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Review

Phenomenology of the Initial Burst Release of Drugs from PLGA Microparticles

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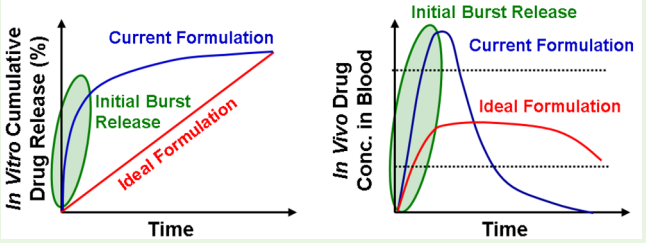
ABSTRACT: Poly(lactic-*co*-glycolic acid) (PLGA) is the most prevalent polymer drug delivery vehicle in use today. There are about 20 commercialized drug products in which PLGA is used as an excipient. In more than half of these formulations, PLGA is used in the form of microparticles (with sizes in the range between 60 nm and 100 μm). The primary role of PLGA is to control the kinetics of drug release toward achieving sustained release of the drug. Unfortunately, most drug-loaded PLGA microparticles exhibit a common drawback: an initial uncontrolled burst of the drug. After 30 years of utilization of PLGA in controlled drug delivery systems, this initial burst drug release still remains an unresolved challenge. In this Review, we present a summary of the proposed mechanisms responsible for this phenomenon and the known factors affecting the burst release process. Also, we discuss examples of recent efforts made to reduce the initial burst release of the drug from PLGA particles.



KEYWORDS: *drug release, zero-order release, PLGA microparticle, initial burst release*

1. INTRODUCTION

1.1. Initial Burst Release of Drug from Injectable PLGA Microparticles. Polymer microparticles are versatile platforms for drug delivery, because the drug release kinetics can easily be tuned by adjusting the chemical (polymer type, composition, molecular weight) and/or physical (particle size, shape, porosity) characteristics of the formulation. However, regardless of detailed physicochemical characteristics, most polymer drug delivery systems exhibit a common feature in their drug release kinetics, an initial burst release of the drug; a significant proportion of the encapsulated drugs is rapidly released within a short period of time following injection.[1] This initial burst of the drug is normally undesirable because it shortens the overall duration of the drug's therapeutic effect, and excessive burst release may even cause toxicity and thus raise a safety concern. Extensive investigations have been made to reduce the initial burst release of drug from polymeric delivery systems and thereby maximize the duration of the drug effect.

An aliphatic polyester, poly(lactic-*co*-glycolic acid) or PLGA, represents the most prevalent type of polymer drug delivery vehicle in use today, because it degrades and thus releases the drug cargo over time scales that are optimal for clinical use (1 week to 6 months[2]). One particular advantage of using PLGA is that, being a copolymer derived from two monomers (lactide and glycolide), its degradation/drug release properties can also be tuned through variation of the monomer composition (ratio).[3] However, PLGA is not an exception in terms of the initial burst release of the drug; overcoming this problem remains a technological challenge for PLGA-based drug delivery systems, too. This review discusses recent advances in understanding of the mechanisms responsible for and strategies developed to reduce the initial burst of the drug from PLGA microparticles. Many review articles have previously been written on this topic; refs 4−6 are examples of such articles published recently. So, in the present article, our review is focused only on very recent developments in this area. We will only consider spherical particles, because most commercial products use that geometry.

1.2. Mechanisms of Drug Release from Microparticles. Drug release from PLGA microparticles is controlled by both (drug/water/polymer) diffusion and (polymer) erosion. Also, because PLGA absorbs water to a certain extent,[7] polymer degradation occurs both within the bulk and at the surface of the particle (called "bulk erosion" and "surface erosion," respectively).[8] These factors interplay with each other in the drug release process, often making it a complicated process to analyze. Experimentally observed *in vitro* overall drug release profiles from PLGA microparticle

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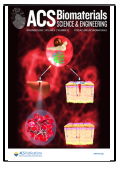

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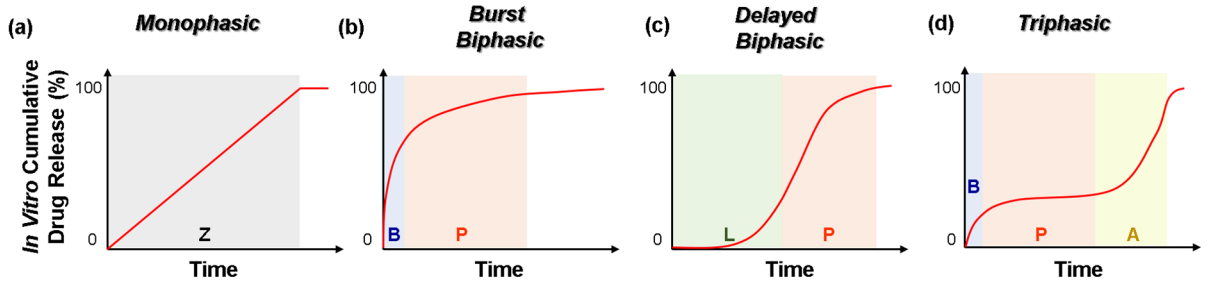

Figure 1. Four different types of *in vitro* overall drug release profiles from polymer microparticle delivery systems.

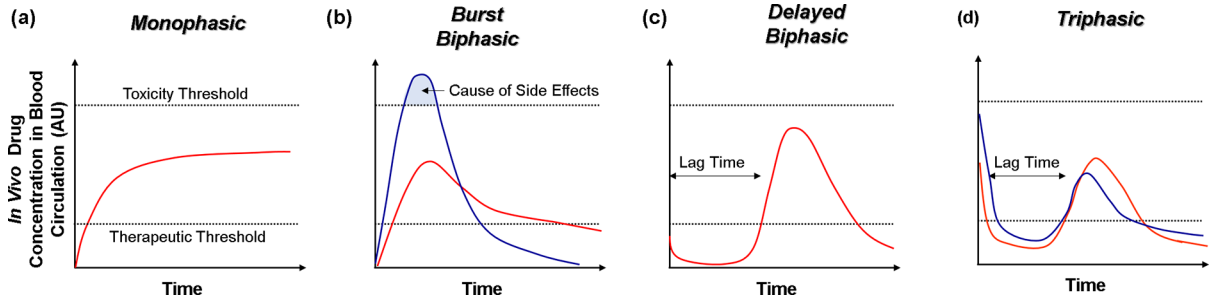

Figure 2. Respective time-dependent *in vivo* drug concentration profiles for the four different types of *in vitro* drug release profiles shown in Figure 1. The upper and lower dotted horizontal lines in each graph represent the minimum toxicity and therapeutic thresholds, respectively.

drug delivery systems can be summarized into four categories: monophasic,[9] burst biphasic,[10] delayed biphasic,[11] and triphasic.[12] Figure 1 schematically summarizes the typical shapes of *in vitro* cumulative drug release profiles for the four different types of drug release behavior.[6,13] There are four distinct drug release periods ("phases"). The so-called "burst release phase (B)" is characterized by rapid drug release typically upon initial exposure of PLGA microparticles to the aqueous environment; the duration of this phase varies from as little as several hours to 1−2 days.[12] This initial burst release phase is often followed by a next phase with a power-law relationship between the cumulative amount of drug released and the time elapsed within this phase ($\Delta c \sim (\Delta t)^n$ where n = 1/2 for Fickian diffusion processes, and $1/2 < n < 1$ for "anomalous" processes involving, for instance, both diffusion of drugs and swelling of glassy polymers[14]); for convenience, we will call this phase a "power-law phase (P)". Particularly, when $n = 1$, the rate of drug release becomes constant (independent of time). This "zero-order release phase (Z)" typically lasts for several days to weeks, and during this period the drugs are constantly released from the polymer depot via non-Fickian diffusion. There also exists an "accelerated release phase (A)" which occurs after the power-law phase ($\Delta c \sim (\Delta t)^n$ with $n >$ 1). In this phase, the drug release is accelerated because of accelerated polymer degradation, eventually leading to complete depletion of the drug. Occasionally, drug release starts after an initial "lag phase (L)", particularly, when PLGA particles are very large or coated with additional protective layers, or drug distribution was adjusted to be entrapped inside the microparticles.[15−17] A monophasic drug release profile consisting only of a zero-order release phase (= Z) exhibits a constant rate of drug release throughout the process. The monophasic, zero-order drug release kinetics is generally desirable, because the time course of drug concentration in the body is completely predictable. A triphasic drug release profile (= B + P + A) typically shows a much smaller amount of initial burst release than does a burst biphasic drug release profile (= B + P). A delayed biphasic drug release profile (= L + P) starts with an initial lag period followed by a rapid release of drug, giving rise to a sigmoidal shaped curve. During the lag phase, an additional prescription (e.g., oral supplementation) may be required, causing inconvenience.[18] A prolonged drug release at a constant rate (zero-order) without any initial burst or delay (monophasic) is currently considered an ideal drug release profile.[19]

As shown in Figure 2, different time-dependent *in vivo* drug concentration profiles following, for instance, intravenous (IV) administration are expected for the four different types of *in vitro* drug release profiles shown in Figure 1. In the monophasic zero-order drug release case (= Z), the steady-state drug concentration in blood circulation can be maintained within the therapeutic range for a long time (Figure 2a). A burst biphasic drug release situation (= B + P) typically has a much shorter time window in which the systemic drug concentration is maintained within the therapeutic range (Figure 2b). Further, the initial burst release causes a safety concern if the drug concentration reaches beyond the toxicity threshold. In a delayed biphasic drug release situation with an initial lag period (= L + P), the drug absorption peak shifts to a later time (Figure 2c).[20] In the triphasic case (= B + P + A), a lower amount of initial burst would prolong the therapeutic period (shown with a red curve in Figure 2d).

In this Review, we will focus our discussion on the initial burst phenomenon. The details of the mechanisms responsible for the initial burst of the drug are still controversial, and it is still difficult to achieve sustained release of drugs without any burst effect.[2] The initial burst release is thought to be related to the liberation of drug molecules trapped near the microparticle surface and a large initial gradient in drug concentration between the carrier and the medium. This idea explains why the burst effect is normally negligible at low drug loading, and becomes more significant with increasing drug loading.[21]

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Polydispersity in particle size increases the burst effect, because small particles that are copresent release drugs more rapidly.[22]

2. FACTORS INFLUENCING THE INITIAL BURST RELEASE OF DRUGS FROM PLGA MICROPARTICLES

Several factors are known to mainly affect the drug release kinetics of PLGA microparticles. They include particle size, porosity, and polymer molecular weight (MW). The effects of these factors are inter-related. Using leuprolide acetate (1.2 kDa)-loaded PLGA microparticles, Ravivarapu et al. showed that low-MW PLGA tends to produce porous, quick-release formulations (21 μm diameter, PLGA M_n = 8.6 kDa, lactide/glycolide monomer ratio (L/G) = 50:50; Figure 1b), whereas high-MW PLGA produces smooth and nonporous microspheres which give rise to a sigmoidal drug release profile (18 μm diameter, PLGA M_n = 28.3 kDa, L/G = 50:50; Figure 1c).[23] In this section, we will discuss how each of these factors individually influences the burst release process and how their effects are interconnected.

2.1. Particle Size. Several studies have shown that particle size is a primary determinant of drug release rate.[17,24,25] Commercial drug-loaded polymeric microparticles are typically produced by oil-in-water (O/W) emulsion processes, and thus have broad size distributions. In order to elucidate the effect of particle size on drug release kinetics, it is desirable to use monodisperse systems. Chen et al. prepared different size fractionations of PLGA microspheres (PLGA inherent viscosity = 0.4 dL/g in chloroform, L/G = 50:50, COOH-terminated) via wet sieving using standard square mesh sieves; Gefitinib(447 Da)-loaded PLGA microparticles prepared by the O/W emulsion method were sieved into four size classes: >100, 50−100, 20−50, and <20 μm.[25] Interestingly, the drug loading content (LC, defined as mass of drug per total mass of polymer and drug) was found to be significantly different among different size fractions; the LC of >100 μm-sized particles was >3× higher than that of <20 μm-sized particles. Different size particles exhibited remarkable differences in drug release kinetics. The drug was completely released from the 20−50 and <20 μm size fractions within 1 week, whereas the larger (>100 and 50−100 μm) size fractions exhibited a slow release over the first week. These larger microparticles showed a sigmoidal release profile (Figure 1c), whereas the smaller ones showed a biphasic profile with a significant initial burst (Figure 1b). These results are in good agreement with results obtained by other researchers. Berkland et al. reported that monodisperse piroxicam(331 Da)-loaded PLGA microparticles of about 10 μm diameter exhibited a diffusion-controlled drug release profile (PLGA M_w = 10−15 kDa, L/G = 50:50);[17] a Fickian diffusion process gives rise to an overall drug release profile similar to Figure 1b.[26] They also showed that larger PLGA particles of 50 and 100 μm diameters exhibited a sigmoidal drug release profile (Figure 1c). The longer diffusion path length contributes to the slower overall drug release from the larger particles. However, the qualitative difference in the drug release profile between the smaller and larger PLGA particles cannot be explained simply by the difference in diffusion distance. An alternative explanation is that the drug release profile is controlled by the surface area to volume ratio of the particles; for a given total mass (or volume) of the polymer, the total surface area of the particles scales inversely with the particle diameter. The surface area affects the rate of water uptake. The water uptake and degree of swelling of the polymer particles, in turn, influence the drug release kinetics; note that all of these processes are expected to occur in nonequilibrium states. Sansdrap et al. reported that 18 μm diameter PLGA particles (PLGA M_w = 38−54 kDa, L/G = 50:50) show a significantly higher water penetration (determined by swelling, 170% volume increase in 3 days) than 80 μm diameter particles (125% volume increase in 3 days);[27] this is likely a kinetic, not thermodynamic, effect. Water uptake increases a polymer's permeability to drugs (the diffusivity of the drug through the polymer). Busatto et al. studied the effects of PLGA particle size on the release kinetics of encapsulated progesterone (314 Da) and observed the same trends as discussed above.[24] They also used a mathematical model to predict drug release profiles, in which both the diffusion/dissolution of the drug from the polymeric matrix and the autocatalytic degradation of the polymer itself are considered; predictions of their model (Figure 1d) were in good agreement with experimental data.[24] Although the initial burst effect can be reduced by increasing the size of PLGA particles, optimal particle sizes must be determined in consideration of specific tissues to which PLGA particles are delivered.[28] For instance, to deliver particles to the lungs via intravenous (IV) administration, the particles must be slightly larger than the diameter of alveolar capillaries so that they can be passively trapped in the lungs and remain there for a long time.[29] Particle size must be optimized in consideration of both the polymer degradation/drug release kinetics (pharmacokinetics) and the biodistribution of the particles in the body.

2.2. Particle Porosity. Studies have been performed to compare the drug release kinetics between porous vs nonporous particles.[30−32] Kim et al. prepared porous sponge-like PLGA microspheres for delivery of the hydrophobic progesterone hormone (~100 μm diameter, PLGA inherent viscosity = 0.28 dL/g in chloroform, L/G = 75:25).[30] They found that the drug release from the porous system was much faster than that from the nonporous analogue, because the porous microparticles have larger surface areas and shorter diffusion distances. For this reason, the porous particles also exhibited an intense initial burst release of the drug (Figure 1b). The same trend was confirmed with other drugs.[31,32] The presence of pores not only affects (increases) the rate of drug release, but it actually qualitatively alters the mechanism of the process (causes the burst release of the drug). Despite the burst effect, porous microparticles are advantageous for some applications. Porous systems have much greater drug loading capacities. They provide faster overall release of the drug without an initial lag period. Also, the porous structure reduces the autocatalytic effect in bulk PLGA degradation reactions.[30] The degradation reaction of nonporous PLGA particles is known to be autocatalytic. The consensus has been that the degradation products of PLGA have −COOH end groups, and the accumulation of these acidic compounds lowers the local pH in the interior of the microparticle and causes the acceleration of the degradation process. Note that the role of pH in causing the accelerated degradation of PLGA is controversial because conflicting results have been found.[33] In the case of porous PLGA particles, the water-soluble degradation products diffuse out of the particle faster (they do not accumulate inside) and thus do not induce autocatalytic reactions.[31] With porous PLGA microparticles, local acidification can be avoided, which is often desirable from a drug stability standpoint.

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2.3. Polymer Molecular Weight (MW). To investigate the isolated effect of PLGA MW, Mylonaki et al. prepared atorvastatin (559 Da)-loaded PLGA microparticles from PLGA materials having different molecular weights (in the range of 8−45 kDa) via the O/W emulsion method; all other parameters were kept constant (i.e., particle diameter ≈ 17 μm, L/G ≈ 50:50, and drug LC ≈ 1.2%).[34] Low MW PLGA microparticles exhibited a burst biphasic drug release profile (Figure 1b), suggesting that the mechanism of drug release was a diffusion-controlled type in this case. In contrast, higher MW PLGA microparticles exhibited triphasic drug release behavior (Figure 1d); the burst of drug release occurred within the first 8 h, followed by the power-low and accelerated release phases afterward over a period of approximately 30 days. The burst effect was suppressed as the MW was increased. Since the particle size and drug loading were kept constant, the diffusivity of the drug must only be controlled by the polymer MW. Lower MW PLGA absorbs a significantly greater amount of water, which facilitates the diffusion of the drug through the polymer matrix.[35] These results are in agreement with transport modeling.[24] The 50 μm diameter PLGA particles exhibited burst biphasic drug release profiles regardless of polymer MW (Figure 1b), because the polymer degradation is negligible during the period of drug release, and the diffusion of the drug through the polymeric matrix is the main mechanism of drug release.[24,36] The drug release profiles of 100 μm diameter PLGA particles, on the other hand, were significantly influenced by polymer MW, because drug release involves polymer degradation in this limit (further discussed in the next paragraph). Low MW PLGA (M_w = 5.0 and 7.5 kDa) showed the triphasic behavior shown in Figure 1d. There are two possible reasons for the occurrence of the acceleration phase in low MW PLGA: faster/greater water absorption (discussed below) and faster generation of water-soluble fragments. High MW PLGA (M_w = 10.0 kDa), on the other hand, exhibited a burst biphasic drug release profile. Interestingly, the magnitudes of the burst effect were virtually the same in the low and high MW polymers.

MW affects the glass transition temperature (T_g) of PLGA. The bulk T_g of, for instance, 49 kDa (M_n) PLGA (L/G = 50:50) has been measured to be about 45 °C.[37] Water has a plasticizing effect on PLGA. PLGA can absorb nonfreezable (bound) water up to about 2.6% of the weight of the dry PLGA, and that can cause a decrease in T_g by about 14 °C.[7] It is reasonable to expect that plasticizing water will nullify the T_g MW effect in PLGA particles, as has been observed with other solvent plasticized polymers.[38] Any additional amount of water absorbed by PLGA beyond the few percent limit exists as freezable (unbound) water, forming water clusters within the PLGA matrix.[7] Decreasing PLGA MW is expected to increase the extent of freezable water inclusions (clusters) within PLGA particles, which will facilitate polymer degradation, but perhaps not drug diffusion, particularly when the drug is hydrophobic.

2.4. Type of Drug. PLGA microparticles are widely used for many different drugs, both hydrophobic and hydrophilic, and both small molecular entities and biopharmaceuticals. In general, it is more difficult to encapsulate hydrophilic drugs with high efficiency within PLGA particles than hydrophobic drugs.[25] Single O/W emulsion and double $W_1/O/W_2$ emulsion procedures (both in combination with solvent evaporation) are, respectively, the most widely used techniques for loading hydrophobic and hydrophilic drugs into PLGA microparticles. The encapsulation efficiencies are typically low for hydrophilic drugs, because the drugs also partition into the outer water phase (W_2) before solidification of the PLGA domain.[9,19,39]

Drug release from PLGA microparticles may involve different molecular processes: drug diffusion through the polymer matrix, drug diffusion through the aqueous pores, drug dissolution into the bulk aqueous phase, and polymer degradation and dissolution into the aqueous phase. The process of diffusion through the polymer matrix is only relevant to small hydrophobic drugs, because PLGA itself is hydrophobic. Hydrophilic drugs (such as water-soluble proteins and peptides) undergo diffusion predominantly through the aqueous pores.[40] Batycky et al. developed a theoretical model describing the release of hydrophilic drugs from PLGA microparticles, which assumed the formation of mesoscopic pores within the microparticles. This model describes the drug release process as being composed of the desorption (from the polymer to aqueous phase), induction, and/or Fickian diffusion steps.[41] The induction step is the period in which porosity increases in the PLGA matrix; once fully space-filling pores are formed, hydrophilic drugs start being released from the polymer particle (Figure 1d). Hydrophobic drugs solely rely on Fickian diffusion through the polymer matrix and thus do not exhibit an induction period (Figure 1b). Due to the different pathways of drug diffusion in the hydrophilic vs hydrophobic cases, a direct comparison of the effective diffusion coefficients of the drugs in aqueous media is irrelevant to understanding the difference in their overall release behaviors. For hydrophilic drugs, the value of the effective diffusion coefficient of a drug has been shown to vary over 5 orders of magnitude with changing particle size or porosity.

Although the majority of the release process occurs after the induction period, some amount of hydrophilic drugs that adsorbed to the exterior surface of the particle and the inner surfaces of the mesoscopic pores are released during the burst stage; the rate of this initial burst is controlled by the rate of drug desorption from the polymer matrix. In a similar vein, Cabezas et al. explained that the initial burst release process can be considered as the process of dissolution of drugs from the particle surfaces into the bulk aqueous phase, and thus the rate of the burst release is controlled by the solubility of the drug in water.[42,43] It has been confirmed that in PLA/PLGA foams, drugs with higher water solubilities dissolve into water faster.[44] Also, in a closed experimental system, a hydrophobic drug may reach its solubility limit during the release experiment.[13] For these reasons, the burst effect is generally much greater for hydrophilic drugs (i.e., because of their higher interfacial concentration gradients and higher water solubility) than it is for hydrophobic drugs.

2.5. Aqueous Boundary Layer. Drug release from polymer matrices typically involves several different molecular mechanisms, including dissolution, diffusion, osmosis, partitioning, swelling, and erosion.[45] Among these, dissolution and diffusion are known to be involved in the initial burst process.[44] Dissolution is the process in which drug molecules dissolve into the aqueous medium surrounding the carrier particle. In thinking about this drug dissolution process, it is typically hypothesized that there exists an interfacial boundary layer around the particle in which the medium is nondraining (i.e., stationary relative to the motion of the particle).[46] This interfacial layer thus causes a significant slowdown of the dissolution process, because within this layer drug transport

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occurs predominantly, if not solely, by diffusion (in the absence of convection (stirring)). Conversely, removal of this boundary layer (i.e., continuously agitating and replenishing the interfacial region with the bulk medium) would significantly increase the dissolution rate. Assuming a small but finite thickness for the boundary layer, the drug dissolution rate can be given by Fick's first law of diffusion

$$\frac{dM}{dt} \cong \frac{DA}{L}(C_o - C) = \frac{DA}{LV}(C_o V - M) \quad (1)$$

where M is the total mass of the drug inside the polymer particle, D is the diffusivity of the drug in the aqueous solution, A is the surface area of the polymer particle, L is the thickness of the boundary layer, C_o and C are the concentrations of the drug at the outer and inner surfaces of the boundary layer, respectively, and V is the volume of the polymer particle.[45] The above equation suggests that in the diffusion-controlled limit, the dissolution rate will decrease with increasing thickness of the boundary layer. Therefore, it is obvious that the stationary aqueous boundary layer acts as a barrier to drug dissolution.

For PLGA particles which exhibit a burst release of drug at the beginning and undergo bulk polymer erosion at later times, an analytical expression for the total fraction of the drug released at a given time t has been derived by applying the above boundary layer concept to the analysis of the kinetics of the burst release process[47]

$$F(t) = \varphi_b\{1 - \exp(-k_b t)\} + (1 - \varphi_b)\left\{\frac{\exp[k(t - t_{max})]}{1 + \exp[k(t - t_{max})]}\right\} \quad (2)$$

where φ_b is the cumulative fraction of the drug released by the burst release mechanism up to time infinity (i.e., the fraction of the drug trapped near the surface of the PLGA particle), k_b is the first-order rate constant associated with the burst release ($= DA/(LV)$), k is the rate constant for drug release due to polymer erosion, and t_{max} is the time to the maximum drug release rate in the polymer erosion phase.[47] Again, a thicker boundary layer would give a reduced value of k_b and would result in a suppression of the burst effect.

It has been experimentally confirmed that mechanical agitation (such as stirring, horizontal shaking, rotation, rocking, etc.) increases the rate of drug release from PLGA microparticles, because it reduces the formation of a boundary layer around the particle.[48] Specifically, a 4-fold difference in the rate of leuprolide acetate release from PLGA microparticles has been found between continuously agitated vs static situations.[49] However, it would be very difficult to predict the boundary layer properties of PLGA microparticles in real physiological tissue environments whose fluid dynamic characteristics are not known.

3. STRATEGIES TO REDUCE AN INTIAL BURST RELEASE FROM PLGA MICROPARTICLES

In this section, we will discuss strategies proposed to overcome the initial burst release problem. Examples include modifications of the drug−polymer interaction, surface permeability, copolymer sequence, and spatial distribution of drugs.

3.1. Drug−Polymer Interaction. Yoo et al. prepared a doxorubicin (544 Da)-conjugated poly(lactic-*co*-glycolic acid)−poly(ethylene glycol) diblock copolymer (DOX−PLGA−PEG; PLGA M_n = 11 kDa, L/G = 50:50, PEG M_n = 2 kDa); DOX and PLGA are linked through a slowly hydrolyzable carbamate bond.[50] DOX−PLGA−PEG micelles (61 nm hydrodynamic diameter) exhibited sustained release of DOX over 2 weeks with a decreased burst release. PLGA−PEG micelles with physically encapsulated DOX showed a significant initial burst of the drug. In a recent study, Yang et al. demonstrated a long sustained release PLGA microparticle formulation (~25 μm diameter, PLGA inherent viscosity = 0.15−0.25 dL/g in chloroform, L/G = 50:50) for palonosetron (PAL, 296 Da) hydrochloride, a therapeutic for delayed chemotherapy-induced nausea and vomiting (CINV).[9] Delayed CINV can be treated if PAL is delivered in a sustained manner over 5−6 days. PAL-loaded PLGA microparticles were prepared using the O/W emulsion-solvent evaporation method. The encapsulation efficiency (EE, defined as mass of PAL encapsulated relative to mass of PAL initially added) was only about 23% at pH 5, which would require high injection doses of PAL-loaded microparticles for clinical treatment.[51] When the pH of the aqueous phase was increased from 5 to 10, the EE was found to increase to about 94%. This result indicates that the interaction between PAL (the tertiary amine group) and PLGA (the −COOH end group) is influenced by the pH of the aqueous phase. However, the increase of pH to 8−10 caused the PLGA particles to become porous. At this high pH > 8, PLGA degradation might have started even during the formulation process, which resulted in the burst effect and a significantly higher overall rate of PAL release (Figure 1b). Overall, the authors identified a pH of 7 as the optimal condition, because PAL-loaded PLGA microparticles prepared at that condition showed a high PAL EE (≈ 87%) while exhibiting the desirable zero-order drug release kinetics (Figure 1a). We suspect that the interaction between the tertiary amine [pK_a (of the conjugate acid) = 8.5] of PAL and the carboxylic acid (pK_a = 4.7) of PLGA becomes strongest at pH 7.

3.2. Surface Permeability. The burst effect can be significantly suppressed by coating of the surface of PLGA microparticles with a polymer, a cross-linked network or an inorganic material. Thote et al. prepared dexamethasone (DMT, 392 Da)-loaded PLGA microparticles (30−40 μm diameter, PLGA inherent viscosity = 0.39 dL/g in hexafluoro-2-propanol, L/G = 50:50) coated with a cross-linked network formed by ethylene glycol dimethacrylate (EGDMA) and tri(ethylene glycol) dimethacrylate (Tri(EG)DMA); EGDMA and Tri(EG)DMA were cross-linked via UV light with the aid of a photoinitiator, 2,2-dimethoxy-2-phenyl-acetophenone.[52] This surface cross-linking produced additional resistance to drug diffusion, and as a result the initial burst was suppressed (Figure 1b) with a significantly reduced amount of initial burst release of DMT from about 61% to about 7%. Several different types of polymers have also been demonstrated for non-cross-linked surface coating. Polydopamine coating has been demonstrated for slowing down the release of encapsulated paclitaxel (PTX, 854 Da) from PLGA−PEG nanoparticles (~160 nm diameter, PLGA M_w = 125 kDa, L/G = 50:50).[53] Onto the polydopamine layer, PEG chains were further end-grafted to prevent phagocytic uptake and clearance of the particles. This approach reduced the cumulative amount of PTX released by a factor of 1.9 during the first 7 h period. The overall drug release profile was similar in shape to Figure 1b. Chitosan has also been used to coat PLGA nanoparticles loaded with PTX (130−170 μm diameter, PLGA M_w = 10−20 kDa, L/G = 75:25).[54] The positive charges (primary amines)

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on chitosan bind to the negative charges (carboxylic acids) on PLGA. Chitosan-coated PLGA nanoparticles exhibited a significant decrease in initial burst release compared to uncoated PLGA nanoparticles (Figure 1b). The initial release rate decreased with increasing chitosan content.

An et al. produced risperidone (410 Da)-loaded PLGA microparticles (74 μm diameter, PLGA M_w = 76−115 kDa, L/G = 75:25) via a suspension-evaporation process which involved the formation of a transient protective, aluminum hydroxide ($Al(OH)_3$) gel layer on the particle surface (SEP-AL).[15] $Al(OH)_3$ layers were formed in situ at the aqueous−organic interfaces during the initial emulsion stage. Concentrated HCl was used to remove aluminum hydroxide from the particle surfaces in the final stage. PLGA particles produced via SEP-AL exhibited a remarkably reduced initial burst release of risperidone both *in vitro* (Figure 1c) and *in vivo* (Figure 2c) when compared with PLGA particles prepared by the conventional O/W emulsion−solvent evaporation method with a poly(vinyl alcohol) emulsifier. A possible explanation is that the $AL(OH)_3$ layer created between the aqueous and organic (dichloromethane (DCM)) phases slowed down DCM evaporation/PLGA precipitation, and thus prevented pore formation in the PLGA domain. Also, the acid post-treatment could have removed risperidone encapsulated near the particle surface at the sample preparation stage.

3.3. Monomer Sequence Distribution. Extensive studies have been conducted on understanding the effects of overall monomer composition (L/G ratio) on the polymer degradation/drug release kinetics of PLGA.[55] However, it is only recently that monomer sequence distribution has started receiving the attention it deserves. Meyer and co-workers have demonstrated that strictly alternating PLGA copolymers (1.8 μm diameter, PLGA M_n = 37 kDa, L/G = 50:50) undergo hydrolysis at a much slower rate and more homogeneously than conventional (random) PLGA copolymers (2.1 μm diameter, PLGA M_n = 32 kDa, L/G = 50:50).[56−58] In random PLGA materials, G-rich regions degrade more rapidly than mixed or L-rich regions. For this reason, random PLGA is first quickly cleaved into shorter segments containing mainly L residues. To the contrary, alternating PLGA degrades slower and more uniformly, because it contains only L−G and G−L linkages. As a result, the burst effect is significantly reduced for alternating PLGA (Figure 1b). However, the exact connection between a slower degradation of the PLGA and a reduced burst release of the loaded rhodamine-B remains to be elucidated, because the burst effect typically does not involve polymer degradation.

3.4. Spatial Distribution of Encapsulated Drugs. Several studies have also demonstrated that initial burst release can be significantly reduced by adjusting the spatial distribution of the drug within a PLGA microparticle. Shen et al. prepared risperidone (410 Da)-loaded PLGA microparticles via the O/W emulsion−solvent evaporation method using a PLGA having a similar molecular weight to that used in a commercial product, Risperdal Consta (PLGA M_w = 80−85 kDa, L/G = 75:25).[16,59] They showed that the physical characteristics of the particles (particle porosity, mean size, and size distribution) are sensitive to such formulation parameters as the type of organic solvent used and particle collection method (i.e., wet sieving (pre lyophilization) vs dry sieving (post lyophilization)). PLGA microparticles prepared using DCM exhibited a greater initial burst release than those prepared using a mixture of ethyl acetate (EA) and benzyl alcohol (BA) (EA/BA = 2.75:1.00 by volume; Figure 1c); BA was used as a cosolvent to facilitate the dissolution of risperidone in EA. Risperidone is highly soluble in DCM. Therefore, during the late stages of the evaporation process, the migration of DCM must have caused risperidone to accumulate near the surface of the microparticle. This effect is expected to be less pronounced with EA/BA, because risperidone is poorly soluble in EA and reasonably soluble in BA. EA evaporates faster than BA, resulting in a precipitation of PLGA between the organic and aqueous phases (PLGA precipitates upon contact with water while EA has a relatively high water solubility); the precipitated PLGA prevents risperidone from migrating toward the organic-aqueous interface (during the evaporation of BA), and as a result, risperidone ends up distributing mainly in the deeper region of the PLGA domain.[60] This is a reasonable explanation as to why PLGA microparticles prepared using EA/BA show a reduced burst release of risperidone. Also, we suspect that PLGA precipitates more rapidly during the evaporation of EA/BA, because EA is more compatible with water[11] (the EA/BA mixture contains more moisture than DCM). The type of organic solvent appears to affect the drug release kinetics through its influence on the spatial distribution of the drug within a PLGA particle.

3.5. Manufacturing Process. Several different manufacturing processes have been developed for producing PLGA microparticles, including the emulsion-evaporation, phase separation, spray freeze-drying, and microfluidics techniques.[61] Most FDA-approved drug-loaded PLGA microparticle products (such as Bydureon, Risperidal Consta, and Vivitrol) are manufactured via the emulsion−evaporation process.[62] While this method has advantages in terms of simplicity, quality control (reproducibility), and efficiency (high throughput), it is limited in producing monodisperse (uniformly sized) PLGA microparticles and is also considered nonenvironmentally friendly because it requires the use of large amounts of organic solvents. Because size heterogeneity hampers precise control of drug release kinetics and generally promotes the burst release of drug,[25] many recent attempts have been focusing on innovating manufacturing methods that can produce monodisperse PLGA microparticles.

One promising approach is spray freeze-drying. Combining spraying with freeze-drying (lyophilization) enables encapsulation of unstable macromolecular substances (such as proteins and peptides) into PLGA particles for use, for instance, in vaccination therapies. This spray freeze-drying process also provides control over the size, size distribution, and shape of the product particles. Recently, it has been demonstrated that spray freeze-dried recombinant human vascular endothelial growth factor (VEGF)-loaded PLGA microparticles (250−500 μm diameter, PLGA M_w = 7−17 kDa, L/G = 50:50) exhibit a significantly reduced level of initial burst (<10% of the total loaded amount).[63]

Microfluidics permits unprecedented, precise spatiotemporal control of the encapsulation process with miniscule consumption of material and energy.[64] Microfluidic processes are particularly attractive because they can address the key limitations of conventional bulk encapsulation processes: low drug loading efficiencies and broad particle size distributions. Monodisperse bupivacaine (288 Da)-loaded PLGA microparticles of various sizes in the range of 10 to 50 μm diameter (PLGA M_w = 50−75 kDa, L/G = 85:15) have been prepared using a capillary microfluidic device. The rate of drug release

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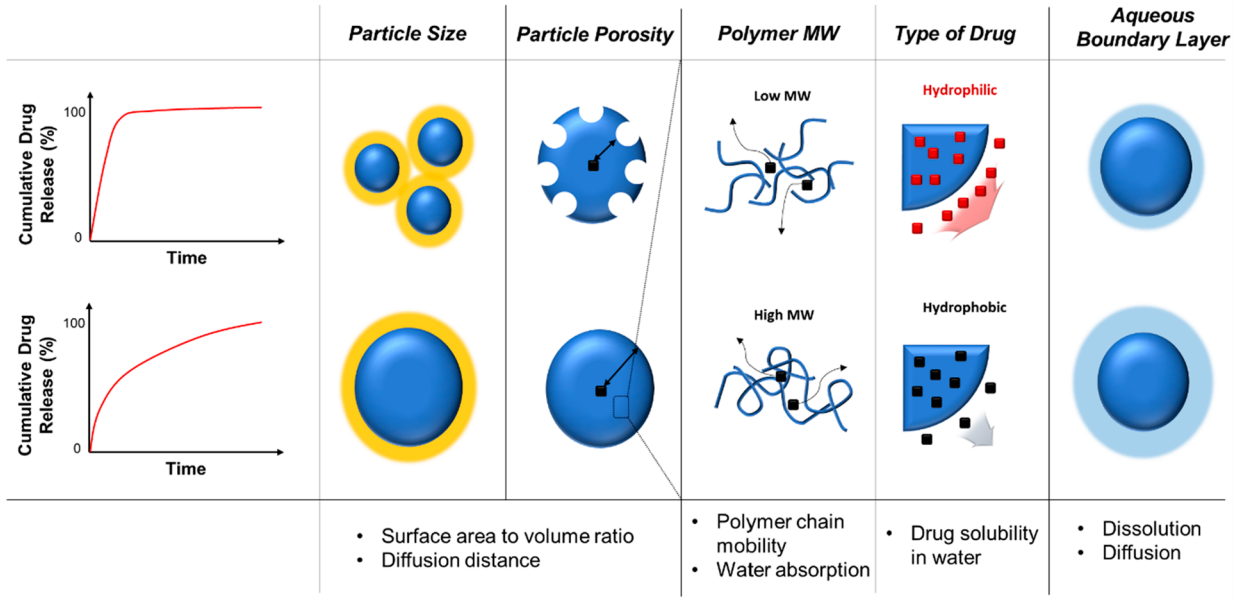

Figure 3. Factors affecting the initial burst release of the drug from PLGA microparticles.

from these monodisperse PLGA particles was slower than that for PLGA particles with the same mean diameter but with a broader size distribution prepared by the conventional single emulsion technique.[65] Further, these monodisperse PLGA particles exhibited significantly lower levels of initial burst release than their polydisperse analogues. This reduced burst effect was attributed to the uniformity of the sizes of the PLGA particles and also to the more uniform distribution of the drug throughout the PLGA matrix enabled by the microfluidic approach.

A new technique called self-healing encapsulation enables the loading of water-soluble macromolecular substances within preformed PLGA microparticles and has been shown to reduce the burst effect.[66] The self-healing encapsulation process works in three steps. First, drug-free porous PLGA microparticles are produced by incorporating large amounts of osmotic agents (such as trehalose or sucrose) within the polymer matrix. Second, these porous PLGA particles are dispersed in an aqueous solution containing the drug under mild agitation at a temperature below the T_g of the PLGA; the drug molecules diffuse into the pores of the PLGA particles. Finally, the temperature is increased above the T_g of the polymer, so that the pores are closed at the particle surface by spontaneous rearrangements of the polymer chains driven by capillary forces.[67] Antigenic tetanus toxoid(150 kDa)-loaded PLGA microparticles (20−63 μm diameter, PLGA M_w = 51 kDa, L/G = 50:50) prepared by this method exhibited a significantly reduced initial burst followed by a slow and continuous release of the drug over a period of 28 days, which is a significant improvement over what is achievable with the conventional $W_1/O/W_2$ emulsion−evaporation procedure.[68]

4. CONCLUDING REMARKS

PLGA is a biodegradable, FDA-approved biocompatible, copolymer of lactide (L) and glycolide (G). PLGA's technological potential was first demonstrated in the late 1990s when Takeda-Abbott introduced the first depot injection of Lupron in PLGA microparticles to treat prostate cancer.[69] Currently, PLGA is the most widely used polymeric

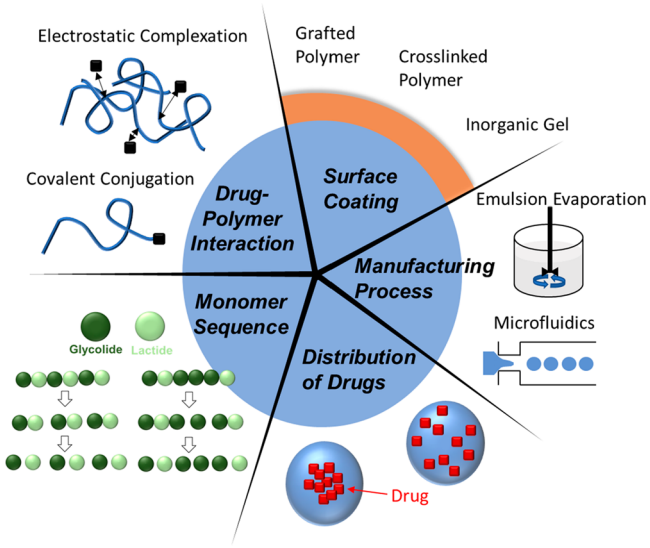

Figure 4. Strategies for suppressing initial drub burst from PLGA microparticles.

material in drug delivery applications. It is most commonly used in the form of microparticles. Drug-loaded PLGA microparticles exhibit a few different kinetic patterns of drug release (Figures 1 and 2). The long-standing challenge associated with PLGA microencapsulation is this hard-to-predict, multiphasic drug release behavior, with initial drug burst being a significant contributor to this behavior.[13] We present some of the basic phenomenological observations regarding how such properties as particle size/porosity, polymer molecular weight, and drug hydrophobicity/hydrophilicity influence the burst release behaviors of PLGA microparticles (Figure 3). We also discuss some of the strategies that have recently been proposed to overcome the burst effect, including modifications of drug−polymer interaction, surface permeability, monomer sequence distribution, and spatial distribution of drugs (Figure 4). It remains to

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be seen whether any of these developments will be adopted in commercial PLGA products.

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Notes

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