HPMC tablets, indicating a non-Fickian drug release mechanism. The study also revealed that polymer erosion, swelling and dissolution were all involved in the release process and the authors suggested that the conclusion of a non-Fickian drug release mechanism, simply based on the diffusional exponent, n , of the Peppas models (see Table 3), can be misleading [62].

4.2 Diffusion-controlled models

Derived from Fick's second law of diffusion, drug release in the case of slab-like devices is described by the following equation [62]:

$$\frac{M_t}{M_0} = 4 \left(\frac{Dt}{\pi h^2} \right)^{1/2} \quad (3)$$

where M_t is the amount of drug released at time t , M_0 is the total mass of drug loaded into the device, D is the diffusion coefficient of the drug within the polymer matrix, π is 3.14, and h is the thickness of the device. This is an early-time approximation that holds for the release of the first 60% of cumulative release, that is, $0 \leq M_t/M_0 \leq 0.6$.

The late-time approximation, which holds for the final portion of the drug release, that is, $0.4 \leq M_t/M_0 \leq 1.0$, is described by the following equation [63]:

$$\frac{M_t}{M_0} = 1 - \left(\frac{8}{\pi^2} \right) \exp \left[\frac{-\pi^2 Dt}{h^2} \right] \quad (4)$$

The assumption for the application of the above equations is the dimension and physical properties of the material matrices

Table 3. Empirical mathematical models for drug release kinetics.

Model	Expression	Application	Ref.
Higuchi	$\frac{M_t}{M_\infty} = kt^{\frac{1}{2}}$	Fickian diffusion	[94]
Ritger-Peppas	$\frac{M_t}{M_\infty} = k_1 t^n$	$n = 1$, case II transport; $n = 0.5$, Fickian diffusion; $0.5 < n < 1$, non-Fickian diffusion	[95]
Peppas-Sahlin	$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}$	Non-Fickian diffusion	[96]
Alfrey	$\frac{M_t}{M_\infty} = k_1 t + k_2 t^{\frac{1}{2}}$	Non-Fickian diffusion (sigmoid)	[97]
Zero order	$\frac{M_t}{M_\infty} = k_d t$	Case II transport	[66]

do not change during the release process, that is, there is no degradation or mass loss of the bulk materials. To predict the release profile, the diffusion coefficient of the solute within the polymer matrix (D) should be available, which could be measured by nuclear magnetic resonance and fluorescence correlation spectroscopy [64]. Furthermore, Equations 3 and 4 have also been used to predict the diffusional coefficients of functional proteins within the self-assembling peptide nanofiber hydrogel scaffold [65] and the diffusional coefficients of theophylline in the poly(acrylic acid-*g*-ethylene glycol) hydrogels [66]. The models achieved good correlations with experimental data in both studies, indicating the transport mechanism was primarily Fickian diffusion.

4.3 Degradation-based models

4.3.1 Polymer dissolution-based model

Polymer dissolution refers to the process where polymer begins to release its contents to the surrounding fluid when in the presence of a thermodynamically compatible solvent [56]. Drug release from such polymeric matrices can be controlled by solute diffusion and/or polymer dissolution. Narasimhan and Peppas developed a model for polymer dissolution based on the molecular mechanism. The model describes solute transport in a one-dimensional system, such as a film, slab, disk or tablet. In Equation 5, $(S - R)$ is defined as the gel layer thickness and the variation of the gel layer thickness $(S - R)$ with time was established [67]:

$$(5)$$

$$-\frac{(S-R)}{B} - \frac{A}{B^2} \ln \left[1 - \frac{B}{A} (S-R) \right] = t$$

In Equation 5, parameters A and B are defined as:

$$(6)$$

$$A = D(v_{1,\text{eq}} - v_1^*) \left(\frac{v_{1,\text{eq}}}{v_{1,\text{eq}} + v_{d,\text{eq}}} + \frac{1}{v_1^* + v_d^*} \right) + D_d(v_d^* - v_{d,\text{eq}}) \cdot$$

$$\left(\frac{v_{d,\text{eq}}}{v_{1,\text{eq}} + v_{d,\text{eq}}} + \frac{1}{v_1^* + v_d^*} \right)$$

$$(7)$$

$$B = \frac{k_d}{v_{1,\text{eq}} + v_{d,\text{eq}}}$$

An expression for the cumulative release was derived as:

$$(8)$$

$$\frac{M_d}{M_{d,\infty}} = \frac{(v_{d,\text{eq}} + v_d^*)}{2l} \cdot (\sqrt{2At} + Bt)$$

l is the half-thickness of the polymer, D is the diffusion coefficient of the solvent and D_d is the diffusion coefficient of the drug. v_1^* and v_d^* are characteristic concentrations of solvent and drug, respectively. $v_{1,\text{eq}}$ and $v_{d,\text{eq}}$ are equilibrium concentrations of solvent and drug. k_d is the disentanglement rate of the polymer chains, which could be calculated using reptation theory [68]. To investigate the effect of various parameters on the drug release behavior, the normalized drug released as a function of time was simulated using drugs of different molecular sizes. An increase of drug release was observed with a higher drug diffusion coefficient. Also, case II behavior was observed as α ($\alpha = A/B$) approaching zero [67]. The model successfully captures Fickian and case II-type behavior and the transition state in between. Both release patterns have been well characterized using this model, for example, cimetidine hydrochloride release from PVA tablet, a Fickian diffusion-driven process and sodium diclofenac release from a PVA tablet, a zero-order release pattern [69]. The model was demonstrated to be valid owing to the good agreement between experimental data and the equation.

4.3.2 Erosion-based model

Hopfenberg's model can be applied to surface-eroding polymer matrices where a zero-order surface detachment of the drug is the rate-limiting release step. The equation is valid for spheres, cylinders and slabs:

$$(9)$$

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{c_0 a} \right)^n$$

M_t and M are the cumulative amounts of drug released at time t and at infinite time; k_0 refers to the erosion rate constant; c_0 denotes the initial drug concentration within the matrix; a is the radius of a cylinder or sphere or the half-thickness of a slab; and n is a 'shape factor' representing spherical ($n = 3$), cylindrical ($n = 2$) or slab geometry ($n = 1$) [70]. Karasulu and co-workers' study showed the predicted values of cylindrical tablet were not in good accordance with the observed values when using Equation 9 [71].

Following the analysis, Katzhendler *et al.* developed a general mathematical model for drug release from an erodible matrix [72]. The model takes into account radial and axial erosion

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_a t}{c_0 a_0}\right)^2 \left(1 - \frac{2k_b t}{c_0 b_0}\right) \quad (10)$$

where k_a is the radial erosion rate constant, k_b is the axial erosion rate constant and a_0 and b_0 are the tablets' initial radius and thickness, respectively. When $k_a \approx k_b$, the release profiles of theophylline from cylindrical tablet could be described well by Equation 10 [71].

Rothstein *et al.* developed a unified model for both surface- and bulk-eroding materials. This model combines diffusion-reaction equations, taking into account the system's hydration kinetics, dissolution and pore formation to compute drug release. Equation 11 describes the presence of water within the polymer matrix.

$$\frac{\partial C_w}{\partial t} = \nabla(D_w \nabla C_w) - k C_w M_r \quad (11)$$

where C_w is the time-dependent concentration of water, D_w is the diffusivity of water in the polymer matrix, k is the degradation rate constant and M_r is the polymer molecular mass.

The kinetics of hydrolysis can be described by following equation.

$$\frac{\partial M_r}{\partial t} = -K C_w M_r \quad (12)$$

The dissolution of the drug can be calculated with a second-order rate expression.

$$\frac{\partial C_s}{\partial t} = -k_{dis} C_{sn} C_{An} C_{Wn} \quad (13)$$

where k_{dis} is the intrinsic dissolution rate constant C_{sn} is the normalized concentration of solid drug in the polymer matrix, C_{An} is the difference between the aqueous agent concentration and its maximum solubility (C_{Amx}) and C_{Wn} is the normalized concentration of water. The position (r) and time (t) dependence in a polymer matrix can be calculated from Fick's second law and the dissolution rate expression

$$\frac{\partial C_A}{\partial t} = \nabla(D_{eff} \nabla C_A) + K_{dis} C_{sn} C_{An} C_{Wn} \quad (14)$$

where D_{eff} is an effective diffusivity term. Integrating the total normalized concentration of agent in the matrix over all space

yields the cumulative fraction of agent remaining in the matrix at each point in time (Equation 15)

$$P(t) = V^{-1} \int \frac{C_s + C_A}{C_{s0}} dv \quad (15)$$

The cumulative fraction of drug release $R(t)$, is simply (Equation 16)

$$R(t) = 1 - P(t) \quad (16)$$

The D_{eff} term depends on the matrix porosity (ϵ) and the diffusivity of the agent through the porous matrix (D_A); ($D_{eff} = D_A \cdot \epsilon$). The time- and space-dependent matrix porosity follows a cumulative normal distribution function based on a molecular mass or degradation rate distribution of the given polymer (Equation 17).

$$\epsilon = 1 - \frac{1}{2} \left[\operatorname{erf} \left(\frac{M_r - M_{r,t}}{\sqrt{2\sigma^2}} \right) + 1 \right] \quad (17)$$

The variance (σ^2) is based on the crystallinity of the polymer matrix and corresponding distribution of degradation rates. The molecular mass of the polymer matrix during release ($M_{r,t}$) has been previously correlated to the molecular mass of the agent for common biodegradable systems [73]. The model has been applied successfully to the dye release data from poly(orthoester) based bulk-eroding and surface eroding matrices (Figure 5).

4.4 Mathematical models for multicomponent systems

Lao and co-workers developed a combined mathematical model for poly(ϵ -caprolactone) (PCL) and PLGA polymer blends. The model development was conducted through the modeling of release kinetics of each material component, respectively. PCL is the type of slowly degrading polymer that takes >2 years to be completely degraded under physiological conditions. Equation 18 was developed for neat PCL film, in which the first term represents the burst phase and the second term describes the diffusion-controlled release. It is also important to note that there is no degradation term in Equation 12 for pure PCL films. The model developed for PLGA took into consideration all three steps, that is, burst release, diffusion and degradation (Equation 19) [74].

$$\left\{ \frac{M_t}{M_\infty} \right\}_{PCL} = \varphi_{b,PCL} [1 - \exp(-k_{b,PCL} t)] + \quad (18)$$

$$\varphi_{d,PCL} \left[1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp \left(\frac{-D_{PCL} (2n+1)^2 \pi^2 (t - t_{b,PCL})}{4l^2} \right) \right] \quad (19)$$

$$\left\{ \frac{M_t}{M_\infty} \right\}_{PLGA} = \varphi_{b,PLGA} [1 - \exp(-k_{b,PLGA} t)] +$$

$$\varphi_{r,PLGA} \{ \exp[k_{r,PLGA} (t - t_{b,PLGA})] - 1 \} +$$

$$\varphi_{d,PLGA} \left[1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp \left(\frac{-D_{PCL} (2n+1)^2 \pi^2 (t - t_{b,PCL})}{4l^2} \right) \right]$$

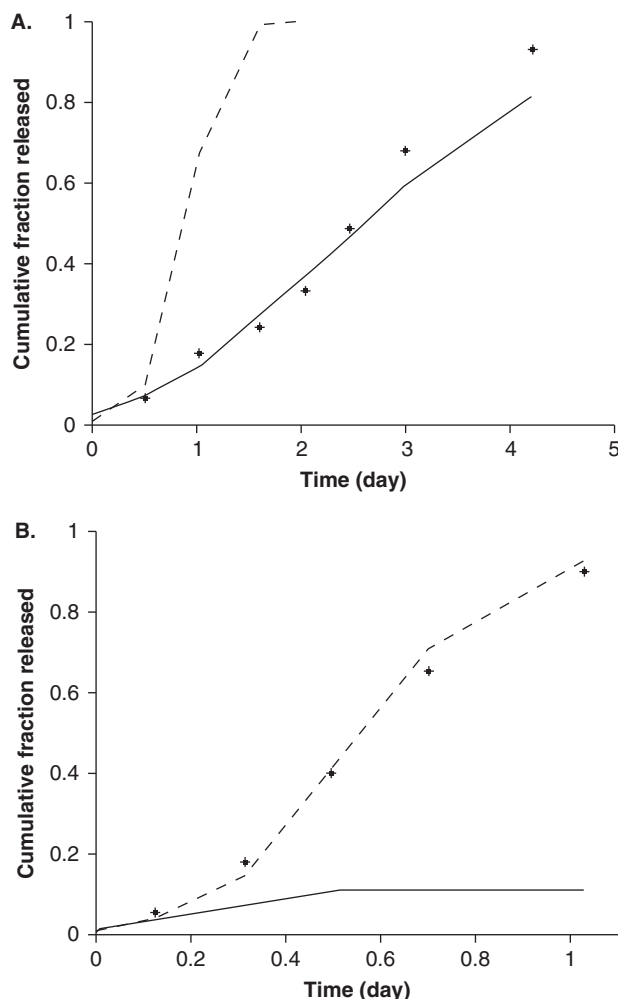


Figure 5. Predictions of release from (A) bulk-eroding and (B) surface-eroding poly(orthoester) matrices. Predictions have been made for the experimental data for dye release asterisks, while accounting for the hydrolysis of the anhydride excipient, with the complete model (unbroken line, (A) SSE = 0.0237 and (B) SSE = 1.1539) and the simplified version, which assumes bulk erosion (dashed line, (A) SSE = 1.0077 and (B) SSE = 0.0061). For calculations in both A and B, the following parameters were used: $M_{r,0} = 28.2$ kDa, $M_{r,r} = 10.2$ kDa, $R_p = 5$ mm and $L = 1.4$ mm. Based on the different anhydride contents, $D_A = 1.44 \times 10^{-12}$ m²/s in A and $D_A = 9.75 \times 10^{-12}$ m²/s in B.

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fraction of release through diffusion from PCL phase, defined as $(1 - \Phi_{b,PCL})$. $\Phi_{b,PLGA}$ is defined as the fraction of burst release from PLGA phase, $\Phi_{d,PLGA}$ is the fraction of release through diffusion from PLGA phase, defined as $(1 - \Phi_{b,PLGA})$, and $\Phi_{r,PLGA}$ is the relaxation release coefficient of PLGA phase.)

Although not discussed in detail, drug release profile is related to the forms of delivery devices, for example sphere, disk, film, cylinder, and so on. The aforementioned mathematical models are applicable to a certain type of device. Table 4 summarizes the applicability and common assumptions for the previously discussed mathematical models. To sum up, no universally applicable mathematical models are available for release kinetics from non-degradable or degradable polymer systems owing to the multiple factors involved during the process of solute transport. The established models seem to be material specific, drug specific and formulation specific. Therefore, the applicability of a specific model should be carefully reviewed before it is applied to experimental data, such as the structural characteristics of materials, physicochemical properties of model drugs, dimensions and geometry of the delivery devices, and any assumptions or limiting cases related to the model.

5. Expert opinion

In the design and development of a therapeutic agent, *in vitro* release study has been considered to be one of the key standards to evaluate and optimize the formulation. The *in vitro* release results reveal the structure–function relationship of the material matrices, contribute to the tailoring of material for optimal controlled release and also provide insights into the performance of the formulation *in vivo*. However, a major concern with *in vitro* release study is the lack of direct correlation between *in vitro* and *in vivo* release profiles. At present, attention is focused on the *in vivo* release studies and the correlation between *in vitro* and *in vivo* release data [75,76]. The physiological conditions are much more complex than buffer solutions that are commonly used for *in vitro* evaluations. The release profile of a drug may be affected by various proteins, cells and enzymes *in vivo*. For example, simulated release medium including intestinal fluid, gastric fluid, saliva, lachrymal fluid and blood serum can be used to enhance the accuracy of evaluation. Alternatively, *in vivo* release models can be developed but they are often time-consuming and costly. Also, the complex compositions of tissue fluids present great challenges on the sensitivity and reliability of a single conventional analytical method. Nevertheless, the rapid development in advanced analytical techniques, such as liquid chromatography coupled with mass spectrometry, fluorescent probes and mass imaging techniques, provide potential means to conquer these difficulties.

In case studies of release kinetics, burst release is a phenomenon commonly observed in delivery devices of different forms and compositions. The burst effect may be favorable for certain indications or applications such as wound treatment, encapsulated flavors, targeted delivery and pulsatile release. However, it is also likely to cause negative effects such as local/systemic

$$\left\{ \frac{M_t}{M_\infty} \right\}_{\text{blend}} = f_{\text{PCL}} \left\{ \frac{M_t}{M_\infty} \right\}_{\text{PCL}} + f_{\text{PLGA}} \left\{ \frac{M_t}{M_\infty} \right\}_{\text{PLGA}} \quad (20)$$

Here, f_{PCL} and f_{PLGA} represent the fractions of drug that partition into and are released from PCL and PLGA phases, respectively, the sum of which is equal to unity. ($\Phi_{b,PCL}$ refers to the fraction of burst release from PCL phase, and $\Phi_{d,PCL}$ is the

Table 4. Summary of the mathematical models.

Mechanism of transport	Equations	Form of devices	Assumptions
Diffusion	(3), (4)	Slab, disk	Diffusion takes place only in one dimension Constant drug diffusion coefficient
Dissolution	(5) – (8)	Slab, disk, film	No matrix swelling or degradation Two moving boundaries: R, the glassy–rubbery interface; S, the rubbery–solvent interface Constant drug and solvent diffusion coefficient
Erosion	(9)	Sphere, cylinder, slab	Zero-order surface detachment of drug Constant material erosion rate
	(10)	Slab, cylinder	Zero-order surface detachment of drug Constant material erosion rate
	(11) – (17)	Slab, disk	Two-dimensional erosion, i.e., axial and radial erosion D_{eff} is related to matrix porosity (ϵ) Second-order polymer degradation kinetics Applicable to both surface- and bulk-eroding materials

toxicity, short *in vivo* half-life, and a shortened release profile that requires more frequent dosing [77]. Burst release is often associated with device geometry, surface characteristics of host material, heterogeneous distribution of drugs within the polymer matrix, intrinsic dissolution rate of drug, heterogeneity of matrices (pore density), and so on. However, few studies have been conducted to develop mechanism-based mathematical models for burst release. To predict better the burst release, it would be worthwhile developing models to elucidate the mechanisms of burst release.

In addition, it would be of great significance to develop models that take into account physiological conditions, including such variables as pH, osmotic pressure, cellular tissue reactions, enzyme concentration, and so on [39]. This would benefit the mathematical prediction for the stimuli-triggered delivery systems as well as material systems used under (patho) physically relevant conditions. Some preliminary studies have been well documented in the review by Lin and Metters [61]. However, mathematical models that can represent the real physiological conditions have yet to be developed. Furthermore, the goal for mathematical modeling of release kinetics is to elucidate the potential transport mechanisms, especially the structure–function relationship of the material system. In return, understanding of the fundamentals will provide guidance for future material design and device development.

A current trend in the controlled drug delivery field is the development of multicomponent material systems, that is, integrating multiple materials with diverse physicochemical properties. For example, semi-interpenetrating networks composed of crosslinked, stable PEG matrices and biodegradable labile gelatin macromolecules have been shown to be effective drug delivery matrices and tissue scaffold for wound healing [78,79]. As a result, the release kinetics is driven by multiple factors and cannot be described by a single mathematical model mentioned previously [80]. To elucidate the drug transport mechanism better and predict transport behavior, it is crucial to ‘build up’ the connection between measurements at the molecular level (e.g., solute diffusion coefficients, drug/polymer interaction parameter, drug/polymer crystallization behavior, etc.) and drug release kinetics.

Acknowledgment

This paper was funded by NIH grant R01-EB006613.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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