Society For Biomaterials

Review Article

Polymer degradation and drug delivery in PLGA-based drug–polymer applications: A review of experiments and theories

Yihan Xu,[1] Chang-Soo Kim,[1]* David M. Saylor,[2] Donghun Koo[3]*

[1]Materials Science and Engineering Department, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, 53211
[2]Division of Biology, Chemistry, and Materials Science, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, Maryland 20993
[3]Materials Science R&D, MilliporeSigma, Milwaukee, Wisconsin 53209

Received 28 October 2015; revised 25 January 2016; accepted 12 February 2016
Published online 21 April 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jbm.b.33648

Abstract: Poly (lactic-co-glycolic acid) (PLGA) copolymers have been broadly used in controlled drug release applications. Because these polymers are biodegradable, they provide an attractive option for drug delivery vehicles. There are a variety of material, processing, and physiological factors that impact the degradation rates of PLGA polymers and concurrent drug release kinetics. This work is intended to provide a comprehensive and collective review of the physicochemical and physiological factors that dictate the degradation behavior of PLGA polymers and drug release from contemporary PLGA-based drug–polymer products. In conjunction with the existing experimental results, analytical and numerical theories developed to predict drug release from PLGA-based polymers are summarized and correlated with the experimental observations. © 2016 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 105B: 1692–1716, 2017.

Key Words: PLGA copolymers, biodegradation, physicochemical properties, drug delivery, analytical theory

How to cite this article: Xu Y, Kim C-S, Saylor DM, Koo D. 2017. Polymer degradation and drug delivery in PLGA-based drug–polymer applications: A review of experiments and theories. J Biomed Mater Res Part B 2017:105B:1692–1716.

INTRODUCTION

Poly (lactic-co-glycolic acid) (PLGA) is a copolymer of poly (lactic acid) (PLA) and poly (glycolic acid) (PGA) that have been widely used as drug delivery vehicles in many controlled release products because of their good biocompatibility and degradability in physiological environments. These PLGA copolymers can be easily formed into drug carriers of all scales, such as millimeter-sized implants, medical device coatings, microparticles, and nanoparticles,[1–8] and they are able to encapsulate a wide range of drugs with nearly any molecular sizes. The biodegradation products from PLGA are lactic acid (LA) and glycolic acid (GA), which are biologically inert to the growing cells and are removed from the body by normal metabolic pathways.[2,3] As a biodegradable polymer with good biocompatibility, low toxicity, relatively high miscibility with other polymers and adjuvants[4] as well as film-forming and capsule-forming properties, during the last several decades, many PLGA-based drug–polymer systems have been developed and employed for treatment of various diseases.[1,5,6] The compositional forms of PLGA are usually identified by their monomer ratio; for instance, PLGA 75/25 indicates a copolymer whose composition is 75 wt % PLA and 25 wt % PGA (i.e., LA/GA = 75/25).

The pharmacokinetics associated with the degradation rate and the drug release of a PLGA-based polymer is influenced by a number of factors, such as the initial molecular weight (M_w), monomer composition ratio of PLGA matrix (i.e., LA/GA ratio), drug type, processing method, and pH value of the release medium.[1–14] To fabricate a PLGA-based drug delivery system with higher efficiency and efficacy within a desired therapeutic window, it is essential to collectively and quantitatively understand the effects of the factors on the degradation rate and the drug release kinetics of PLGA-based polymers and to properly accommodate these factors in fabricating the drug-polymer composites.

The aim of this work is to collectively address the impacts of factors determining the degradation and subsequent drug release kinetics from PLGA-based polymers. It

Correspondence to: C.-S. Kim; e-mail: kimcs@uwm.edu and D. Koo; e-mail: donghun.koo@sial.com
Contract grant sponsor: MilliporeSigma
Contract grant sponsor: College of Engineering and Applied Science (CEAS) Dean's fellowship award program, UWM

© 2016 WILEY PERIODICALS, INC.

must be noted that, there are already multiple review literatures regarding this topic.[1,13] In our report, for more comprehensive understanding, the influencing factors were systematically categorized based on the material, processing, and physiological perspectives. Here, we classified the material factors to include the inherent physicochemical properties of the drugs and the PLGA copolymers and the interaction characteristics between them. The processing parameters, on the other hand, were considered as the system design factors that can be controlled and adjusted during synthesis, such as the monomer ratio, the drug loading, and the size and the shape of drug–polymer particles. Last, the conditions of the release environments including pH values, types of release medium, temperatures, and *in vivo* and *in vitro* testing have been grouped as the physiological factors. Among those factors, M_w and LA/GA ratio are of major importance and can be easily controlled as one of the material and the processing factors; thus, a special emphasis has been placed on the quantitative analysis of the effects of M_w and LA/GA ratio of PLGA copolymers on the degradation behavior and the drug delivery kinetics. In addition to the experimental findings, in this work, we provide a thorough review of the analytic mathematical and numerical models developed to predict the drug release behavior from PLGA-based drug delivery systems. When applicable, the results of the model predictions are discussed with respect to the individual material, processing, and/or physiological factors in the corresponding subsections. In the next section, theoretical and computational models developed to predict the pharmacokinetics from PLGA copolymers are reviewed and summarized. The following sections will then present up-to-date results, both qualitative and quantitative, of the impacts of material, processing, physiological factors on degradation, and drug release based on the existing experimental and theoretical work. Next, a section to discuss the drug delivery modulation approach using the material and processing factors is provided. Final remarks and summary statements are given in the last section.

THEORETICAL AND COMPUTATIONAL MODELS

Drug release profile

PLGA-based drug–polymer particle systems can exhibit a wide range of release profiles.[7] In Figure 1, we schematically present the characteristics of three typical release profiles. The drug release from PLGA systems can exhibit one or multiple phases in the release (i.e., mono-, bi-, or triphasic release) behaviors. In Figure 1, Type I curve shows the monophasic release from a single homogeneous phase, Type II curve corresponds to the biphasic release that is characterized by the initial burst and saturation (i.e., zero-order release), and Type III curve represents the triphasic (i.e., phase I, phase II, and phase III) release profile.[7] Phase I is often referred to as a burst release phase caused by disintegration of particles, formation of cracks on the matrix, nonencapsulated drug particles, or hydration of drug molecules on the surface. If the initial solubility of a drug is high, the fraction of initial burst release could be relatively high.[15]

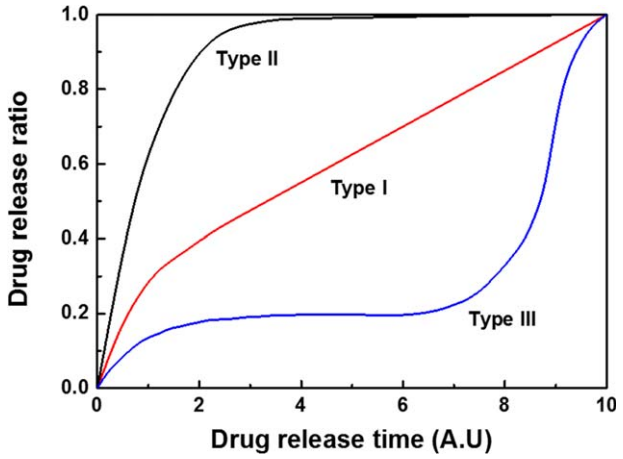

FIGURE 1. Typical profiles of drug release including different release phases. Arbitrary unit (A.U.) is used for drug release time.

For example, a hydrophilic drug is more readily hydrated than a hydrophobic drug, so that the initial burst can be more prominent, as schematically described in Figure 2. As another schematic example shown in Figure 3, lower M_w produces a higher initial burst and shorter drug release duration because lower M_w would result in a less hydrophobic polymer which will increase the rates of water absorption, hydrolysis, and erosion.[7] On the contrary, it is known that a lower M_w can increase the diffusivity (D) of drugs, which would accelerate the release kinetics. Phase II is commonly known as a period of a slower release, during which drug release is dictated by diffusion through the relatively dense polymer with few pores. Phase III is described as a rapid release period or sometimes is called as the second burst. The onset of "erosion" (i.e., the point at which the degradation products and drugs release much more rapidly) is usually considered responsible for this accelerated

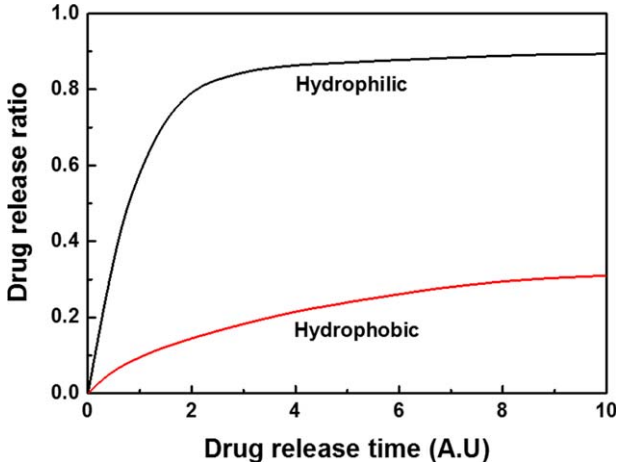

FIGURE 2. Typical Type II profiles of relative release amount of hydrophobic and hydrophilic drugs from PLGA-based polymers. Arbitrary unit (A.U.) is used for drug release time.

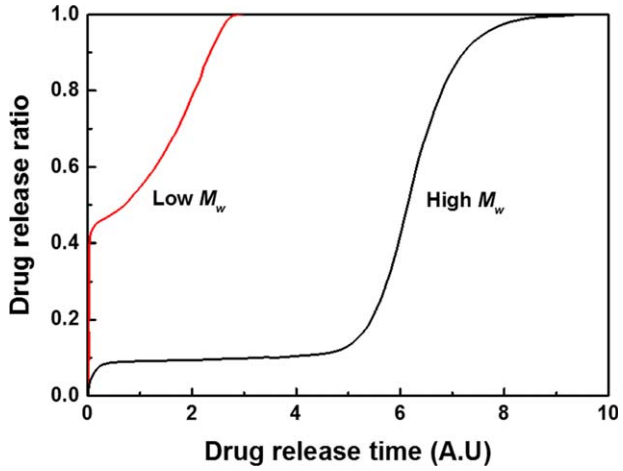

FIGURE 3. Typical Type III release profiles of drugs with different molecular weights (M_w) from PLGA-based polymers. Arbitrary unit (A.U.) is used for drug release time.

release, and the drug release during the period is mainly degradation-controlled.

There are many factors or events that can affect these release characteristics; therefore, the detailed shapes of such release profiles are the outcome of complicated factors influencing the polymer degradation and drug dissolution in the media. For instance, the existence of a slow second phase can be explained not only by pore closure but also by drug–drug interactions and drug–polymer interactions. Besides, some factors influence drug release in more than one aspect. For example, hydrolysis can result in pore formation and erosion, which may increase the drug release rate, but hydrolysis can also cause polymer chain rearrangement and pore closure that may decelerate release.[7] Therefore, it is difficult to understand the drug release mechanism merely or directly from the drug release profile and it is not easy to predict which profile would be prominent for a specific system, if factors, such as pore closure and polymer–drug interactions, are not well established. However, observations suggest some consistency between the physicochemical properties of the system and drug release character types. Generally, large PLGA particles show the triphasic release profile because of heterogeneous degradation, while small PLGA particles and thin-PLGA-film-coated particles exhibit a biphasic release profile with a relatively rapid second phase.[16] It was also reported that some basic drugs tend to result in a biphasic release pattern, while neutral drugs may lead triphasic release profiles.[17] In addition, the amount of initial burst can be lowered and the drug release can be prolonged when PLGA systems with free COOH groups interact with drugs.[18,19] Among the three phases shown in the Type III curve of Figure 1, the initial burst phase is relatively easy to understand and even a quantitative expression could be obtained to calculate the drug release fraction during this phase.[20]

Theoretical modeling

Existing literatures offer various kinds of mathematical (analytical), computational (numerical), and theoretical models of drug release from polymeric microspheres.[21–25] With different transport phenomena, one can classify these into diffusion-, swelling-, and erosion-based models.[21,23] Because PLGA is a bulk erosion copolymer and its swelling phenomenon is not obvious, not all available models can be applied to PLGA-based drug delivery systems including swelling-based and surface erosion-based models. This subsection furnishes a review of analytical, computational, and theoretical models that describe both the drug release and the bulk degradation suitable for PLGA-based drug delivery systems.

Diffusion-based models. For theoretical modeling, the analytical solutions of Fick's second law for various geometries of PLGA drug delivery systems are the most widely used mechanistic models. For example, for spherical microparticles, the drug release ratio is given by the following Eq. (1).[26]

$$\frac{c_t}{c_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{n^2\pi^2}{R^2}Dt\right) \tag{1}$$

where c_t and c_∞ are the cumulative amounts of drug that are released at time t and ∞; and n, R, and D are the integer, the radius of the microparticles, and the diffusion coefficient of drugs, respectively. Note that all of the analytical solutions of Fick's second law involve empirical determination of certain variables. Although application of these models is limited based on such empiricism, these analytical approaches can be applied in the following ways[27]; (i) the analytical model can be applied to predict the drug release rate at any time when D is known for a given size and specific PLGA polymer, (ii) the model can be used to empirically predict the value of D for a particular drug-PLGA system, and (iii) the model can also be employed to determine the influencing factors such as the optimal combination of geometric (i.e., size) and/or material (i.e., D) parameters to attain a desired rate for drug release.

Higuchi model[28] is an empirical model based on the exact integration of Fick's law, in which the instantaneous rate of drug release at time t is given by

$$\frac{dQ}{dt} = \frac{1}{2}\sqrt{\frac{(2c_{init} - C_{sat})DC_{sat}}{t}} \tag{2}$$

where Q is the cumulative amount of released drug at time t per unit area of exposure. c_{init} and C_{sat} are the initial concentration and the saturated concentration of drug, respectively. When the initial concentration of drug is much higher than the saturated concentration ($c_{init} \gg C_{sat}$), the cumulative amount can be simplified as

$$Q = \sqrt{2c_{init}DC_{sat}t} \tag{3}$$

Higuchi model is one of the earliest models that were used in previous literatures to describe the drug release in a quantitative way.[28–30] The major limitation of this model is that it assumes the surrounding environment is a perfect sink, the drug distribution in the matrix is uniform, and $c_{init} \gg C_{sat}$.

Korsmeyer et al.[31] derived a simpler semiempiric power law model as given by

$$\frac{c_t}{c_\infty} = kt^n \tag{4}$$

where k is the rate constant that dictates the geometric and structural characteristics of the drug release systems and n is the diffusional exponent. By adjusting n, this model was claimed to be able to describe a wide range of release phenomena such as Fickian diffusion, anomalous transport, type II transport, and so on.[32,33]

Bulk erosion-based models. Traditionally, analytical solutions of Fick's second law have successfully been applied to quantify the drug release from PLGA microparticles and thin films.[8,34] However, they are applicable only for mono- or biphasic release shown in Figure 1 due to the constant drug diffusivity (D) in Eq. (1). A common approach to expand the applicable range of Fick's second law is to correlate D with the changing M_w upon degradation. For example, Raman et al.[15] have proposed a mathematical model quantifying the drug release from spherical PLGA-based microparticles. Their model takes into account the drug diffusion, the polymer degradation, and the initial nonhomogeneous drug distribution within the system. The resulting equation is expressed as[15]

$$\frac{\partial c}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left[r^2 D(M_w)\frac{\partial c}{\partial r}\right] \tag{5}$$

where c is the concentration of the drug, t is the releasing time, r is the radial coordinate, and $D(M_w)$ is the polymer M_w-dependent drug diffusion coefficient, respectively. This model considers the polymer degradation by associating the drug diffusion coefficient with M_w of degrading polymer; therefore, $D(M_w)$ is no longer a constant. In their model, an empirical cubic polynomial fit was used to relate $D(M_w)$ for piroxicam-loaded PLGA-based microparticles.[15] As a result, the following empirical dependence of the diffusion coefficient, $D(M_w)$, on the average M_w was found.[15]

$$\ln D(M_w) = -0.347(\ln M_w)^3 + 10.394(\ln M_w)^2 - 104.950(\ln M_w) + 316.950 \tag{6}$$

$$M_w(t) = M_{w0}\exp\left[k_d\left(t - t_{lag}\right)\right] \tag{7}$$

where M_{w0} is the unchanged M_w of the polymer in the early release stage, t_{lag} is the duration during which the M_w of the polymer is unchanged (i.e., $t > t_{lag}$), and k_d is the polymer degradation constant, respectively. Because the diffusion coefficient ($D(M_w)$) of drug is a function of M_w, this empirical model can be readily used to describe a triphasic release.

Another widely used model deems a three-step release sequence from PLGA film, that is, (i) solvent penetration into the polymer, (ii) polymer relaxation controlled by degradation and drug dissolution, and (iii) drug transport generally controlled by diffusion.[35] The drug release ratio, (c_t/c_∞), is then a summation of burst release [first term on the right-hand side of Eq. (8)],[35,36] relaxation-induced drug dissolution release [second term on the right-hand side of Eq. (8)], and diffusion controlled release [third term on the right-hand side of Eq. (8)], as given by Eq. (8)[35]

$$\frac{c_t}{c_\infty} = \phi_b\{1-\exp(-k_b t)\} + \phi_r\{\exp[k_r(t-t_b)]-1\} + \phi_d\left\{1 - \sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left[\frac{-D(2n+1)^2\pi^2(t-t_r)}{4l^2}\right]\right\} \tag{8}$$

where c_t and c_∞ are the cumulative amounts of drug released at time t and ∞, respectively, l is the half-thickness of film, k_r is the degradative relaxation constant of PLGA, and ϕ_b and ϕ_d represent the fraction of initial burst release and the fraction of diffusion-controlled release, respectively. These three (l, k_r, ϕ_b) are known parameters. D is the diffusion coefficient of drug in PLGA, k_b is the burst constant of PLGA, t_b is the end time of burst release from PLGA, t_r is the end time of relaxation release from PLGA, and ϕ_r is the relaxation release coefficient of PLGA, respectively. These parameters (D, k_b, t_b, t_r, ϕ_r, and ϕ_d) can be empirically determined (i.e., fitting). Note that the last term in Eq. (8) is identical to the analytical solution of Fick's second law for thin films with negligible edge effects (1D).[26] It has been shown that the empirical prediction from this model matches well with the paclitaxel release profile from the thin PLGA film of 80 μm thickness.[35]

A similar model has been proposed that takes into account a two-step release sequence, that is, (i) initial burst (diffusion controlled) and (ii) bulk-degradation controlled drug release. In this case, the drug release ratio (c_t/c_∞) at a given time t can be described by[20]

$$\frac{c_t}{c_\infty} = \phi_b[1-\exp(-k_b t)] + (1-\phi_b)\left[\frac{\exp(kt-kt_{max})}{1+\exp(kt-kt_{max})}\right] \tag{9}$$

where t_{max} is the time to the maximum degradation rate and k is the rate constant of the second step, respectively. Here, the rate constant k_b is expressed as

$$k_b = \frac{DAC_S}{W_L\phi_b h} \tag{10}$$

where D is the diffusion coefficient, A is the surface area of drug accessible to the medium, C_S is the solubility of the drug, h is the apparent aqueous diffusion boundary layer thickness, and ϕ_b is the fraction of initial burst. Equation (9) has been successfully used to describe drug release from PLGA nanoparticles with low drug loadings.[20]

A number of stochastic models of polymer erosion have been proposed with potential applications for drug delivery systems. As an example of stochastic models for PLGA erosion, Chen et al.[25] uniformly discretized the model domain into a finite number of degradation cells (elements). In their model, the diffusion coefficient of monomers during degradation (D_m) was defined as a function of the hydrolysis state:

TABLE I. Effects of Crystallinity on Drug Release

Drug	Polymer/Copolymer	Factors, Crystallinity (%)	Results	Ref.
Lidobase	PDLLA	0	Diffusion coefficient: $D = 2.7 \times 10^{-11}$ cm^2 s^{-1}	17
	PLLA	40	Diffusion coefficient: $D = 6.95 \times 10^{-14}$ cm^2 s^{-1}	
	PLLA	50	Diffusion coefficient: $D = 3.84 \times 10^{-14}$ cm^2 s^{-1}	
Papaverine	PLLA	0	Drug release amount: 3 wt % (4th hour)	41
		43	Drug release amount: 8 wt % (4th hour)	
Theophylline	PLA	5	Drug release amount: 0.7 ± 0.3 wt % (1st day)	43
		24	Drug release amount: 8.3 ± 0.8 wt % (1st day)	

$$D_m = D_{m0} \exp\left[R_m\left(\frac{X_H - X}{X_H}\right)\right] \quad (11)$$

where D_{m0} is the diffusion coefficient of monomers before degradation, R_m is the material constant, X is the status variable for degradation cells. The authors used $X_H = 1$ for "hydrolysable" cells, $X_h = 0.001$ for "hydrolyzed" cells, and $X_v = 0$ for "void" cells. The diffusion of the monomer was expressed by combining Fick's second law with a monomer source term ($S(t)$) as given by[25]

$$\frac{\partial C_m}{\partial t} = \nabla(D_m \nabla C_m) + S(t) \quad (12)$$

where C_m is the concentration of monomers.

Siepmann et al.[24,37] proposed a stochastic Monte-Carlo computational model to include the time- and the direction-dependent porosities in the PLGA matrix. The authors first divided the PLGA-drug particle into finite computational pixels to represent the nondegraded polymer and the drug regimes. Then, the "lifetime" of a pixel was estimated using a random stochastic variable that ranges from 0 to 99. After this lifetime is reached, the corresponding computational pixel was assumed to erode instantaneously to indicate degraded parts (i.e., pores). With this approach, the diffusivities of radial and height directions were separately averaged out for temporal evolution of the internal structure of drug-PLGA particles. Using this Monte-Carlo model, the authors claimed that the developed model can describe various experimental observations such as initial burst, zero-order release, and triphasic release, and so forth Hadjitheodorou and Kalosakas[38] also utilized the similar Monte-Carlo computation approach to elucidate the diffusion-controlled drug release mechanism. In their model, the time-exponent (b) and relaxation time (τ) in $\frac{c_t}{c_\infty} = 1 - \exp\left[-\left(\frac{t}{\tau}\right)^b\right]$ expression were empirically fitted and Eq. (1) was used to predict the diffusion process.

MATERIAL FACTORS (MATERIAL PROPERTIES)

PLGA copolymers

Crystallinity. The crystallinity of PLGA copolymers impacts both degradation rate and drug release. Lower crystallinity accelerates the hydrolysis and degradation rates of PLGA. Generally, the drug release in these systems is accelerated by lesser crystallinity, especially when the release is controlled solely by diffusion.[17,39]

The crystallinity of PLGA depends on the PLA enantiomer used. LA has two optical isomers: L-(+)-lactic acid and D-(−)-lactic acid. As a result, PLA generally includes poly-L-lactic acid (PLLA), poly-D-lactic acid (PDLA), and poly-D,L-lactide (PDLLA), and so forth PLLA tends to be semicrystalline or amorphous depending on the processing method.[40,41] PDLA commonly exhibits higher crystallinity compared with PLLA whereas PDLLA is amorphous. PLGA prepared from PGA and PLLA is crystalline/semicrystalline copolymer while that from PGA and PDLLA is amorphous which is preferred, as it enables more homogeneous drug dispersion in the matrix.[40] The crystallinity in these systems also depends on the compositional proportion (composition) of LA and GA in the polymer chains. Although PGA itself is typically highly crystalline, increasing the proportion of GA in the polymer can reduce the degree of crystallinity of PLGA, and an amorphous PLGA structure could be observed with higher portion of GA (25∼70%) because the long range order of the polymer is disrupted by the GA content.[42]

Table I summarizes the effects of the higher crystallinity on drug release. As shown in Table I, the impact of crystallinity was mostly studied by comparing single polymer materials (typically, PLA types), likely to avoid complications in interpreting results from copolymer systems. For instance, increasing the proportion of LA leads to a slowdown in the rate of hydrolysis and degradation. This can be explained not only from the view that LA content increases the crystallinity but also from the view that LA contains the methyl group would increase the hydrophobicity of PLGA.

In contrast to the general negative effect of the degree of crystallinity on the drug release,[17] there are some evidences of the opposite influence of crystallinity under certain circumstances as reported in Refs. 41,43 in Table I. For instance, Hurrell and Cameron[43] showed that PLA matrices with higher initial crystallinity released more drug (theophylline, 5 wt % initial loading) at the initial stage. The authors explained that this might be attributed to the redistribution of drug concentration during the process of preparing the sample; the drug concentration on the surface was higher than in the bulk.

Wang et al.[44] developed the following expression to correlate crystallinity (X_C) with degradation.

$$\frac{dC_e}{dt} = -\frac{dR}{dt} - \omega\frac{dX_C}{dt} \quad (13)$$

where C_e is the molar concentration of ester bonds in amorphous phase polymer, R is the molar concentration of monomers produced by the hydrolysis process, t is the degradation time, ω is the molar concentration of polymer

TABLE II. Effects of Molecular Weights (M_w) on Drug Release

Drug	Polymer/Copolymer	Factors, M_w (kDa)	Results	Ref.
Theophylline	PDLLA	3.5	Drug release amount: 100 wt % (1st hour)	4
		42	Drug release amount: 47 wt % (2nd hour)	
		92	Drug release amount: 37 wt % (2nd hour)	
		138	Drug release amount: 35 wt % (2nd hour)	
		553	Drug release amount: 32 wt % (2nd hour)	
Piroxicam	PLGA 50/50	6	Diffusion coefficient: $D = 6 \times 10^{-13}$ cm^2 s^{-1}	15
		20	Diffusion coefficient: $D = 5 \times 10^{-14}$ cm^2 s^{-1}	
		34	Diffusion coefficient: $D = 2 \times 10^{-14}$ cm^2 s^{-1}	
		49	Diffusion coefficient: $D = 9 \times 10^{-15}$ cm^2 s^{-1}	
		68	Diffusion coefficient: $D = 7 \times 10^{-15}$ cm^2 s^{-1}	
Ovalbumin	PLGA 50/50	33	Initial burst: 94 wt %	45
		58	Initial burst: 39 wt %	
		84	Initial burst: 11 wt %	
Estradiol	PLGA 50/50	14.5	Drug release amount: 95 wt % (18th day)	46
		45	Drug release amount: 66 wt % (18th day)	
		85	Drug release amount: 50 wt % (18th day) Diffusion coefficient: $D = 5.91 \times 10^{-19}$ cm^2 s^{-1}	
		213	Drug release amount: 26 wt % (18th day) Diffusion coefficient: $D = 1.64 \times 10^{-19}$ cm^2 s^{-1}	
Paclitaxel	PLLA	2	Drug release amount: 64 wt % (14th day)	47
		4	Drug release amount: 77 wt % (14th day)	
		10	Drug release amount: 57 wt % (14th day)	
		50	Drug release amount: 13 wt % (14th day)	
Rifampicin	PLGA 50/50	5	Drug release amount: 100 wt % (10th day) Diffusion coefficient: $D = 4.76 \times 10^{-15}$ cm^2 s^{-1}	48
		10	Drug release amount: 100 wt % (10th day) Diffusion coefficient: $D = 4.44 \times 10^{-15}$ cm^2 s^{-1}	
		20	Drug release amount: 50 wt % (10th day)	
	PLGA 75/25	5	Drug release amount: 85 wt % (10th day) Diffusion coefficient: $D = 2.64 \times 10^{-15}$ cm^2 s^{-1}	
		10	Drug release amount: 90 wt % (10th day) Diffusion coefficient: $D = 3.92 \times 10^{-15}$ cm^2 s^{-1}	
		20	Drug release amount: 25 wt % (10th day)	
Tetanus toxoid	PLGA 50/50	3	Drug release amount: 69 wt % (30th day)	50
		100	Drug release amount: 32 wt % (30th day)	
Fentanyl	PLGA	5	50% release in 7.2 days	51
		8	50% release in 7.9 days	
		33	50% release in 11 days	
Doxorubicin hydrochloride	PLLA	7.2	Drug release amount: 60.1 wt % (60th day)	52
		10	Drug release amount: 53.4 wt % (60th day)	

chains in crystalline phase, and X_C is the crystallinity. This model considered that the concentration of the amorphous polymers (C_e) was reduced by crystallization, and the model showed a good agreement with the experimental data of PLGA for (weight loss vs time) and (crystallinity vs time) except at long times.

Molecular weight (M_w). Molecular weight (M_w) of PLGA polymer significantly influences the physicochemical properties of PLGA copolymers. M_w of PLGA used in controlled release applications ranges typically between 5 and 150 kDa (i.e., 5000–150,000 g/mol).[7] As presented in Table II, it is generally observed that the degradation and the drug release increase with decreasing M_w of PLGA. For example, it has been reported that the initial burst amount can be increased by as much as 8.5 times by controlling M_w (33 kDa compared to 84 kDa)[45] and that the drug release amount in 18 days can be increased by 3.7 times (from 95 to 26 wt %) when the M_w changes from 14.5 to 213 kDa.[46] For the diffusion coefficient of drug, an example of piroxicam release from PLGA 50/50 showed that increasing M_w from 6 to 68 kDa resulted in decreased D from 6×10^{-13} cm^2 s^{-1} to 7×10^{-15} cm^2 s^{-1} (reduction of 85.7 times).[15] For PLLA, however, the impact could be directly opposite to these observations since there is an inversely proportional relationship between M_w and crystallinity. For instance, in Table II, it is seen that a 2 kDa PLLA polymer system had smaller drug release amount than the 4 kDa PLLA polymer system in 14 days in Ref. 47 because the former was more crystalline than the latter; however, the drug release amount from this PLLA was again decreased by as high as 6 times from 77 to 13 wt % by increasing M_w from 4 to 50 kDa.[47]

Figure 4(a) shows some examples to illustrate the trend of the drug release ratio of initial drug loading from PLGA polymer systems with different M_w. Here, all the drug release profiles were characterized at 37°C and pH 7.4.

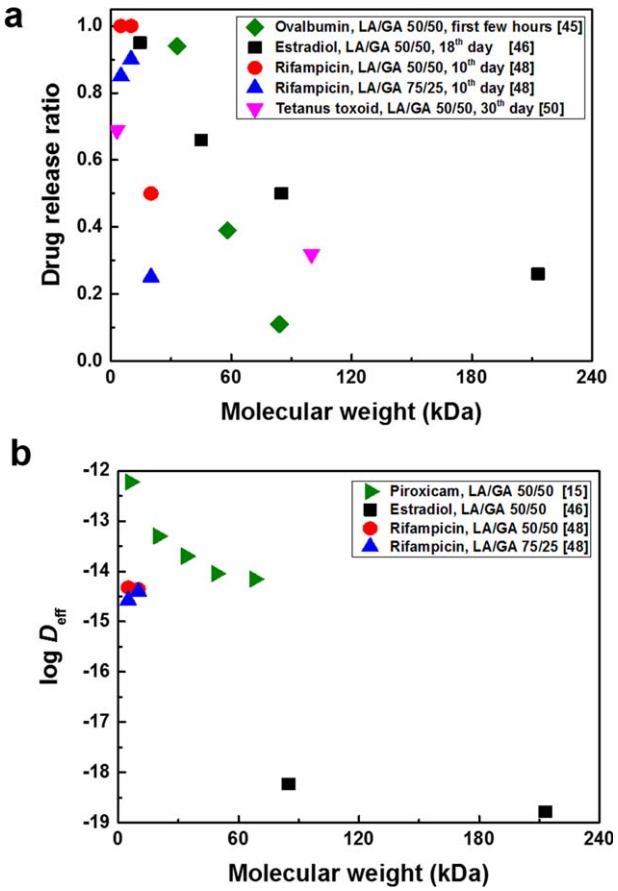

FIGURE 4. Selected examples of data to show (a) drug release ratios and (b) log D_{eff} as a function of molecular weights (M_w) of PLGA polymers. [$cm^2\ s^{-1}$] is used for the unit of D_{eff}.

Although the quantitative degree of impact is determined by many other factors and the observation times are different for each data set, the overall trend shows that the drug release ratio decreases as the M_w increases. It can be seen that the rifampicin release from PLGA 50/50 (5 and 10 kDa) achieved 100% in 10^{th} day, and the rifampicin release from PLGA 50/50 (20 kDa) achieved 50 wt % in 10^{th} day, 75 wt % in 18^{th} day, and 100% in 36^{th} day, respectively.[48] Compared with this, the estradiol release from PLGA 50/50 with comparable M_w (14.5 kDa) did not achieve 100% but 95 wt % in 18^{th} day.[46] This could probably be explained by the shorter observation time or smaller particle size. The rifampicin release from PLGA 75/25 (blue symbols) was slower compared with that from the PLGA 50/50 (red symbols) with comparable M_w due to the higher LA/GA ratio.[48] For the rifampicin release from PLGA 75/25, drug release from PLGA of 10 kDa was faster than that from PLGA 5 kDa, and this seemed due to the higher drug loading and interaction of amino groups of rifampicin and carboxyl groups of PLGA. Figure 4(b) shows the examples of extracted effective diffusivities (D_{eff}) of drugs with M_w of PLGA polymers. Here, D_{eff} was extracted from experiments to exhibit biphasic release in Table II. To extract the D_{eff} values of selected examples with a sphere shape, we adopted a regression approach in solving the Fick's second law expression as given in Eq. (1). In the figure, D_{eff} was represented using log D_{eff} values. Although D_{eff} would be influenced by many other factors in addition to M_w, as seen in Figure 4(b), D_{eff} is generally decreased by increasing M_w except when M_w is small.

As described above in Eqs. (5–7), models coupling M_w and drug release have been proposed based on Fick's second law.[15] The dependence of D on M_w has been determined empirically for selected systems.[49] Inspection of the drug release profiles from PLGA systems referred in Table II reveals that some drug release kinetics[46,48] followed Type II behavior. In Ref. 46, as M_w of PLGA 50/50 increased from 14.5 to 213 kDa, the drug release profiles were altered from Type I to Type II. When the swelling effect of polymers is relatively minor, these drug release behaviors are controlled by the diffusion mechanism derived from the concentration gradient of drug. With releasing time, the concentration gradient of drug decreases while the degradation rate of PLGA matrix gradually increases. When the diffusion of drug is fast enough, the drugs are released completely before the on onset of polymer erosion. If the diffusion of drug is relatively slower, then the degradation cannot compensate the diminished effect of concentration gradient, which results in the Type II release of Figure 1.[46,48] On the other hand, if the effect of degradation compensates the diminished effect of concentration gradient or if the onset of erosion occurs relatively in an earlier stage, the duration time of lag release could be shorter, therefore, the Type III release or even Type I could take place.[45,46,50]

Glass transition temperature (T_g). It is generally accepted that the drug release rates decrease with increasing T_g of the matrix polymers.[1] For example, Frank et al.[17] reported that, for PLLA with intrinsic viscosity of 4.37 dl/g, PLLA with intrinsic viscosity of 2.04 dl/g, PDLLA, PLGA 80/20, and PLGA 53/47 samples, T_g decreased gradually and were 70, 62, 50, 48, and 40°C, respectively, and the corresponding D values were 3.84×10^{-14}, 6.95×10^{-14}, 2.7×10^{-11}, 3.11×10^{-11}, and 1.596×10^{-10} $cm^2\ s^{-1}$, respectively. As another example, Karavelidis et al.[53] showed the effect of T_g of polyesteric nanoparticles on the release kinetics of ropinirole HCl. The highest release rate was found from the poly-(propylene suberate) (PPSub) and the poly(propylene sebacate) (PPSeb), having the lowest T_g, −57.8°C and −53.1°C, respectively. On the contrary, the slowest release kinetics of the drug was found from the PLA with the highest T_g, 58.7°C. After 12 days, PPSub, PPSeb, and PLA released 98%, 96%, and 50% of ropinirole HCl, respectively. It must be mentioned that T_g of PLGA/PLLA polymers may not be controlled independently, rather it is a function of other material or processing parameters such as M_w or composition ratios. It has been reported that T_g of PLGA decreases with the increasing GA composition and decreasing M_w (or decreasing viscosity)[54–56]; therefore, the resultant effects of T_g must be considered in conjunction with other multiple factors such as intrinsic viscosity and/or D.

TABLE III. Effective Diffusivities (D_{eff}) of Hydrophobic Drugs

Drug	Polymer/Copolymer	Factors, Matrix Structure	Results, D_{eff} ($cm^2\ s^{-1}$)	Ref.
Piroxicam	PLGA	Dense microspheres	$10^{-15}-10^{-13}$	15
Lidocaine	PLGA	Dense microspheres	$(0.4–8) \times 10^{-12}$	34
		Thin films	0.8×10^{-12}	
Ibuprofen	PLGA	Dense microspheres	$(0.2–2) \times 10^{-12}$	
		Thin films	2×10^{-12}	
Paclitaxel	PLA	Dense microparticles	$(1.04–2.78) \times 10^{-11}$	47
Indomethacin	PLGA	Porous foams	1.75×10^{-9}	57
Indomethacin	PLA	Porous foams	3.01×10^{-9}	
Indomethacin	PLA	Dense nanoparticles	2.25×10^{-12}	60
	PLGA	Dense nanoparticles	$(1.98–2.35) \times 10^{-12}$	
	PLA-PEG	Dense nanoparticles	1.06×10^{-12}	
Lidocaine	PDLLA	Dense nanospheres	$(1.35–7.13) \times 10^{-16}$	61
Lidocaine	PLA	Dense nanospheres	$(7.7–7.9) \times 10^{-16}$	62
p-Cymene	PLA	Dense microcapsules	5.21×10^{-13}	63
Thymol	PLA	Dense microcapsules	1.39×10^{-11}	

Drugs

Drug type: hydrophilic or hydrophobic. PLGA-based products have been widely studied for controlled delivery of a variety of medicaments including macromolecular drugs (such as human growth factors, genes, peptides, proteins, vaccines, antigens, and so forth) and relatively small molecular drugs (hydrophilic/hydrophobic drugs). Since undesired pharmacokinetic properties have been associated with low aqueous solubility of the drug, the prediction of drug solubility is very important.[57] As introduced before, Figure 2 shows the typical example of release profiles of relative release amount of hydrophobic and hydrophilic drugs from PLGA-based polymers. The degree of initial burst is much lower for hydrophobic drugs because their low aqueous solubility leads to a sustained low driving force.[57]

There are numerous earlier studies to investigate the effects of drug type (hydrophilic or hydrophobic) on the degradation rate of PLGA matrices. For example, it has been reported that the diffusion (or swelling) rate of aspirin (relatively hydrophilic drug with aqueous solubility of 4.99 mg/mL) was substantially higher (i.e., 57.5 times) than that of haloperidol (relatively hydrophobic drug with aqueous solubility of 0.13 mg/mL).[58] As another example, Liu et al.[59] examined the difference of the release patterns of ciprofloxacin hydrochloride (hydrophilic) and sirolimus (hydrophobic) from 50/50 PLGA films. The results showed that more hydrophilic ciprofloxacin hydrochloride induced faster release curves than more hydrophobic sirolimus and that ciprofloxacin hydrochloride promoted the weight loss of films while sirolimus inhibited the weight loss of films. However, it was also observed that both drugs inhibited the degradation of biodegradable carrier. As expected, there could be a wide range of variations in the release behavior from similar types of drugs depending on other physicochemical factors. Tables III and IV list examples of the effective diffusivity (D_{eff}) values of hydrophobic and hydrophilic drugs, respectively, in a variety of biodegradable polymer matrices. One can see that the D_{eff} values of hydrophobic and hydrophilic drugs are within the bounds of 10^{-16} to 10^{-9} and 10^{-12} to 10^{-7} $cm^2\ s^{-1}$, respectively. D_{eff} of hydrophobic drugs have been studied more commonly compared to that of hydrophilic drugs, which could be ascribable to the low encapsulation efficiency and the issues related to drug leakage of water-soluble drugs.[66] In Figure 5, selected examples of log D_{eff} are plotted with their log P (octanol/water) values at pH 7.4.[67–69] In the figure, the red and black symbols indicate hydrophilic and hydrophobic drugs, respectively, and open and solid symbols represent log D_{eff} measurements from porous and dense polymer matrices, respectively. It is seen that D_{eff} from porous matrices (i.e., open symbols) substantially higher values compared with those from dense matrices (i.e., solid symbols). Also, although D_{eff} cannot be solely determined from hydrophobicity and must be correlated with other factors, it is observed that D_{eff} of hydrophilic 5-fluorouracil (5-FU) drugs (i.e., red symbols) is higher than that of hydrophobic drugs (i.e., black symbols).

As for the theoretical aspect, the three-step release model (i.e., Eq. (8)) is suitable for describing the hydrophobic drug (e.g., paclitaxel) release from PLGA.[35,70] Equation (8) with $\phi_r = 0$ can be applied to the release of hydrophilic drugs

TABLE IV. Effective Diffusivities (D_{eff}) of Hydrophilic Drugs

Drug	Polymer/Copolymer	Factors, Matrix Structure	Results, D_{eff} ($cm^2\ s^{-1}$)	Ref.
5-Fluorouracil (5-FU)	PLGA	Porous foams	1.41×10^{-7}	2
	PLA	Porous foams	2.21×10^{-7}	
	PLGA	Dense microparticles	$10^{-12}-10^{-10}$	64
Ovalbumin	PLGA	Porous microparticles	7.2×10^{-7}	65
Bovine serum albumin	PLGA	Porous microparticles	5.9×10^{-7}	

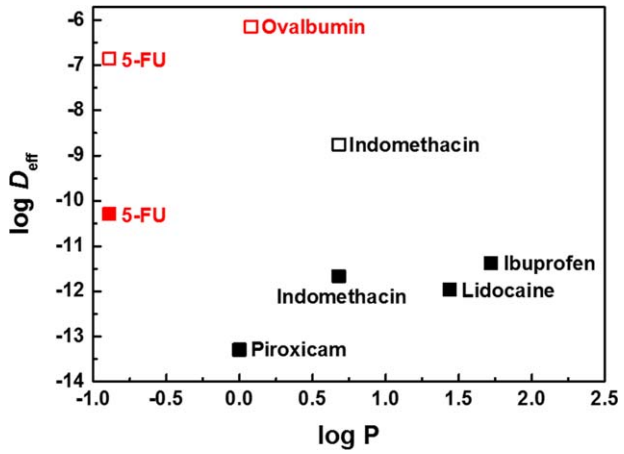

FIGURE 5. Selected examples to show log D_{eff} variations with partition coefficients (log P at pH 7.4).[67–69] Open and solid symbols indicate porous PLGA matrices and dense PLGA matrices, and red and black symbols indicate hydrophilic and hydrophobic drugs, respectively. [$cm^2\ s^{-1}$] is used for the unit of D_{eff}.

such as metoclopramide.[70] This implies that the PLGA relaxation is important for the dissolution of hydrophobic drugs because the drugs have a strong affinity with polymers. On the other hand, it is thought that models with initial burst and diffusion-controlled drug transport are adequate for describing the release of hydrophilic drugs because D_{eff} is relatively higher.

Size of drug particles. The effect of drug particle size in the matrix on the drug release is highly dependent on the aqueous solubility of the drug; if a drug is moderately soluble or insoluble, the influence of drug particle size is especially important.[71–73] On the other hand, for soluble drugs, the effect of drug size is only noticeable when the polymer is highly hydrophobic and/or the drug particle size is very large.[71] It is relatively easier for the drug with smaller particles to dissolve and diffuse out of the matrix while the drug with larger particles will dissolve less readily. However, not many previous studies were found for PLGA-based drug delivery systems regarding these drug size effects.[74]

Perale et al.[75] proposed a model considering the release process mainly including (i) solubilization of drug particles (related to drug size) and (ii) the diffusion of the solubilized drug, and they validated this model for the PGA, PLLA, and PLGA drug delivery systems. The fitting results were qualitatively consistent with the observed trends in release; however, there were numerical discrepancies that were attributed to small amount of available data and settings of experiments. The authors used the following equation to express the solubilization of a solid drug particle

$$\frac{\partial n_d}{\partial t} = -k_C([c]^* - [c])\pi d_p^2 \tag{14}$$

where n_d is the number of moles of drug in the drug particle, t is the time, k_C is the drug mass transport coefficient, $[c]^*$ is the solubility of the drug in the solvent, $[c]$ is the molar concentration of drug in the solid particle, and d_p is the diameter of the solid particle. This model assumes that the particle is a sphere (i.e., $n_d = \rho_d \pi d_p^3/6$, where ρ_d is the density of drugs) and that N particles are present in the unit volume, and the expression describing the overall drug dissolution rate is given by

$$\Delta_d = N\rho_d k_C([c]^* - [c])\pi(6n_d/\pi\rho_d)^{2/3} \tag{15}$$

The mass balance of drug can be evaluated as

$$\varepsilon\frac{\partial [c]}{\partial t} = D\nabla^2[c] + \Delta_d \tag{16}$$

where ε is the polymer porosity after swelling. Thus, by combining Eqs. (14) and (16), it is possible to express the final conservation equations for the dispersed drug. Compared with Fick's second law, Eq. (16) considers the drug solubilization dynamics by including the Δ_d term that relates the size of drug particles.

Drug–polymer interaction: acidic or basic. If the impregnated drug is a weak base or an acid, the effect of drug–polymer interaction on polymer degradation needs to be carefully considered. For acidic drugs, it is known that degradation is faster due to autocatalysis, which will be discussed in the "Size of the matrix" section. For basic drugs, however, there are conflicting views of the impact on degradation. One viewpoint is that degradation will be accelerated; basic drugs, such as tertiary amine or nucleophilic drugs, catalyze the matrix degradation that will accelerate the release rate because of a bulk erosion of the matrix.[17,76,77] An opposite viewpoint is that drug release can be suppressed; basic drugs can neutralize the generating acid from polymer hydrolysis so as to minimize the autocatalytic effect, thereby leading to a slower degradation rate and consequent reduced drug release rates.[43,78,79]

As an example of the studies to address the impact of drug–polymer interaction on the release behavior, Klose et al.[34] reported *in vitro* release behaviors of lidocaine and ibuprofen drugs from PLGA-based polymers at pH 7.4 as

TABLE V. Effects of Drug Types on Drug Release

Polymer/Copolymer	Factors, Drug Type	Results, Complete Release	Ref.
PLGA microparticles	Ibuprofen (pKa 4.4)	Complete drug release in 7 days	34
	Lidocaine (pKa 7.9)	Complete drug release in 45 days	
PLGA films	Ibuprofen (pKa 4.4)	Complete drug release in 7 days	
	Lidocaine (pKa 7.9)	Complete drug release in 20 days	

shown in Table V. Lidocaine is slightly basic with a pKa value of 7.9, thus it will be protonated and positively charged at pH 7.4. In contrast, ibuprofen is an acid with a pKa value of 4.4, hence it will be deprotonated and negatively charged at pH 7.4. *D* of ibuprofen was around 4 times higher than that of lidocaine, probably due to the attractive interactions between the positively charged lidocaine ions and the negatively charged deprotonated carboxylic end groups of PLGA, which would hinder the lidocaine release from PLGA-based microparticles and thin films. The effect of drug–polymer interactions is also observed in Ref. 79. In this work, it was observed that PLGA loaded with aspirin degraded faster compared to PLGA without drug loading (i.e., blank formulation). The relative M_w of PLGA residuals of PLGA 50/50 (30%, w/v)/NMP (1-methyl-2-pyrrolidinone) without drug loading was 43%, while the relative M_w of PLGA residuals of aspirin loaded formulation of PLGA50/50 (30%, w/v)/NMP was 13%. The relative M_w of PLGA residuals of blank formulation of PLGA50/50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v) was 40% while the relative M_w of PLGA residuals from aspirin loaded formulation of PLGA50:50 (30%, w/v)/NMP (80%, v/v)/PEG400 (20%, v/v) was 18%, which implies that containing aspirin substantially accelerates the degradation of PLGA. Aspirin is an acidic (pKa = 3.5) and hydrophilic (i.e., aqueous solubility = 3.3 mg/mL) drug. One can see that both of the acidic property and the hydrophilicity of aspirin were responsible for the enhanced PLGA degradation. Because of its acidity, aspirin was deprotonated in the water accessible regions of the PLGA matrix and decreased the pH inside the matrix, causing faster bulk erosion, and the hydrophilicity of aspirin facilitated the water absorption of PLGA thus increasing the degradation rates of PLGA.

PROCESSING FACTORS (DELIVERY SYSTEM DESIGNS)

As previously mentioned, we categorized the processing factors as the system design parameters that can be changed during synthesis, not the processing methodologies themselves. Unlike inherent material properties discussed in the previous section, the composition, the drug loading, the size/shape of the matrix, and the surface modifications in the drug-PLGA products can be modified as desired during processing.

Composition (LA/GA ratio)

Composition of PLGA (LA/GA ratio) is probably the most important influencing factor for controlling the degradation rates of the copolymer matrix. Since a higher content of GA will render PLGA more hydrophilic and more amorphous, it is clear that higher GA ratio will lead to much faster degradation as well as the drug release. Because altering the LA/GA composition ratio can be accomplished relatively easily during synthesis, and it exhibits a prominent effect on the drug release, there have been a large number of studies that have examined its impact.[5,17,39,45,50,80–83]

Lee et al.[5] investigated the difference in paclitaxel release patterns from LA/GA 85/15 and LA/GA 50/50. It was observed that, with initial paclitaxel drug loading of 2 wt %, the release rate from LA/GA 85/15 was 1.67 times lower than that of LA/GA 50/50. The release rate from LA/GA 85/15 was 2 times slower than that of LA/GA 50/50 in the case of 10 wt % initial drug loading. Other quantitative results supporting this correlation are tabulated in Table VI. The results of Ref. 80 in Table VI show that the release rate of mitomycin-C was 2.5-fold higher when the LA/GA ratio was altered from 90/10 to 70/30. Frank et al.[17] showed that in the first 120 days, the release amount of lidobase was nearly threefold higher when the LA/GA ratios were varied from 100/0 to 80/20 and *D* of lidobase became 472-fold higher (6.95×10^{-14} to 3.11×10^{-11} $cm^2\ s^{-1}$). Most studied PLGAs are synthesized with LA/GA ratios of 50/50 or higher. This is presumably due to the difficulty in synthesizing the PLGA systems with a low LA/GA ratio that is resulted from the higher probability of an uneven distribution of M_w and the limited solubility in solvents used during synthesis. Much of the prior work demonstrated that drugs are released substantially faster from PLGA 50/50 than from the copolymers with higher LA/GA ratio.[40,80] Therefore, PLGA 50/50 is likely an optimal choice for the most rapid release if only the effect of LA/GA ratio is considered. In Table VI, however, the data from Ref. 84 show that drug release amount from PLGA 75/25 was 68 wt % in 30 days, higher than 60 wt % from PLGA 50/50. This unexpected phenomenon may be accounted for the increasing nanoparticle size and narrower particle size distribution as the LA/GA ratio decreases; it was found that PLGA 75/25 and PLGA 50/50 enclosed drug particles with the size ranges of 50–1000 nm and 1000–1100 nm, respectively.

Figure 6(a) shows the drug release ratio with reference to the PLA proportions of PLGA copolymers from various PLGA drug delivery systems referred in Table VI. Note that the measurement time frames are varied for the data points in the figure. One can clearly see the overall trend that the drug release ratio decreases as the LA/GA ratio increases from 50/50 to 100/0. Of the data sets listed in Table VI, the drug release ratios of lidobase from PLGA thin films[17] were the smallest compared with that of drug release systems with the same LA/GA ratio, despite having the longest observation time. The main reason for this is likely the very large M_w of the polymers (i.e., 810 or 910 kDa) used in this study. In Table VI, only the release of imatinib mesylate from PLGA 50/50 exhibited 100% release of the initial loading in 30 days.[83] Reasons for such uncompleted release could be very complex. If the release is slow due to the drug–polymer interactions[17,80,81] or M_w of PLGA,[17,50] then the saturation amount in *in vitro* drug release could be limited by the types and the relative molecular sizes of solvents. Also, some release profiles were only given a part, not the whole duration of observation.[45,50] In Figure 6(b), selected examples of extracted log D_{eff} are plotted with their PLA proportion in the copolymers.[80,83,84] log D_{eff} values were estimated using Fick's second law equation for the systems to show biphasic release in Table VI. In these selected examples, it was found that c_∞ (released drug amount at infinite time) was substantially reduced by

TABLE VI. Effects of Compositions of Polymers/Copolymers (LA/GA Ratios) on Drug Release

Drug	Polymer/Copolymer	Factors, LA/GA Ratio	Results	Ref.
Lidobase	PLLA, PLGA (films)	100:0 (810 kDa)	Drug release amount: 9 wt % (80^{th} day) Diffusion coefficient: $D = 6.95 \times 10^{-14}$ cm^2 s^{-1}	17
		80:20 (910 kDa)	Drug release amount: 24 wt % (80^{th} day) Diffusion coefficient: $D = 3.11 \times 10^{-11}$ cm^2 s^{-1}	
Ovalbumin	PLGA (84 kDa, 1.6 μm)	75:25	Drug release amount: 45 wt % (7^{th} day)	45
		50:50	Drug release amount: 63 wt % (7^{th} day)	
Tetanus toxoid	PLA (9 ± 5 μm), PLGA(6 ± 3 μm) (3 kDa)	100:0	Drug release amount: 31 wt % (30^{th} day)	50
		50:50	Drug release amount: 69 wt % (30^{th} day)	
	PLA, PLGA (100 kDa, 60 ± 20 μm)	100:0	Drug release amount: 16 wt % (30^{th} day)	
		50:50	Drug release amount: 32 wt % (30^{th} day)	
Fentanyl	PLGA (630 nm)	75:25 (20 kDa, 8.5 ± 11.2 μm)	50% release in 7.1 days	51
		50:50 (33 kDa, 26.7 ± 3.4 μm)	50% release in 6.9 days	
Mitomycin-C	PLGA (150 μm)	90:10	Drug release amount: 30 wt % (90^{th} day) Diffusion coefficient: $D = 5.27 \times 10^{-12}$ cm^2 s^{-1}	80
		70:30	Drug release amount: 70 wt % (90^{th} day) Diffusion coefficient: $D = 8.14 \times 10^{-12}$ cm^2 s^{-1}	
Phenobarbitone	PLA, PLGA (240 nm)	100:0	Drug release amount: 50 wt % (30^{th} day)	81
		85:15	Drug release amount: 72 wt % (30^{th} day)	
		75:25	Drug release amount: 94 wt % (30^{th} day)	
Haloperidol	PLGA	95:5	Complete drug release in 13 days	82
		50:50	Complete drug release in 2 days	
Imatinib mesylate	PLGA (20 kDa, 33.83 μm)	85:15	Drug release amount: 64 wt % (6^{th} day)	83
		75:25	Drug release amount: 75 wt % (6^{th} day) Diffusion coefficient: $D = 6.27 \times 10^{-13}$ cm^2 s^{-1}	
		50:50	Drug release amount: 90 wt % (6^{th} day) Diffusion coefficient: $D = 1.49 \times 10^{-12}$ cm^2 s^{-1}	
Paclitaxel	PLA (589 nm)	100:0 (106 kDa)	Drug release amount: 53 wt % (30^{th} day) Diffusion coefficient: $D = 1.26 \times 10^{-17}$ cm^2 s^{-1}	84
	PLGA (272.5 nm)	75:25 (90–120 kDa)	Drug release amount: 68 wt % (30^{th} day) Diffusion coefficient: $D = 5.61 \times 10^{-18}$ cm^2 s^{-1}	
	PLGA (515.5 nm)	50:50 (40–75 kDa)	Drug release amount: 60 wt % (30^{th} day) Diffusion coefficient: $D = 1.48 \times 10^{-17}$ cm^2 s^{-1}	

increasing LA/GA ratios; therefore, estimated log D_{eff} values were nearly independent of the corresponding PLA proportions. This implies that, in many cases of *in vitro* dissolution experiments to show biphasic release, the LA/GA ratio affects the total release amount of drugs (c_∞), not D_{eff}.

Assuming that the matrix would completely erode at the end of the drug release, if the contribution of the matrix erosion and the diffusion to the drug release kinetics is combined, the following model can be used to describe a triphasic release for spherical system at time t.[85,86]

$$\frac{c_t}{c_\infty} = 6\sqrt{\frac{D_t t}{\pi r^2}} - 3\frac{D_t t}{r^2} + F_E\left[\frac{\exp(k_e t - k_e t_{max})}{1+\exp(k_e t - k_e t_{max})}\right] \quad (17)$$

$$D_t = D_0 \exp(kt) \quad (18)$$

where D_0, k, r, F_E, k_e, and t_{max} are the initial diffusion coefficient, the degradation constant, the radial coordinate, a parameter to regulate the contribution of matrix erosion, the acceleratory coefficient, and the time for the maximum erosion rate of polymers, respectively. Here, the parameters D_0, k, F_E, k_e, and t_{max} can be correlated to the composition and other factors such as initial loading.[85,86]

Drug loading

The relative amount of drug release is increased by incorporating higher initial drug loading.[18,39] This observation can be attributed to either of the following: (i) because the polymer network acts as a physical barrier for drug diffusion, smaller percent amount of network can weaken the physical barrier function of the network, and (ii) after the drug release out of the matrix, more voids will be left for water entrance, which can further attenuate the strength of polymer networks. However, when the initial drug loading reaches a certain level, it is generally observed that this drug loading effect is diminished.[39,87]

Leroux et al.[88] found that 90 wt % of savoxepine was released from PLA nanoparticles within 24 h with 16.7 wt % initial loading. In contrast, particles released their content over 3 weeks in the case of 7.1 wt % initial loading. As another example, Gümüşderelioğlu and Deniz[80] reported that when the initial drug (mitomycin-C) loadings were 0.5, 1.0, and 2.0 mg, the drug released 40, 48, and 70 wt %, respectively, from PLGA 70/30 after 90 days. Sampath et al.[87] studied gentamicin sulfate release from PLLA microcapsules. When the initial loadings were 10 and 33 wt %,

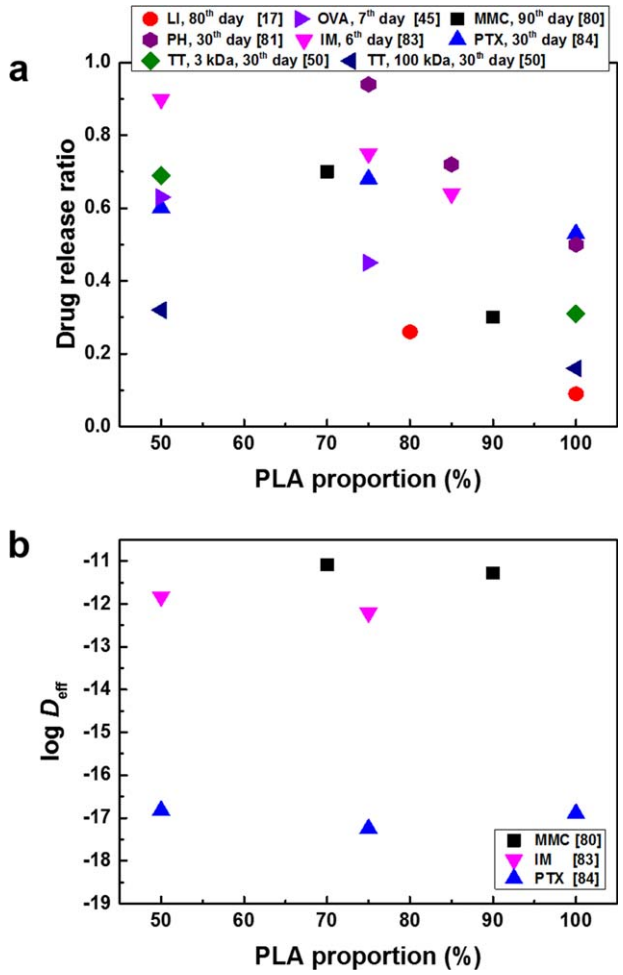

FIGURE 6. Selected examples of data to show (a) drug release ratios and (b) log D_{eff} as a function of PLA proportions of PLGA polymers. [$cm^2\ s^{-1}$] is used for the unit of D_{eff} (LI-lidobase, OVA-Ovalbumin, MMC-Mitomycin C, PH-Phenobarbitone, IM-Imatinib mesylate, PTX-Paclitaxel, TT-Tetanus toxoid).

essentially complete release of gentamicin sulfate occurred in 9 and 3 days, respectively. In their work, for initial loading of 5 wt %, complete release duration was more prolonged, but microcapsules containing 50 and 67 wt % gentamicin sulfate showed a similar release profile to that with 33 wt % initial loading. Such initial loading effect can be included in the mathematical model by determining an empirical D as a function of the initial loading amounts. For example, Siepmann et al.[89] established an exponential relationship between the D values of 5-FU in PDLLGA 50/50 and the initial drug loading, C_0 (%, w/w), as given by

$$D = 2.4\exp\left[0.21C_0(\%, w/w)\right]\times 10^{-14}\ \ [\mathrm{cm^2 s^{-1}}] \qquad (19)$$

However, the initial drug loading and the release amount do not necessarily exhibit a positive relationship. Mu and Feng[90] drew a conclusion according to their research results, as shown in the Table VII. They found that, for nanoparticles in a same dimension, the higher initial loading of drug leads to more compact internal structure, obstructing the water absorption into the matrix and consequently decelerating the drug diffusion rates. There are some other results that are in agreement with this finding. In Lee et al.'s study,[5] a fivefold higher relative paclitaxel release rate was observed at a low initial loading (2 wt %) as compared to a higher initial loading (10 wt %) from PLGA 50/50, and a 6-fold higher relative release rate was observed at a low paclitaxel loading (2 wt %) as compared with a higher paclitaxel loading (10 wt %) from PLGA 85/15. In Liu et al.'s work,[59] for the sirolimus containing 50/50 PLGA films, a slow release and a lack of an initial burst release were observed at low loading of 1 wt %. The authors reported that although the initial burst release increased after increasing the loading to 5 and 10 wt %, the drug release rates did not change significantly.[59] The effect of drug initial loading is, therefore, nontrivial, and is convoluted with other factors such as the dispersity of drug (or drug size) in the matrix.

Size of the matrix

The dimension or size of PLGA-based drug controlled release systems can impact the extent of autocatalysis and is therefore an important factor in the design of these systems.[8] Upon contact with water, PLGA can be cleaved into LA and GA. On one hand, the generated acids decrease pH of the surrounding environment, and because protons catalyze the degradation of PLGA, result in the acceleration of PLGA degradation, that is, autocatalysis. On the other hand, the bases can penetrate into the matrix from the outside environment neutralizing the generated acids. In general, the acid generation rate is higher than the neutralization rate for PLGA systems. It is expected that the longer the pathways of the diffusion are, the slower the bases diffuse into the system. Therefore, a larger size of PLGA matrix generally slows the process of neutralization and enhances the autocatalytic effect. This impacts the drug release rate in the following three ways; as the matrix size increases, it will (i) decrease the drug concentration gradient that will decelerate the drug release rate; (ii) lengthen the diffusion pathway that will decrease relative release rate; and (iii) create a more porous structure more rapidly due to the increasing autocatalytic effects, which will promote the drug release. From these, one can understand that the size of matrix can have either a negative (i.e., (i) or (ii)) or a positive (i.e., (iii)) impact on drug release.

In Table VIII, the examples of the accelerating effects of the matrix size on the degradation and the drug release are shown. As seen in the table, the relative and absolute release rates were found to increase with increasing microparticle size. As an example of the positive effects of the matrix size, it was reported that the D values of both ibuprofen and lidocaine drugs were found to greatly increase as the PLGA-based microparticle sizes increase.[34] One possible explanation for the observed behavior is the occurrence of positive autocatalytic effects (i.e., (i) and (ii) in the previous paragraph).[91–95] In Ref. 89, 5-FU-loaded PLGA-based microparticles have been prepared, and an empirical positive relationship between D and

TABLE VII. Negative Effects of the Drug Loading on Drug Release

Drug	Drug Carrier	Factors, Initial Drug Loading (wt %)	Results, Drug Release Amount Ratio After 1 month	Ref.
Paclitaxel	PLGA (TPGS as emulsifier)	2	30 wt %	90
		6	8 wt %	
		12	5 wt %	
	PLGA together with TPGS (PVA as emulsifier)	2	27%	
		6	20%	
		12	12.5%	

TPGS indicates D-α-tocopheryl polyethylene glycol 1000 succinate and PVA indicates poly(vinyl alcohol), respectively.

the size (i.e., radius R) of biodegradable microparticles has been established by

$$D = 2.4\exp\{0.21 \cdot 16.7 \cdot \ln[2R(\mu m)]\} \times 10^{-14} \ [cm^2 s^{-1}] \quad (20)$$

However, the data tabulated in Table IX also show a negative correlation between the size of the matrix and the drug release rate; larger polymeric nanoparticles exhibit a lower initial burst release and a slower sustained release compared to smaller particles.[18,97] It is interesting to note that positive autocatalytic effects should be reduced or even completely suppressed in highly porous PLGA particles even though they depend on the polymer degradation rate and the mobility of the species, because the diffusion of water-soluble acids and bases can be expected to be much more rapid.[98] In contrast to the either positive or negative effects of the polymer matrix size, results of some studies showed no obvious correlation between the size of the matrix and drug release. For instance, Klose et al.[34] investigated the release of ibuprofen and lidocaine from PLGA microparticles (diameters of around 16, 51, 76, and 104 μm), and Siepmann et al.[8] studied the kinetics of lidocaine release from PLGA-based microparticles with diameters of 7.2, 24, 37, and 53 μm. Both concluded that the relative drug release rates were similar for the ranges of microparticles size studied. This may stem from the combination that is compensated by the opposing two effects described above.

Analytical solutions of Fick's second law discussed in the "THEORETICAL AND COMPUTATIONAL MODELS" section can be generally used for estimating the effects of the shape and the size of matrix on drug release[8,26,34] by considering a dimensional parameter such as the radius R of the matrix in Eq. (1). In Ref. 99, mathematical models addressing the effects of phenomena attributed to autocatalysis on the drug release from PLGA systems have been reviewed. In this review, mathematical models were classified according to their focused phenomena; degradation, erosion, or drug transport. As an example of stochastic models for PLGA erosion, the probability of hydrolysis of an element (P_A) can be expressed by combining stochastic hydrolysis and diffusion-controlled autocatalysis as given by[25]

$$P_A = P_F + P_C = P_F + \beta\left(e^{C_m} - 1\right)P_F \quad (21)$$

where P_A, P_F, P_C, β, and C_m are the accelerated probability function for an element, the intrinsic probability of hydrolysis, the probability of hydrolysis due to autocatalysis, a system-specific multiplicative factor, and the local concentration of monomeric degradation products, respectively. Here, the size-dependent degradation and the erosion behavior could be predicted by fitting β to experimental data. As an example of a mathematical model for drug transport, Ref. 86 introduced Eq. (17) in which D can be considered to be inversely proportional to M_w, and the change of the M_w was

TABLE VIII. Accelerating Effects of the Sizes of the Matrix on Drug Release

Drug	Polymer/Copolymer	Factors, Matrix Diameter (μm)	Results	Ref.
Ibuprofen	PLGA	14–16	Diffusion coefficient: $D = 0.4 \times 10^{-12}$ cm^2 s^{-1}	34
		48–51	Diffusion coefficient: $D = 2.0 \times 10^{-12}$ cm^2 s^{-1}	
		74–76	Diffusion coefficient: $D = 4.4 \times 10^{-12}$ cm^2 s^{-1}	
		104–106	Diffusion coefficient: $D = 8.0 \times 10^{-12}$ cm^2 s^{-1}	
Lidocaine	PLGA	14–16	Diffusion coefficient: $D = 0.2 \times 10^{-12}$ cm^2 s^{-1}	
		48–51	Diffusion coefficient: $D = 0.7 \times 10^{-12}$ cm^2 s^{-1}	
		74–76	Diffusion coefficient: $D = 1.2 \times 10^{-12}$ cm^2 s^{-1}	
		104–106	Diffusion coefficient: $D = 2.0 \times 10^{-12}$ cm^2 s^{-1}	
5-Fluorouracil (5-FU)	PLGA	<36	Drug release amount: 56% (7th day)	89
		36–56	Drug release amount: 63% (7th day)	
		56–72	Drug release amount: 73% (7th day)	
		72–125	Drug release amount: 87% (7th day)	

TABLE IX. Decelerating Effects of the Sizes of the Matrix on Drug Release

Drug	Polymer/Copolymer	Factors, Size of the Matrix	Results	Ref.
Rhodamine B chloride	PLGA	Diameter 20 μm	Complete drug release in 8 days	91
		Diameter 40 μm	Complete drug release in 9 days	
		Diameter 65 μm	Complete drug release in 10 days	
Piroxicam	PLGA	Diameter 10 μm	Complete drug release in 5 days	
		Diameter 50 μm	Complete drug release in 8 days	
		Diameter 100 μm	Complete drug release in 10 days	
Cyclosporin A	PLGA 50/50	Size 312 nm	Drug release amount: 40 wt % (21^{st} day)	96
		Size 1842 nm	Drug release amount: 35 wt % (21^{st} day)	
		Size 5663 nm	Drug release amount: 25 wt % (21^{st} day)	

described by a first-order autocatalyzed polymer chain cleavage kinetics.[56,85,86]

Shape of the matrix

In addition to the size of the matrix, the shape of the matrix also has an effect on drug release kinetics. It has been shown that the ratio of surface area to volume can influence the degradation and drug release of polymer matrices significantly.[1,100–102] Generally, a larger surface area ratio will lead to larger degradation and drug release rates of the matrix.

Witt et al.[101] observed that as the surface-to-volume ratio increased, the onset time of erosion decreased in the rank order of rods (30 days) = tablets (30 days) > films (19 days) > microspheres (16 days) and the rate of erosion decreased in the rank order of rods (0.11 day^{-1}) > tablets (0.10 day^{-1}) > films (0.094 day^{-1}) > microspheres (0.042 day^{-1}), as shown in Table X. In Ref. 34, drug release from thin films and microspheres of comparable sizes were studied and compared. The authors found that the D values of ibuprofen and lidocaine were 4–5 times higher in thin films than those in spherical microparticles at comparable film thicknesses/microparticle diameters. Furthermore, Acharya et al.[103] studied the felodipine (FDP)-loaded PLGA with cylindrical structures. In their work, samples with distinct four particle dimensions were prepared: 10 × 10, 50 × 5, 20 × 20, 50 × 50 (diameter in μm × height in μm). After 14 days, the cumulative release amount for those samples were 100%, 100%, 70%, and 60%, respectively. The release kinetics for FDP (10 × 10) and FDP (50 × 5) were similar, which was not surprising since the total surface area for FDP (50 × 5) was 80% of that for FDP (10 × 10). This study, therefore, clearly demonstrates that the amount of drug release depends strongly on the total surface area available for drug release. As mentioned above, the appropriate form of Fick's second law may be applied to predict the drug release from the PLGA systems with various shapes.[26,27,104]

Microstructure of drug–polymer composites

Polymer block length. Drug release kinetics also depends on the microstructure, including the morphology and the porosity, of the drug-PLGA polymer matrix. The importance of microstructure was illustrated in a study of hydrolytic degradation from PLGA microspheres by Li et al.[105] This study demonstrated that the microspheres prepared from alternating copolymers of PLGA underwent 1.5 times slower hydrolysis than those made from the PLGA copolymers with longer blocks of LA and GA units. In Ref. 106, the influence of polymer structure of PEG (polyethylene glycol)–PLGA–PEG triblock copolymer hydrogel on the release of spironolactone drug was studied. In aqueous environment, the PEG–PLGA–PEG triblock copolymer hydrogel system had a structure of core-shell micelle; the hydrophobic PLGAs occupied the inner core region and hydrophilic PEGs constituted the outer shell region to decrease the free energy of

TABLE X. Effects of the Shapes of the Matrix on Polymer Degradation and Drug Release

Drug	Polymer/Copolymer	Factors, Shape of the matrix	Results	Ref.
Ibuprofen	PLGA	Films	Diffusion coefficient: $D = 2 \times 10^{-12}$ cm^2 s^{-1}	34
		Microspheres	Diffusion coefficient: $D = 0.4 \times 10^{-12}$ cm^2 s^{-1}	
Lidocaine	PLGA	Films	Diffusion coefficient: $D = 0.8 \times 10^{-12}$ cm^2 s^{-1}	
		Microspheres	Diffusion coefficient: $D = 0.2 \times 10^{-12}$ cm^2 s^{-1}	
N/A	PLGA	Tablets	Onset time of erosion: 30^{th} day Rate of erosion: 0.10 day^{-1}	101
		Rods	Onset time of erosion: 30^{th} day Rate of erosion: 0.11 day^{-1}	
		Films	Onset time of erosion: 19^{th} day Rate of erosion: 0.094 day^{-1}	
		Microspheres	Onset time of erosion: 16^{th} day Rate of erosion: 0.042 day^{-1}	

TABLE XI. Effects of the Morphologies of the Matrix on Polymer Degradation and Drug Release

Drug	Polymer/Copolymer	Factors, Morphology	Results	Ref.
Lidocaine	PLGA	Porous microparticles	Complete drug release in 30 days	98
		Nonporous microparticles	Complete drug release in 45 days	
N/A	PLGA	Alternating PLGA	M_w decreased 47 wt % (28^{th} day)	105
		Random PLGA	M_w decreased 71 wt % (28^{th} day)	
Spironolactone	PEG–PLGA–PEG (core–shell micelle)	PEG–PLGA–PEG block length: 550–2310–550	Permeability coefficient: 9.87×10^{-12} cm^2 s^{-1}	106
		PEG–PLGA–PEG block length: 550–2810–550	Permeability coefficient: 8.63×10^{-12} cm^2 s^{-1}	
Dextran	PLGA	Porous microspheres	Initial burst: 14.7%	108
		Nonporous microspheres	Initial burst: 6.6%	

hydration. The initial drug and polymer concentrations were fixed at 0.25 and 27 wt %, respectively. The permeability coefficients of spironolactone in the polymer PEG–PLGA–PEG with block lengths of (550–2310–550) and polymer PEG–PLGA–PEG (550–2810–550) were calculated as 9.87×10^{-12} and 8.63×10^{-12} cm^2 s^{-1}, respectively, indicating that if a structure included hydrophilic PEG and PLGA, then the larger PLGA block resulted in a lower apparent permeability of spironolactone due to reduced hydration.[106] Table XI summarizes the effects of morphology on the degradation of polymers and the drug release.

Drug distribution. Depending on the chemical interactions between drug and PLGA polymer matrix, the matrix size, and the processing history, the distribution aspects of drug phases inside PLGA matrix can be varied. In particular, highly hydrophobic drugs in polymeric microparticles often exhibit nonuniform drug distributions, which can impact the temporal amounts of release and the shape of release profiles.[15,107] Casalini et al.[107] presented a mathematical mechanistic model considering the nonuniform drug distribution in PLGA microparticles. In their model, the initial distribution of drugs as a function of radial distance from the center of microsphere was used to describe the degradation and the drug release behaviors of devices. The authors demonstrated that incorporating initial drug distribution into the model successfully reproduced the experimental measurements. Raman et al.[15] also introduced a model to include the influence of non-uniform initial drug distribution. In developing their model, the initial drug distribution was obtained explicitly by analyzing the confocal micrographs of drug-loaded microparticles, and then it was used to solve the classical Fick's diffusion equation as given in Eq. (5). With this model, a good agreement between model fitting and experimental data was achieved in piroxicam-PLGA microsphere systems.

Porosity. Porosity is another factor that influences the degradation processes and the drug release mechanisms of PLGA particles. Generally, the presence of pores is expected to increase the mobility of drug molecules in the PLGA system. Table XI contains two examples that show the effects of the porosity on the drug release. Klose et al.[98] studied the effects of the size of matrix on the release rate of lidocaine from porous PLGA-based microparticles and nonporous PLGA-based microparticles. In their experiments, it took 30 days for 100% drug release from the porous microparticles, while it took 45 days in nonporous microparticles.[98] The porosity not only influences drug mobility but also influences the drug transport mechanisms. It turned out that for porous microparticles, the relative lidocaine release rates were increased with decreasing particle sizes in PBS (phosphate-buffered saline) at pH 7.4; however, for initially nonporous microparticles with identical composition, the results were exactly opposite.[98] Porosity also affects the behavior of the initial and the second release phases from PLGA-based systems.[108,109] For example, by increasing the porosity of the PLGA microspheres, the initial burst release of fluorescein isothiocyanate-labeled dextran more than doubled, from 6.6% for the nonporous microspheres to 14.7% for the porous microspheres. However, the porous PLGA microspheres presented a lower release rate in the second stage; at 21 h of release, the cumulative release was around 30% for both the nonporous and porous particles.[108] This may be due to faster neutralization of autocatalysis effect because of the presence of the pores.

As for a mathematical modeling approach that includes the impact of the porosity, the model by Perale et al.[75] considers the polymer porosity (ε in Eq. (16)) that can be measured by calculating the volume increase of the polymer after swelling. The work of Siepmann et al.[24] should be mentioned as they developed a Monte-Carlo computation technique to consider a time- and spatial-dependent matrix porosity in describing the degradation and the release behaviors from bioerodible microparticles. As mentioned earlier, the authors included the microscopic nondegraded polymer, drug, and pore sectors in the computational model to predict the triphasic release kinetics. Stabenfeldt and Willits[110] employed the thin-film solution to Fick's second law for describing the ovalbumin (OVA) release from porous PLGA-PEG matrices. Zhao et al.[65] introduced an effective transient diffusion coefficient $D(t)_{eff}$ and related it to the diffusive protein release by considering the following expression.

TABLE XII. Effects of PEG on Drug Release

Drug	Polymer/Copolymer	Factors	Results	Ref.
Spironolactone	PEG–PLGA–PEG (core–shell micelle)	Block length: 550–2310–550	Permeability coefficient: 9.87×10^{-12} cm^2 s^{-1}	106
		Block length: 550–2810–550	Permeability coefficient: 8.63×10^{-12} cm^2 s^{-1}	
Ovalbumin	PEG–PLGA (discs, constant PLGA content)	OVA:PEG molar ratio 1:10	Diffusion coefficient: $D = 9.4 \times 10^{-11}$ cm^2 s^{-1}	110
		OVA:PEG molar ratio 1:100	Diffusion coefficient: $D = 2.4 \times 10^{-10}$ cm^2 s^{-1}	
		OVA:PEG molar ratio 1:1000	Diffusion coefficient: $D = 7.0 \times 10^{-9}$ cm^2 s^{-1}	
Bovine serum albumin	PLGA (particles)	PEG–PLGA	Initial burst: 30.1% Drug release amount: 71.4% (7th day)	115
		PLGA	Initial burst: 20.7% Drug release amount: 49.8% (7th day)	
Indomethacin	PEG-PLGA (films)	PEG 1.45 kDa	Drug release amount: 85% (21st day)	118
		PEG 10 kDa	Drug release amount: 100% (21st day)	

$$D(t)_{eff} = \frac{D(t)}{\tau} \quad (22)$$

where τ refers to the tortuosity factor, which reflects the influence of drug release via the serpentine channel.[111–113] $D(t)$ was defined as the hindered diffusion coefficient of drug in growing pore.

Surface modification (PEG)

As a surface modification agent, PEG—a hydrophilic, flexible, and nonionic polymer—has been broadly used to protect proteins from denaturation,[114,115] to maintain bioactivity of nerve growth factor,[114] and to improve the stability and dispersion of PLGA nanoparticles in biological fluids.[6]

PEG-PLGA micro/nanoparticles prepared from A–B diblock or A–B–A triblock structure polymers are commonly used.[106,116,117] Generally, it has been shown that adding PEG as the surface modification agent increases the amount of drug release. As discussed in the previous "Microstructure of drug–polymer composites" section, Jeong et al.[106] studied the drug delivery behavior from PEG–PLGA–PEG triblock copolymer hydrogel, and they showed that higher relative PEG content resulted in a larger apparent permeability of spironolactone drugs. In Ref. 117, PLGA nanospheres with a coating of diblock copolymer PEG–PLA (ratios of 5:2 and 4:3) displayed increased blood circulation time as well as reduced protein adsorption and liver uptake as compared with the uncoated PLGA nanospheres, suggesting they may be good candidates for modified site-specific drug delivery (i.e., targeted delivery) applications.

As another example, in Ref. 118, PEG–PLGA films have been used for implantable devices containing indomethacin (INC) cores. In this study, to predict the behavior of the implants during use, the effects of M_w of PEG (i.e., 1.45 and 10 kDa) on the drug release kinetics, the blood compatibility, and the morphology of the implants were studied *in vitro* (in blood and PBS at pH 7.4). Sustained release of INC was maintained over 21 days for both PLGA–PEG films consisting 1.45 kDa PEGs and PLGA–PEG films consisting 10 kDa PEGs, and the release profiles nearly followed zero-order release. For low M_w (1.45 kDa) PEGs, the release rates of INC were slightly lower compared to high M_w (10 kDa) PEG. At the end of the 21-day interval, PLGA–PEG films containing PEG of low M_w released 85% of the initial INC loading, whereas for PLGA–PEG films containing PEG of higher M_w, the release of INC was 100%. In terms of morphology, larger pores appeared on the surface of implants with high M_w of PEG after 2 days PBS immersion; therefore, the drug delivery rates/blood compatibility of the implants were enhanced. Good agreement between the Higuchi model and the drug release data indicated that the release of INC was likely governed by diffusion via the pores formed in PLGA-PEG films. The effective D of ovalbumin (OVA) in PLGA discs with varying amounts of PEG (1:10, 1:100, 1:1000 OVA:-PEG molar ratio) have been obtained by Stabenfeldt and Willits.[110] The authors found that higher PEG molar ratios increase the effective D of OVA. As another example, bovine serum albumin (BSA)-loaded PEG-PLGA particles had a higher release rate than BSA-loaded PLGA particles in Ref. 115. The BSA release ratio was 71.4% and 49.8% for PEG–PLGA and PLGA, respectively, on 7th day. Example studies to show these effects of PEG on the degradation and the drug release are summarized in Table XII.

Sterilization

Sterilization to avoid serious infection could be extremely important in drug delivery systems for physiological applications. ^{60}Co γ-irradiation sterilization has been a preferred method over other routes such as electron beam, ethylene oxide gas, steam, or dry heat for terminally sterilizing moisture- and heat-sensitive substances. γ-irradiation is a commonly employed sterilization method also for PLGA-based drug delivery systems because of its absence of post-sterilization treatment, negligible thermal effects, and high efficiency.[119–126] γ-irradiation can, however, change the internal structure in the irradiated polymers that will influence the drug release characteristics; γ-irradiation may lead to random chain cleavage of PLGA chains and accelerated degradation of M_w of PLGA copolymers.[119–126] For example, Montanari et al.[127] observed that the M_w-degradation was

TABLE XIII. Effects of pH on Polymer Degradation and Drug Release

Drug	Polymer/Copolymer	Factors, pH	Results	Ref.
5-Fluorouracil (5-FU)	PLGA	pH 1.3	Initial burst: 17% Complete drug release in 35 days	64
		pH 4.5	Initial burst: 17% Complete drug release in 35 days	
		pH 7.4	Initial burst: 63% Complete drug release in 21 days	
		pH 10.8	Initial burst: 97% Complete drug release in 2 days	
N/A	PLGA	pH 5.0	Mass loss: 82 wt % (25^{th} week)	129
		pH 6.4	Mass loss: 45 wt % (25^{th} week)	
		pH 7.4	Mass loss: 45 wt % (25^{th} week)	
Dexamethasone	PLGA 25 kDa	pH 2.4	Initial burst: 46% Zero-order rate constant: 3.48 day^{-1}	130
		pH 7.4	Initial burst: 52% Zero-order rate constant: 2.13 day^{-1}	
Dexamethasone	PLGA 70 kDa	pH 2.4	Zero-order rate constant: 5.45 day^{-1} 80% release in 52 days	
		pH 7.4	Zero-order rate constant: 1.85 day^{-1} 80% release in 84 days	

negligible when low irradiation dose (i.e., <15 kGy) was used, however, as the irradiation dose was increased to 25 kGy, a 10% decrease in M_w was observed. Irradiation can also induce other structural properties in PLGA copolymers. According to the differential scanning calorimetry (DSC) analysis in Ref. 128, γ-irradiation leads to decrease in the crystallinity and T_g. The decrease of the average M_w, crystallinity and T_g in turn accelerates the release rate of drugs. Generally, the drug release rate increases with increasing irradiation dose if the irradiation dose is larger than a specific threshold value.[123,126,128] For instance, no significant change in release curve of vancomycin-loaded PLGA microparticle was observed below 20 kGy irradiation, while a pronounced release peak in the first few days was observed above 25 kGy irradiation.[128]

PHYSIOLOGICAL FACTORS (TESTING ENVIRONMENTS)

pH

In general, it is believed that strongly acidic and basic media will expedite the polymer degradation[129]; however, if the media are only slightly acidic and/or neutral, there will be no significant difference in the degradation rates.[130] Table XIII summarizes the effects of pH on the degradation of polymers and the drug release. The mass loss data for PLGA 75/25 foams degraded at pH 5.0, 6.4, and 7.4 have been summarized by Holy et al.[129] They found that the mass loss rates of PLGA 75/25 foams degraded at pH 6.4 and 7.4 were ~2 times lower than that of foams degraded at pH 5.0. During the first 16 weeks, a similar mass loss (i.e., lower than 3%) was observed for all foams degraded at pH 5.0, 6.4, and 7.4. After 16 weeks, foams degraded at pH 6.4 and 7.4 lost mass at a lower rate, losing 45% of their initial mass by the end of week 25. In contrast, foams degraded at pH 5.0 showed a higher mass loss rate after 18 weeks, losing 82% of their initial mass by week 25.

Zolnik and Burgess[130] showed that dexamethasone release kinetics from the 25 kDa PLGA microspheres followed a triphasic release profile at both pH 2.4 and 7.4, similar to the curves shown in Figure 3. From 25 kDa PLGA microspheres, the initial burst reached 46% and 52% for pH 2.4 and 7.4, respectively, and the lag phases were comparable for both pH conditions. The kinetics of the secondary zero-order phase was faster in the system at pH 2.4 (3.48 day^{-1}) than pH 7.4 (2.13 day^{-1}). The release profiles reached a plateau in 19 days and in 30 days for pH 2.4 and 7.4, respectively. For 70 kDa PLGA microspheres, the release behavior in the initial burst and lag phases were similar at both pH values. However, the kinetics of the secondary zero-order phase was faster at pH 2.4 (5.45 day^{-1}) than that in the case of pH 7.4 (1.85 day^{-1}). The time to reach 80% of drug release was increased from 52 days at pH 2.4 to 84 days at pH 7.4. The release profiles of 5-FU from PLGA 50/50 have been studied in Ref. 64. The initial burst release reached 17%, 63%, and 97% for pH 1.3/4.5, 7.4, and 10.8, respectively, and the 100% release plateaus were reached in 35, 21, and 2 days for pH 1.3/4.5, 7.4, and 10.8, respectively. Therefore, one can see that, in these two studies, strong acidic and basic environment would accelerate the PLGA polymer degradation rates as well as the drug delivery rates.

Drug release medium

The release kinetics is generally influenced by the types and the compositions of drug release medium (pH, ionic strength, buffer species, and so forth),[131–133] and different types of release medium may be tested to identify the adequate *in vitro* release environment that can reproduce *in vivo* testing.

PBS, serum, and plasma solution are one of the candidate release media that were tested conventionally. For *in vitro* release experiments, PBS is a commonly used release medium to maintain constant pH and osmolarity that match with body fluids. To further imitate *in vivo* situation in blood, however, testing in serum (i.e., plasma from which the clotting proteins have been removed) or plasma-contained media is more suitable because they include the

TABLE XIV. Effects of Temperatures on Drug Release

Drug	Polymer/Copolymer	Factors, Temperature (°C)	Results	Ref.
5-Fluorouracil (5-FU)	PLGA	37	Drug release amount: 56% (75^{th} hour)	64
		45	Drug release amount: 85% (75^{th} hour)	
		53	Drug release amount: 100% (75^{th} hour)	
		60	Drug release amount: 100% (25^{th} hour)	
		65		
Dexamethasone	PLGA	53	Initial burst: 26% Zero-order rate constant: 13.76 day^{-1} Complete drug release in 4 days	139
		60	Initial burst: 36% Zero-order rate constant: 18.33 day^{-1} Complete drug release in 3 days	
Peptide	PLGA (T_g = 40∼50°C)	37	Drug release amount: 23% (40^{th} hour)	140
		40	Drug release amount: 33% (40^{th} hour)	
		50	Drug release amount: 100% (40^{th} hour)	
		55		
		60		

effects of plasma/serum proteins[131,134–137] and different ionic species in tissue fluids.[138] Generally, it was found that the drug release and degradation rates are faster in serum and plasma than in PBS. For example, Blanco-Príeto et al.[131] compared the release of vapreotide pamoate from PLGA in PBS of pH 7.4 and in serum. In their work, 52% of the peptide drug was released in PBS, whereas 68% was released in serum within the first 15 days. The authors attributed the faster release in serum to the higher solubility of the peptide drug and binding to plasma proteins in this medium. They concluded that serum was a more appropriate release test medium for vapreotide pamoate compared to PBS because a better correlation to *in vivo* results was found using serum compared to PBS pH 7.4.[131] Zhang et al.[134] also found that the doxorubicin release rate from PLGA-based nanoparticles were slightly faster in fetal bovine serum than in PBS; in 90 h, the cumulative doxorubicin released from PLGA, PLGA-*b*-D-α-tocopheryl polyethylene glycol 1000 succinate (PLGA-*b*-TPGS), and mannitol-functionalized PLGA-*b*-TPGS nanoparticles were 45.14 vs 53.12%, 58.94 vs 73.44%, and 76.41 vs 83.11% for PBS and fetal bovine serum, respectively. This could be explained by the adsorption of serum proteins onto the nanoparticle surface reducing the stability of partial particles. Gido et al.[137] demonstrated that using diluted plasma as dissolution medium for doxepin-loaded PLGA microspheres could obtain a better *in vitro–in vivo* correlation compared to phosphate buffer pH 7.4 and this probably was a result of the plasma protein binding as well. To find the correlation between *in vitro* and *in vivo* degradation behaviors of PLGA, Fredenberg et al.[138] used PBS and another buffer containing salts similar to plasma, and they found that PLGA degraded faster in the plasma buffer than in PBS due to the catalyzing effect of divalent ions (Ca^{2+}, Mg^{2+}) on degradation.

Temperature

Increasing temperature will enhance the polymer mobility and thereby accelerating the drug diffusion. Although the drug dissolution testing is typically conducted at physiological temperature (i.e., 37°C), *in vitro* experiments at higher temperatures are often carried out, because the drug release testing at 37°C is a time-consuming process ranging from days to months. Increasing temperature is one of the strategies to accelerate the release, and it is used to correlate the "real-time" release profile/kinetics and the accelerated release profile/kinetics of a particular batch. Therefore, the "real-time" release profile or kinetics can be predicted by implementing the accelerated testing at high temperatures. Table XIV summarizes temperature effects on drug release. For instance, Zolnik et al.[139] studied the release kinetics of dexamethasone from 25 kDa PLGA at different temperatures. In their experiments, the burst release values increased from 26% at 53°C to 36% at 60°C. After initial burst release, drug release of both cases followed a zero-order release profile. The zero-order rate constants (i.e., slope of the profile) were 13.76 and 18.33 day^{-1} at 53 and 60°C, respectively. The time to reach 100% release was 3 days at 60°C compared to 4 days at 53°C, respectively. In a study by Faisant et al.,[64] the release of 5-FU from PLGA-based microparticles have been examined. The drug release rates for 65 and 60°C were similar, and the time to complete release for them were both 25 h. The time to complete release for 53°C was 75 h, while the drug was just released 85% and 56% for 45°C and 37°C, respectively, after 75 h.

For mathematical modeling, the following exponential relationship between the initial drug diffusion coefficient, D, and the temperature, T, has been developed by Faisant et al.[64]

$$D = 2.68\exp\left[0.1557\ T(^{\circ}\mathrm{C})\right] \times 10^{-14}\ \left[\mathrm{cm^2 s^{-1}}\right] \qquad (23)$$

The degree of temperature effects is also associated with the T_g values of PLGA polymers. To support the impact of temperature in conjunction with T_g, Shameem et al.[140] measured the release of peptide from 50/50 PLGA microspheres without buffer at temperatures 37, 40, 50, 55, and 60°C. The T_g values of the host polymer were between 40 and 50°C. By comparing the % peptide released profiles, it

TABLE XV. Effects of *in vitro* and *in vivo* Testing on Polymer Degradation and Drug Release

Drug	Polymer/Copolymer	Factors, Testing Environment	Results	Ref.
Thymosin alpha 1	PLGA	*in vitro*	Drug release amount (28^{th} day): 90 wt %	143
		in vivo	Drug release amount (28^{th} day): 95 wt %	
N/A	PLGA (500 nm particles)	*in vitro* and *in vivo*	Degradation rate ratio (*in vitro*:*in vivo*) in spleen (170^{th} hour): 1:0.67	144
			Degradation rate ratio (*in vitro*:*in vivo*)in liver (170^{th} hour): 1:1	
	PLGA (200 nm particles)	*in vitro* and *in vivo*	Degradation rate ratio (*in vitro*:*in vivo*)in spleen (170^{th} hour): 1:2	
			Degradation rate ratio (*in vitro*:*in vivo*)in liver (170^{th} hour): 1:2	

was found that at the temperature above T_g, the release of peptide was faster. The release acceleration was more significant after temperature changes of 40 to 50°C compared with 50 to 60°C due to T_g of the polymer. Peptide release was completed in 40 h at 50–60°C, while the relative release amounts of peptide were only 23% at 37°C and 33% at 40°C, respectively.

In vitro and *in vivo*

Current *in vitro* release models are able to mimic the kinetics processes that the drug substance may encounter in the biological environment at the administration site. However, one can recognize that the difference of the release performance of a controlled release device would exist between *in vitro* and *in vivo* environments especially when the drug-polymer product is degradable. Currently, no firm correlation between *in vitro* and *in vivo* testing exists.

It has been reported that *in vivo* polymer degradation could be faster than *in vitro* assays in buffer solution due to the immunological response which might cause *in situ* release of radicals or other harmful compounds[141] and a plasticizing effect of biological substances like lipids.[142] Thymosin alpha 1 was released from PLGA *in vivo* at a slightly higher rate (95 wt % in 28 days) than that of the *in vitro* release (90 wt % in 28 days).[143] However, *in vivo* polymer degradation could also be slower than *in vitro* assays.[144] In other words, a relationship—if any—between the delivery kinetics *in vitro* and *in vivo* is not straightforward to identify.

Table XV lists some examples for the effects of *in vitro* and *in vivo* on the degradation of polymers and drug release. Liu et al.[143] showed a similarity in the drug release amounts in the 28^{th} day from *in vitro* and *in vivo* testing. Mohammad and Reineke[144] quantitatively measured the *in vivo* degradation of PLGA nanoparticles after injection in tail vein of mice and compared the results with those from *in vitro* testing. Both in liver and spleen, the 200 nm nanoparticles had a degradation rates nearly double of that in the *in vitro* experiments. In the liver, the 500 nm nanoparticles had a similar degradation rate as *in vitro*, whereas in spleen, the degradation rate of the 500 nm nanoparticles was only 0.67 times of that *in vitro*. This may be attributed to the autocatalytic degradation behavior described previously for PLGA where it is known that larger particles degrade more rapidly *in vitro*. Zolnik and Burgess[145] evaluated the release of dexamethasone from PLGA microspheres *in vivo* and *in vitro* and established the following relationship (Eq. (24)) for the 28 kDa formulation.[145] The authors then applied the equation to predict the *in vivo* release of the 13 kDa formulation and showed that the predicted values for 13 kDa formulation *in vivo* match well with the experimental data.

$$\%\ \textit{in vivo}\ \text{release} = 1.6381\ (\%\ \textit{in vitro}\ \text{release}) - 24.457 \quad (24)$$

DRUG DELIVERY MODULATION

There have been extensive efforts to modulate the release kinetics for stimulated or sustained drug delivery from PLGA-based systems. Few functional groups in the polymeric chain and hydrophobic surface can hamper the extended usage of PLGA. Intrinsic limitations of parenteral bare PLGA nanoparticles include rapid removal from circulation in the blood, disability to distinguish different cell types, poor uptake by cells, proteins and peptides aggregation during the loading process, and so forth.[146,147] To overcome such drawbacks, versatile approaches have been explored to functionalize bare PLGA materials, generally including conjugation with cell-targeting ligands, polyion complexation, lipid- or surfactant-coating, and surface modification by PEG.[146,147] Because PLGA has been widely used in controlled release systems, especially in parenteral and implantation applications,[146–148] stimulated drug delivery systems based on PLGA have been developed including light-triggered drug delivery,[149,150] electro-responsive systems,[151] and pH-sensitive systems.[152–155] Also, a "random"

TABLE XVI. Summary of the Correlation Between the Corresponding Factors and the Drug Release Rates from PLGA-Based Drug Delivery Systems

Factors			Correlation
Material factors	Polymer	Crystallinity	Negative
		Molecular weight (M_w)	Negative
		Cross-linking density of a polymer network	Negative
		Glass transition temperature (T_g)	Negative
	Drug	Drug type (hydrophobicity)	Negative
		Drug size	Negative
		Drug–polymer interaction	Acidic drugs: positive; basic drugs: positive/negative
Processing factors		Composition (GA content)	Positive
		Drug loading	Positive/negative/no correlation
		Size of the matrix	Size of the matrix in general: Positive/negative; autocatalysis: positive
		Shape of the matrix	Surface area ratio: positive
		Block length	Positive
		Porosity	Positive/negative
		PEG	Positive
		γ-irradiation sterilization	Positive
Physiological factors		Physiological pH	Positive/negative/no correlation
		Drug release medium	Drug release and polymer degradation rates: in serum/plasma > in PBS
		Physiological temperature	Positive

copolymerization technique has been applied to control the dispersity of PLGA copolymers for stimulated drug release.[105,156,157]

On the other hand, sustained delivery forms are sometimes highly desirable to avoid concentration peak and valley in human body and enhance patient compliance. The main problem with using PLGA for sustained release is a high initial burst release of drugs.[148,158] Means of controlling the initial burst release can be developed based on considering the material and the processing factors addressed in this document. For instance, low M_w often exhibits a higher initial burst and earlier start of erosion than high M_w-PLGA systems.[7] Intermediate properties can be achieved by combining PLGA particles of various M_w.[159] Combining PLGA particles of different sizes can alter the drug release profile, from a triphasic profile to a preferred zero-order profile.[16] Also, increasing the LA/GA ratio can modulate the burst by increasing the hydrophobicity of PLGA.[46]

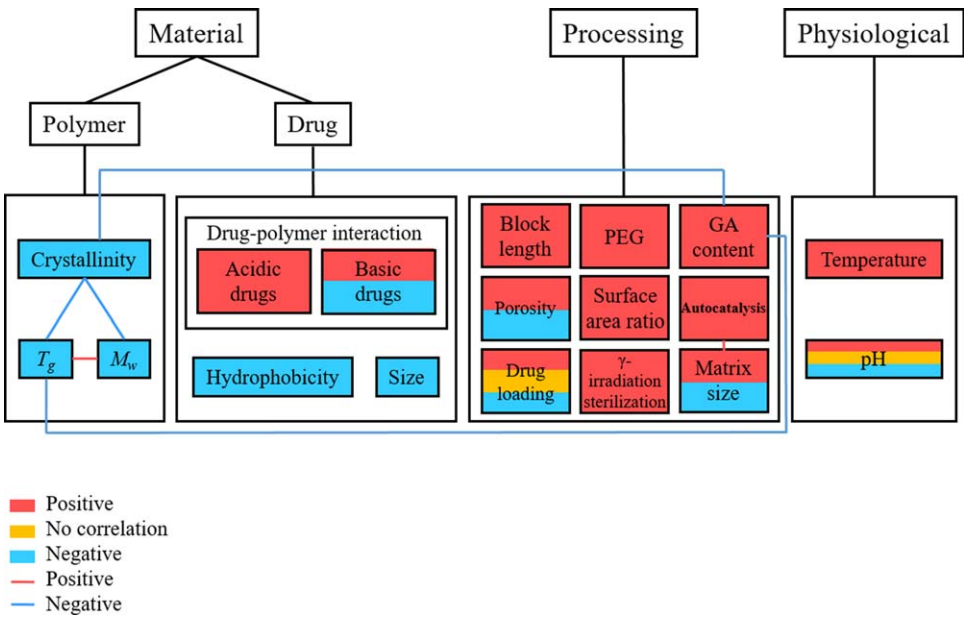

FIGURE 7. Summary chart of the correlation between the corresponding factors and the drug release rates from PLGA-based drug delivery systems.

Additionally, the burst release caused by the onset of erosion also could be controlled through decreasing the hydrolysis rate. In Ref. 160, it was reported that end-capping PLGA with alcohols decreases the hydrolysis rates because this renders PLGA more hydrophobic and the capped acids cannot participate in autocatalysis. PLGA with alternating LA/GA sequence undergoes slower hydrolysis than those with longer blocks of LA and GA units.[105] Besides PLGA polymer factors, other factors such as initial drug loading, hydrophobicity of drug, and drug–polymer interactions can also play an important role in achieving sustained release behaviors.

SUMMARY AND CONCLUDING REMARKS

This article reviews correlations between drug release rates and the physicochemical factors that influence them in biodegradable PLGA-based delivery systems. We systematically categorized these factors considering the material, the processing, and the physiological (i.e., testing environment) factors. Table XVI summarizes the general correlations between the physicochemical factors and the release rates from PLGA-based drug delivery systems. In the table, the impact of increasing a given factor is associated with either a "positive" or "negative" correlation, corresponding to the accelerating and the decelerating effects on the drug release rates, respectively. Some factors listed in Table XVI show both of the positive and negative effects. Also, there are some factors to impose "no correlation" under certain situations, such as the drug loading and the pH value of the testing environments. These correlations are schematically illustrated in the summary chart presented in Figure 7. In this figure, the backgrounds of individual factors are filled with colors to indicate the observed correlations between the factor and the degree of drug release. The color of solid lines also denotes the direct (red lines) or the indirect/inverse (blue lines) correlations between two mutual factors in a qualitative sense.

Among the factors addressed in Table XVI and Figure 7, M_w and LA/GA composition ratio of PLGA are the ones that have been most widely studied because they can present explicit relationship with the degradation/drug release rates of PLGA and can be easily controlled during manufacturing. Based on research results collected in this work, it is at least known that increasing the M_w can reduce D of the drug as much as 85.7 times, the drug release by 3.7 times, and the initial burst amount by 8.5 times. By increasing the LA/GA ratio, D could be decreased as much as 472-fold in a certain situation, and the drug release amount could be decreased as much as 3 times. However, as shown in Table XVI and Figure 7, there are numerous physicochemical factors that are interrelated to dictate the drug release kinetics in a convoluted, nontrivial way. The combined impacts of these material, processing, and physiological parameters must be carefully considered when tailoring the polymer degradation and the drug release for a specific application.

DISCLAIMERS

The mention of commercial products, their source, or their use in connection with the material reported herein is not to be construed as either an actual or implied endorsement of the U.S. Food and Drug Administration.

REFERENCES

1. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers 2011;3:1377–1397.
2. Cabezas LI, Gracia I, de Lucas A, Rodríguez JF. Novel model for the description of the controlled release of 5-fluorouracil from PLGA and PLA foamed scaffolds impregnated in supercritical CO_2. Ind Eng Chem Res 2014;53:15374–15382.
3. Göpferich RA. Mechanisms of polymer degradation and erosion. Biomaterials 1996;17:103–114.
4. Omelczuk MO, McGinity JW. The influence of polymer glass transition temperature and molecular weight on drug release from tablets containing poly(DL-lactic acid)). Pharm Res 1992;9:26–32.
5. Lee LY, Ranganath SH, Fu Y, Zheng JL, Lee HS, Wang CH, Smith KA. Paclitaxel release from micro-porous PLGA disks. Chem Eng Sci 2009;64:4341–4349.
6. Alonso-Sande M, des Rieux A, Fievez V, Sarmento B, Delgado A, Evora C, Remuñán-López C, Préat V, Alonso MJ. Development of PLGA-mannosamine nanoparticles as oral protein carriers. Biomacromolecules 2013;14:4046–4052.
7. Fredenberg S, Wahlgren M, Reslow M, Axelsson A. The mechanisms of drug release in poly (lactic-co-glycolic acid)-based drug delivery systems-A review. Int J Pharmaceut 2011;415:34–52.
8. Siepmann J, Elkharraz K, Siepmann F, Klose D. How autocatalysis accelerates drug release from PLGA-based microparticles: A quantitative treatment. Biomacromolecules 2005;6:2312–2319.
9. Grayson ACR, Voskerician G, Lynn A, Anderson JM, Cima MJ, Langer R. Differential degradation rates *in vivo* and *in vitro* of biocompatible poly (lactic acid) and poly (glycolic acid) homo- and co-polymers for a polymeric drug-delivery microchip. J Biomat Sci Polym E 2004;15:1281–1304.
10. Wu XS, Wang N. Synthesis, characterization, biodegradation, and drug delivery application of biodegradable lactic/glycolic acid polymers. Part II: Biodegradation. J Biomat Sci Polym E 2001;12:21–34.
11. Lee JS, Chae GS, Kim MS, Cho SH, Lee HB, Khang G. Degradation behaviour *in vitro* for poly (D, L-lactide-co-glycolide) as drug carrier. Biomed Mater Eng 2004;14:185–192.
12. Braunecker J, Baba M, Milroy GE, Cameron RE. The effects of molecular weight and porosity on the degradation and drug release from polyglycolide. Int J Pharmaceut 2004;282:19–34.
13. Sonam, Chaudhary H, Arora V, Kholi K, Kumar V. Effect of physicochemical properties of biodegradable polymers on nano drug delivery. Polym Rev 2013;53:546–567.
14. Mundargi RC, Babu VR, Rangaswamy V, Patel P, Aminabhavi TM. Nano/micro technologies for delivering macromolecular therapeutics using poly (D, L-lactide-co-glycolide) and its derivatives. J Control Release 2008;125:193–209.
15. Raman C, Berkland C, Kim KK, Pack DW. Modeling small-molecule release from PLG microspheres: Effects of polymer degradation and nonuniform drug distribution. J Control Release 2005;103:149–158.
16. Berkland C, King M, Cox A, Kim KK, Pack DW. Precise control of PLG microsphere size provides enhanced control of drug release rate. J Control Release 2002;82:137–147.
17. Frank A, Rath SK, Venkatraman SS. Controlled release from bioerodible polymers: Effect of drug type and polymer composition. J Control Release 2005;102:333–344.
18. Hans ML, Lowman AM. Biodegradable nanoparticles for drug delivery and targeting. Curr Opin Solid St M 2002;6:319–327.
19. Nicoli S, Santi P, Couvreur P, Couarraze G, Colombo P, Fattal E. Design of triptorelin loaded nanospheres for transdermal iontophoretic administration. Int J Pharmaceut 2001;214:31–35.
20. Corrigan OI, Li X. Quantifying drug release from PLGA nanoparticulates. Eur J Pharm Sci 2009;37:477–485.

21. Lauzon MA, Bergeron E, Marcos B, Faucheux N. Bone repair: New developments in growth factor delivery systems and their mathematical modeling. J Control Release 2012;162:502–520.
22. Sackett CK, Narasimhan B. Mathematical modeling of polymer erosion: Consequences for drug delivery. Int J Pharmaceut 2011; 418:104–114.
23. Arifin DY, Lee LY, Wang CH. Mathematical modeling and simulation of drug release from microspheres: Implication to drug delivery systems. Adv Drug Deliv Rev 2006;58:1274–1325.
24. Siepmann J, Faisant N, Benoit JP. A new mathematical model quantifying drug release from bioerodible microparticles using Monte Carlo simulations. Pharm Res 2002;19:1885–1893.
25. Chen Y, Zhou S, Qing L. Mathematical modeling of degradation for bulk-erosive polymers: Applications in tissue engineering scaffolds and drug delivery systems. Acta Biomaterialia 2011;7: 1140–1149.
26. Crank J. The mathematics of Diffusion, 2nd ed. Oxford: Clarendon Press; 1975. pp 48–91.
27. Fu JC, Hagemeir C, Moyer DL, Ng EW. A unified mathematical model for diffusion from drug-polymer composite tablets. J Biomed Mater Res 1976;10:743–758.
28. Higuchi T. Rate of release of medicaments from ointment, bases containing drugs in suspensions. J Pharm Sci 1961;50:874–875.
29. Siepmann J, Siepmann F. Modeling of diffusion controlled drug delivery. J Control Release 2012;161:351–362.
30. Siepmann J, Peppas NA. Higuchi equation: Derivation, applications, use and misuse. Int J Pharmaceut 2011;418:6–12.
31. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharmaceut 1983;15:25–35.
32. Ritger PL, Peppas NA. A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J Control Release 1987;5:23–36.
33. Ritger PL, Peppas NA. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Control Release 1987;5:37–42.
34. Klose D, Siepmann F, Elkharraz K, Siepmann J. PLGA-based drug delivery systems: Importance of the type of drug and device geometry. Int J Pharmaceut 2008;354:95–103.
35. Lao LL, Venkatraman SS, Peppas NA. Modeling of drug release from biodegradable polymer blends. Eur J Pharm Biopharm 2008;70:796–803.
36. Batycky RP, Hanes J, Langer R, Edwards DA. A theoretical model of erosion and macromolecular drug release from biodegrading microspheres. J Pharm Sci 1997;86:1464–1477.
37. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. Int J Pharmaceut 2008;364:328–343.
38. Hadjitheodorou A, Kalosakas G. Quantifying diffusion-controlled drug release from spherical devices using Monte Carlo simulations. Mat Sci Eng C 2013;33:763–768.
39. Alexis F. Factors affecting the degradation and drug-release mechanism of poly (lactic acid) and poly [(lactic acid)-co-(glycolic acid)]. Polym Int 2005;54:36–46.
40. Jain RA. The manufacturing techniques of various drug loaded biodegradable poly (lactide-co-glycolide)(PLGA) devices. Biomaterials 2000;21:2475–2490.
41. Miyajima M, Koshika A, Okada JI, Ikeda M, Nishimura K. Effect of polymer crystallinity on papaverine release from poly (L-lactic acid) matrix. J Control Release 1997;49:207–215.
42. Kaur MAS. Poly (dl-lactide-co-glycolide) 50:50-hydrophilic polymer blends: Hydrolysis, bioadhesion and drug release characterization. ProQuest; 2008:22.
43. Hurrell S, Cameron RE. The effect of initial polymer morphology on the degradation and drug release from polyglycolide. Biomaterials 2002;23:2401–2409.
44. Wang Y, Pan J, Han X, Sinka C, Ding L. A phenomenological model for the degradation of biodegradable polymers. Biomaterials 2008;29:3393–3401.
45. O'Hagan DT, Jeffery H, Davis SS. The preparation and characterization of poly (lactide-co-glycolide) microparticles: III. Microparticle/polymer degradation rates and the *in vitro* release of a model protein. Int J Pharmaceut 1994;103:37–45.
46. Mittal G, Sahana DK, Bhardwaj V, Kumar MR. Estradiol loaded PLGA nanoparticles for oral administration: Effect of polymer molecular weight and copolymer composition on release behavior *in vitro* and *in vivo*. J Control Release 2007;119:77–85.
47. Liggins RT, Burt HM. Paclitaxel loaded poly (L-lactic acid) microspheres: Properties of microspheres made with low molecular weight polymers. Int J Pharmaceut 2001;222:19–33.
48. Makino K, Nakajima T, Shikamura M, Ito F, Ando S, Kochi C, Inagawa H, Soma GI, Terada H. Efficient intracellular delivery of rifampicin to alveolar macrophages using rifampicin-loaded PLGA microspheres: Effects of molecular weight and composition of PLGA on release of rifampicin. Colloids Surf B 2004;36: 35–42.
49. Zhu X, Braatz RD. A mechanistic model for drug release in PLGA biodegradable stent coatings coupled with polymer degradation and erosion. J Biomed Mater Res A 2015;103A:2269–2279.
50. Alonso MJ, Gupta RK, Min C, Siber GR, Langer R. Biodegradable microspheres as controlled-release tetanus toxoid delivery systems. Vaccine 1994;12:299–306.
51. Seo SA, Khang G, Rhee JM, Kim J, Lee HB. Study on *in vitro* release patterns of fentanyl-loaded PLGA microspheres. J Microencapsul 2003;20:569–579.
52. Wada R, Hyon SH, Ikada Y. Lactic acid oligomer microspheres containing hydrophilic drugs. J Pharm Sci 1990;79:919–924.
53. Karavelidis V, Giliopoulos D, Karavas E, Bikiaris D. Nanoencapsulation of a water soluble drug in biocompatible polyesters. Effect of polyesters melting point and glass transition temperature on drug release behavior. Eur J Pharm Sci 2010;41:636–643.
54. Gu Z. Bioinspired and Biomimetic Polymer Systems for Drug and Gene Delivery. John Wiley & Sons; 2015. 113.
55. Wang N, Wu XS, Li C, Venkatraman SS. Synthesis, characterization, biodegradation, and drug delivery application of biodegradable lactic/glycolic acid polymers: I. Synthesis and characterization. J Biomat Sci Polym E 2000;11:301–318.
56. Pitt CG, Gu Z. Modification of the rates of chain cleavage of poly (-caprolactone) and related polyesters in the solid state. J Control Release 1987;4:283–292.
57. Cabezas LI, Gracia I, de Lucas A, Rodríguez JF. Validation of a mathematical model for the description of hydrophilic and hydrophobic drug delivery from biodegradable foams: Experimental and comparison using indomethacin as released drug. Ind Eng Chem Res 2014;53:8866–8873.
58. Siegel SJ, Kahn JB, Metzger K, Winey KI, Werner K, Dan N. Effect of drug type on the degradation rate of PLGA matrices. Eur J Pharm Biopharm 2006;64:287–293.
59. Liu HZ, Qi M, Guo B, Liu HH. Effects of hydrophilicity/hydrophobicity of a drug on its release from PLGA films. Mater Sci Forum 2011;675-677:369–372.
60. Liu H, Finn N, Yates MZ. Encapsulation and sustained release of a model drug, indomethacin, using CO_2-based microencapsulation. Langmuir 2005;21:379–385.
61. Polakovič M, Görner T, Gref R, Dellacherie E. Lidocaine loaded biodegradable nanospheres: II. Modelling of drug release. J Control Release 1999;60:169–177.
62. Rouzes C, Leonard M, Durand A, Dellacherie A. Influence of polymeric surfactants on the properties of drug-loaded PLA nanospheres. Colloids Surf B 2003;32:125–135.
63. Martins IM, Rodrigues SN, Barreiro MF, Rodrigues AE. Release of thyme oil from polylactide microcapsules. Ind Eng Chem Res 2011;50:13752–13761.
64. Faisant N, Akiki J, Siepmann F, Benoit JP, Siepmann J. Effects of the type of release medium on drug release from PLGA-based microparticles: Experiment and theory. Int J Pharmaceut 2006; 314:189–197.
65. Zhao A, Hunter SK, Rodgers VGJ. Theoretical prediction of induction period from transient pore evolvement in polyester-based microparticles. J Pharm Sci 2010;99:4477–4487.
66. Barichello JM, Morishita M, Takayama K, Nagai T. Encapsulation of hydrophilic and lipophilic drugs in PLGA nanoparticles by the nanoprecipitation method. Drug Dev Ind Pharm 1999;25:471–476.
67. Avdeef A. Absorption and Drug Development: Solubility, Permeability, and Charge State. John Wiley & Sons; 2012. pp 201–209.

68. Hansch C, Leo A, Hoekman D. Exploring QSAR: Volume 2: Hydrophobic, Electronic and Steric Constants. American Chemical Society; 1995. p 7.
69. Berthod A, Ruiz-Angel MJ, Carda-Broch S. Ionic liquids as stationary phases in countercurrent chromatography. In: Koel M, editor. Ionic Liquids in Chemical Analysis, ch 7. CRC Press; 2008. p 225.
70. Lao LL, Venkatraman SS, Peppas NA. A novel model and experimental analysis of hydrophilic and hydrophobic agent release from biodegradable polymers. J Biomed Mater Res A 2009;90: 1054–1065.
71. Ford JL, Rubinstein MH, Hogan JE. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl-methylcellulose matrices. Int J Pharmaceut 1985; 24(2):327–338.
72. Ford JL, Rubinstein MH, Hogan JE. Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. Int J Pharmaceut 1985;24:339–350.
73. Ford JL, Rubinstein MH, Hogan JE. Dissolution of a poorly water soluble drug, indomethacin, from hydroxypropylmethylcellulose controlled release tablets. J Pharm Pharmacol 1985;37:33.
74. Choi J, Jang BN, Park BJ, Joung YK, Han DK. Effect of solvent on drug release and a spray-coated matrix of a sirolimus-eluting stent coated with poly (lactic-co-glycolic acid). Langmuir 2014;30: 10098–10106.
75. Perale G, Arosio P, Moscatelli D, Barri V, Müller M, Maccagnan S, Masi M. A new model of resorbable device degradation and drug release: Transient 1-dimension diffusional model. J Control Release 2009;136:196–205.
76. Li S, Girod-Holland S, Vert M. Hydrolytic degradation of poly (DL-lactic acid) in the presence of caffeine base. J Control Release 1996;40:41–53.
77. D'Souza S, Faraj JA, Dorati R, DeLuca PP. Enhanced degradation of lactide-co-glycolide polymer with basic nucleophilic drugs. Adv Pharm 2015;Article ID 154239.
78. Weiler W, Gogolewski S. Enhancement of the mechanical properties of polylactides by solid-state extrusion: I. Poly (D-lactide). Biomaterials 1996;17:529–535.
79. Tang Y, Singh J. Controlled delivery of aspirin: Effect of aspirin on polymer degradation and *in vitro* release from PLGA based phase sensitive systems. Int J Pharmaceut 2008;357:119–125.
80. Gümüşderelioglu M, Deniz G. Sustained release of mitomycin-C from poly (DL-lactide)/poly (DL-lactide-co-glycolide) films. J Biomat Sci Polym E 2000;11:1039–1050.
81. Avgoustakis K, Nixon JR. Biodegradable controlled release tablets: III. Effect of polymer characteristics on drug release from heterogeneous poly (lactide-co-glycolide) matrices. Int J Pharmaceut 1993;99:247–252.
82. Budhian A, Siegel SJ, Winey KI. Production of haloperidol-loaded PLGA nanoparticles for extended controlled drug release of haloperidol. J Microencapsul 2005;22:773–785.
83. Benny O, Menon LG, Ariel G, Goren E, Kim SK, Stewman C, Black PM, Carroll RS, Machluf M. Local delivery of poly lactic-co-glycolic acid microspheres containing imatinib mesylate inhibits intracranial xenograft glioma growth. Clin Cancer Res 2009;15: 1222–1231.
84. Mu L, Feng SS. A novel controlled release formulation for the anticancer drug paclitaxel (Taxol®): PLGA nanoparticles containing vitamin E TPGS. J Control Release 2003;86:33–48.
85. Lao LL, Peppas NA, Boey FYC, Venkatraman SS. Modeling of drug release from bulk-degrading polymers. Int J Pharmaceut 2011;418:28–41.
86. He J, Zhong C, Mi J. Modeling of drug release from bioerodible polymer matrices. Drug Deliv 2005;12:251–259.
87. Sampath SS, Garvin K, Robinson DH. Preparation and characterization of biodegradable poly (L-lactic acid) gentamicin delivery systems. Int J Pharmaceut 1992;78:165–174.
88. Leroux JC, Allémann E, De Jaeghere F, Doelker E, Gurny R. Biodegradable nanoparticles-from sustained release formulations to improved site specific drug delivery. J Control Release 1996;39: 339–350.
89. Siepmann J, Faisant N, Akiki J, Doelker E, Gurny R. Effect of the size of biodegradable microparticles on drug release: Experiment and theory. J Control Release 2004;96:123–134.
90. Mu L, Feng SS. PLGA/TPGS nanoparticles for controlled release of paclitaxel: Effects of the emulsifier and drug loading ratio. Pharm Res 2003;20:1864–1872.
91. Berkland C, Kim KK, Pack DW. PLG microsphere size controls drug release rate through several competing factors. Pharm Res 2003;20:1055–1062.
92. Dunne M, Corrigan OI, Ramtoola Z. Influence of particle size and dissolution conditions on the degradation properties of polylactide-co-glycolide particles. Biomaterials 2000;21:1659–1668.
93. Shenderova A, Burke TG, Schwendeman SP. The acidic microclimate in poly (lactide-co-glycolide) microspheres stabilizes camptothecins. Pharm Res 1999;16:241–248.
94. Fu K, Pack DW, Klibanov AM, Langer R. Visual evidence of acidic environment within degrading poly (lactic-co-glycolic acid)(-PLGA) microspheres. Pharm Res 2000;17:100–106.
95. Brunner A, Mäder K, Göpferich A. pH and osmotic pressure inside biodegradable microspheres during erosion1. Pharm Res 1999;16:847–853.
96. Lee W, Park J, Yang EH, Suh H, Kim SH, Chung DS, Choi K, Yang CW, Park J. Investigation of the factors influencing the release rates of cyclosporin A-loaded micro-and nanoparticles prepared by high-pressure homogenizer. J Control Release 2002; 84:115–123.
97. Sun YM, Chang JN. Solute transport in poly (2-hydroxyethyl methacrylate) hydrogel membranes. J Polym Res 1995;2:71–82.
98. Klose D, Siepmann F, Elkharraz K, Krenzlin S, Siepmann J. How porosity and size affect the drug release mechanisms from PLGA-based microparticles. Int J Pharmaceut 2006;314:198–206.
99. Versypt ANF, Pack DW, Braatz RD. Mathematical modeling of drug delivery from autocatalytically degradable PLGA microspheres-A review. J Control Release 2013;165:29–37.
100. Schliecker G, Schmidt C, Fuchs S, Wombacher R, Kissel T. Hydrolytic degradation of poly (lactide-co-glycolide) films: Effect of oligomers on degradation rate and crystallinity. Int J Pharmaceut 2003;266:39–49.
101. Witt C, Kissel T. Morphological characterization of microspheres, films and implants prepared from poly (lactide-co-glycolide) and ABA triblock copolymers: Is the erosion controlled by degradation, swelling or diffusion? Eur J Pharm Biopharm 2001;51:171–181.
102. Grizzi I, Garreau H, Li S, Vert M. Hydrolytic degradation of devices based on poly (DL-lactic acid) size-dependence. Biomaterials 1995;16:305–311.
103. Acharya G, Shin CS, Vedantham K, McDermott M, Rish T, Hansen K, Fu Y, Park K. A study of drug release from homogeneous PLGA microstructures. J Control Release 2010;146: 201–206.
104. Vergnaud JM. Controlled Drug Release of Oral Dosage Forms. CRC Press; 1993. p 92.
105. Li J, Stayshich RM, Meyer TY. Exploiting sequence to control the hydrolysis behavior of biodegradable PLGA copolymers. J Am Chem Soc 2011;133:6910–6913.
106. Jeong B, Bae YH, Kim SW. Drug release from biodegradable injectable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymers. J Control Release 2000;63:155–163.
107. Casalini T, Rossi F, Lazzari S, Perale G, Masi M. Mathematical modeling of PLGA microparticles: From polymer degradation to drug release. Mol Pharmaceut 2014;11:4036–4048.
108. Cai C, Mao S, Germershaus O, Schaper A, Rytting E, Chen D, Kissel T. Influence of morphology and drug distribution on the release process of FITC-dextran-loaded microspheres prepared with different types of PLGA. J Microencapsul 2009; 26(4):334–345.
109. Stevanovic M, Uskokovic D. Poly (lactide-co-glycolide)-based micro and nanoparticles for the controlled drug delivery of vitamins. Curr Nanosci 2009;5:1–14.
110. Stabenfeldt SE, Willits RK. Guidance channel development: controlled release of NGF from PLGA scaffolds. Engineering in Medicine and Biology, 2002. 24th Annual Conference and the Annual Fall Meeting of the Biomedical Engineering Society EMBS/BMES Conference, 2002. Proceedings of the Second Joint. IEEE 2002;1: 484–485.

111. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145–1149.
112. Zhang MP, Yang ZC, Chow LL, Wang CH. Simulation of drug release from biodegradable polymeric microspheres with bulk and surface erosions. J Pharm Sci 2003;92:2040–2056.
113. Ehtezazi T, Washington C. Controlled release of macromolecules from PLA microspheres: Using porous structure topology. J Control Release 2000;68:361–372.
114. Johnson PJ, Skornia SL, Stabenfeldt SE, Willits RK. Maintaining bioactivity of NGF for controlled release from PLGA using PEG. J Biomed Mater Res A 2008;86:420–427.
115. Li YP, Pei YY, Zhang XY, Gu ZH, Zhou ZH, Yuan WF, Zhou JJ, Zhua JH, Gao XJ. PEGylated PLGA nanoparticles as protein carriers: Synthesis, preparation and biodistribution in rats. J Control Release 2001;71:203–211.
116. Zhang K, Tang X, Zhang J, Lu W, Lin X, Zhang Y, Tian B, Yang H, He H. PEG-PLGA copolymers: Their structure and structure-influenced drug delivery applications. J Control Release 2014; 183:77–86.
117. Stolnik S, Dunn SE, Garnett MC, Davies MC, Coombes AGA, Taylor DC, Irving MP, Purkiss SC, Tadros TF, Davis SS, Illum L. Surface modification of poly (lactide-co-glycolide) nanospheres by biodegradable poly (lactide)-poly (ethylene glycol) copolymers. Pharm Res 1994;11:1800–1808.
118. Paun IA, Moldovan A, Luculescu CR, Staicu A, Dinescu M. MAPLE deposition of PLGA:PEG films for controlled drug delivery: Influence of PEG molecular weight. Appl Surf Sci 2012;258: 9302–9308.
119. Desai KGH, Kadous S, Schwendeman SP. Gamma irradiation of active self-healing PLGA microspheres for efficient aqueous encapsulation of vaccine antigens. Pharm Res 2013;30:1768–1778.
120. Volland C, Wolff M, Kissel T. The influence of terminal gamma-sterilization on captopril containing poly (D, L-lactide-co-glycolide) microspheres. J Control Release 1994;31:293–305.
121. Hausberger AG, Kenley RA, DeLuca PP. Gamma irradiation effects on molecular weight and *in vitro* degradation of poly (D, L-lactide-co-glycolide) microparticles. Pharm Res 1995;12:851–856.
122. Bittner B, Mader K, Kroll C, Borchert HH, Kissel T. Tetracycline-HCl, glutathione and L-alanine loaded poly (DL-lactide-co-glycolide) microspheres prepared by a spray drying technique: Influence of gamma irradiation on radical formation and polymer degradation. J Control Release 1999;59:23–32.
123. Spenlehauer G, Vert M, Benoit JP, Boddaert A. *In vitro* and *in vivo* degradation of poly (D, L lactide/glycolide) type microspheres made by solvent evaporation method. Biomaterials 1989;10:557–563.
124. Bushell JA, Claybourn M, Williams HE, Murphy DM. An EPR and ENDOR study of gamma- and beta-radiation sterilization in poly(lactide-co-glycolide) polymers and microspheres. J Control Release 2005;110:49–57.
125. Faisant N, Siepmann J, Oury P, Laffineur V, Bruna E, Haffner J, Benoit JP. The effect of gamma-irradiation on drug release from bioerodible microparticles: A quantitative treatment. Int J Pharmaceut 2002;242:281–284.
126. Faisant N, Siepmann J, Richard J, Benoit JP. Mathematical modeling of drug release from bioerodible microparticles: Effect of gamma-irradiation. Eur J Pharm Biopharm 2003;56:271–279.
127. Montanari L, Costantini M, Signoretti EC, Valvo L, Santucci M, Bartolomei M, Fattibene P, Onori S, Faucitano A, Conti B, Genta I. Gamma irradiation effects on poly(D, L-lactide-co-glycolide) microspheres. J Control Release 1996;56:219–229.
128. Hsiao CY, Liu SJ, Ueng SWN, Chan EC. The influence of γ irradiation and ethylene oxide treatment on the release characteristics of biodegradable poly (lactide-co-glycolide) composites. Polym Degrad Stabil 2012;97:715–720.
129. Holy CE, Dang SM, Davies JE, Shoichet MS. *In vitro* degradation of a novel poly (lactide-co-glycolide) 75/25 foam. Biomaterials 1999;20:1177–1185.
130. Zolnik BS, Burgess DJ. Effect of acidic pH on PLGA microsphere degradation and release. J Control Release 2007;122:338–344.
131. Blanco-Prı́eto MJ, Besseghir K, Orsolini P, Heimgartner F, Deuschel C, Merkle HP, Nam-Trân H, Gander B. Importance of the test medium for the release kinetics of a somatostatin analogue from poly (D, L-lactide-co-glycolide) microspheres. Int J Pharmaceut 1999;184:243–250.
132. Johansen P, Corradin G, Merkle HP, Gandera B. Release of tetanus toxoid from adjuvants and PLGA microspheres: How experimental set-up and surface adsorption fool the pattern. J Control Release 1998;56:209–217.
133. Yang J, Cleland JL. Factors affecting the *in vitro* release of recombinant human interferon-γ (rhIFN-γ) from PLGA microspheres. J Pharm Sci 1997;86:908–914.
134. Zhang J, Tao W, Chen Y, Chang D, Wang T, Zhang X, Mei L, Zeng X, Huang L. Doxorubicin-loaded star-shaped copolymer PLGA-vitamin E TPGS nanoparticles for lung cancer therapy. J Mater Sci Mater Med 2015;26:1–12.
135. Banker MJ, Clark TH. Plasma/serum protein binding determinations. Curr Drug Metab 2008;9:854–859.
136. Boix-Garriga E, Acedo P, Casadó A, Villanueva A, Stockert JC, Cañete M, Mora M, Sagristá ML, Nonell S. Poly (D, L-lactide-co-glycolide) nanoparticles as delivery agents for photodynamic therapy: Enhancing singlet oxygen release and phototoxicity by surface PEG coating. Nanotechnology 2015;26:365104.
137. Gido C, Langguth P, Mutschler E. Predictions of *in vivo* plasma concentrations from *in vitro* release kinetics: Application to doxepin parenteral (im) suspensions in lipophilic vehicles in dogs. Pharm Res 1994;11:800–808.
138. Fredenberg S, Reslow M, Axelsson A. Effect of divalent cations on pore formation and degradation of poly (D, L-lactide-co-glycolide). Pharm Dev Technol 2007;12:563–572.
139. Zolnik BS, Leary PE, Burgess DJ. Elevated temperature accelerated release testing of PLGA microspheres. J Control Release 2006;112:293–300.
140. Shameem M, Lee H, DeLuca PP. A short-term (accelerated release) approach to evaluate peptide release from PLGA depot formulations. AAPS PharmSci 1999;1:1–6.
141. Ali SAM, Doherty PJ, Williams DF. Molecular biointeractions of biomedical polymers with extracellular exudate and inflammatory cells and their effects on the biocompatibility, *in vivo*. Biomaterials 1994;15:779–785.
142. Menei P, Daniel V, Montero-Menei C, Brouillard M, Pouplard-Barthelaix A, Benoit JP. Biodegradation and brain tissue reaction to poly (D, L-lactide-co-glycolide) microspheres. Biomaterials 1993;14:470–478.
143. Liu Q, Zhang H, Zhou G, Xie S, Zou H, Yu Y, Li G, Sun D, Zhang G, Lu Y, Zhong Y. *In vitro* and *in vivo* study of thymosin alpha1 biodegradable in situ forming poly (lactide-co-glycolide) implants. Int J Pharmaceut 2010;397:122–129.
144. Mohammad AK, Reineke JJ. Quantitative detection of PLGA nanoparticle degradation in tissues following intravenous administration. Mol Pharmaceut 2013;10:2183–2189.
145. Zolnik BS, Burgess DJ. Evaluation of *in vivo-in vitro* release of dexamethasone from PLGA microspheres. J Control Release 2008;127:137–145.
146. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 2001;70:1–20.
147. Sah H, Thoma L A, Desu H R, Sah E, Wood GC. Concepts and practices used to develop functional PLGA-based nanoparticulate systems. Int J Nanomed 2013;8:747–765.
148. Parent M, Nouvel C, Koerber M, Sapin A, Maincent P, Boudier A. PLGA in situ implants formed by phase inversion: Critical physicochemical parameters to modulate drug release. J Control Release 2013;172:292–304.
149. Yang J, Lee J, Kang J, Oh SJ, Ko HJ, Son JH, Lee K, Suh JS, Huh YM, Haam S. Smart drug-loaded polymer gold nanoshells for systemic and localized therapy of human epithelial cancer. Adv Mater 2009;21:4339–4342.
150. Lee SM, Park H, Choi JW, Park YN, Yun CO, Yoo KH. Multifunctional nanoparticles for targeted chemophotothermal treatment of cancer cells. Angew Chem Int Ed 2011;50:7581–7586.
151. Tomoda K, Watanabe A, Suzuki K, Inagi T, Terada H, Makino K. Enhanced transdermal permeability of estradiol using

combination of PLGA nanoparticles system and iontophoresis. Colloids Surf B 2012;97:84–89.
152. Radovic-Moreno AF, Lu TK, Puscasu VA, Yoon CJ, Langer R, Farokhzad OC. Surface charge-switching polymeric nanoparticles for bacterial cell wall-targeted delivery of antibiotics. ACS Nano 2012;6:4279–4287.
153. Bennewitz MF, Lobo TL, Nkansah MK, Ulas G, Brudvig GW, Shapiro EM. Biocompatible and pH-sensitive PLGA encapsulated MnO nanocrystals for molecular and cellular MRI. ACS Nano 2011;5:3438–3446.
154. Zhou Z, Badkas A, Stevenson M, Lee JY, Leung YK. Herceptin conjugated PLGA-PHis-PEG pH sensitive nanoparticles for targeted and controlled drug delivery. Int J Pharmaceut 2015;487:81–90.
155. Sun S, Liang N, Yamamoto H, Kawashima Y, Cui F, Yan P. pH-sensitive poly (lactide-co-glycolide) nanoparticle composite microcapsules for oral delivery of insulin. Int J Nanomed 2015; 10:3489–3498.
156. Meduri A, Fuoco T, Lamberti M, Pellecchia C, Pappalardo D. Versatile copolymerization of glycolide and rac-lactide by dimethyl (salicylaldiminato) aluminum compounds. Macromolecules 2014;47:534–543.
157. Qian H, Wohl AR, Crow JT, Macosko CW, Hoye TR. A strategy for control of "random" copolymerization of lactide and glycolide: Application to synthesis of PEG-b-PLGA block polymers having narrow dispersity. Macromolecules 2011;44:7132–7140.
158. Rahmani-Neishaboor E, Jackson J, Burt H, Ghahary A. Composite hydrogel formulations of stratifin to control MMP-1 expression in dermal fibroblasts. Pharm Res 2009;26:2002–2014.
159. Solorio L, Olear AM, Hamilton JI, Patel RB, Beiswenger AC, Wallace JE, Zhou H, Exner AA. Noninvasive characterization of the effect of varying PLGA molecular weight blends on in situ forming implant behavior using ultrasound imaging. Theranostics 2012;2:1064–1077.
160. Tracy MA, Ward KL, Firouzabadian L, Wang Y, Dong N, Qian R, Zhang Y. Factors affecting the degradation rate of poly(lactide-co-glycolide) microspheres *in vivo* and *in vitro*. Biomaterials 1999;20:1057–1062.