

Review

Poly Lactic-*co*-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier

Hirenkumar K. Makadia ¹ and Steven J. Siegel ^{2,*}

¹ Materials Science and Engineering, University of Pennsylvania, Philadelphia, PA 19104, USA;
E-Mail: hiren.makadia@gmail.com

² Translational Neuroscience Program, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104, USA

* Author to whom correspondence should be addressed; E-Mail: siegels@mail.med.upenn.edu;
Tel.: +1-215-573-0278; Fax: +1-215-573-2041.

Received: 20 June 2011; in revised form: 8 August 2011 / Accepted: 22 August 2011 /

Published: 26 August 2011

Abstract: In past two decades poly lactic-*co*-glycolic acid (PLGA) has been among the most attractive polymeric candidates used to fabricate devices for drug delivery and tissue engineering applications. PLGA is biocompatible and biodegradable, exhibits a wide range of erosion times, has tunable mechanical properties and most importantly, is a FDA approved polymer. In particular, PLGA has been extensively studied for the development of devices for controlled delivery of small molecule drugs, proteins and other macromolecules in commercial use and in research. This manuscript describes the various fabrication techniques for these devices and the factors affecting their degradation and drug release.

Keywords: poly lactic-*co*-glycolic acid; drug delivery; PLGA degradation; sustained release; PLGA fabrication techniques

1. Introduction

A considerable amount of research has been conducted on drug delivery by biodegradable polymers since their introduction as bioresorbable surgical devices about three decades ago. Amongst all the biomaterials, application of the biodegradable polymer poly lactic-*co*-glycolic acid (PLGA) has shown immense potential as a drug delivery carrier and as scaffolds for tissue engineering. PLGA are a family

of FDA-approved biodegradable polymers that are physically strong and highly biocompatible and have been extensively studied as delivery vehicles for drugs, proteins and various other macromolecules such as DNA, RNA and peptides [1–3]. PLGA is most popular among the various available biodegradable polymers because of its long clinical experience, favorable degradation characteristics and possibilities for sustained drug delivery. Recent literature has shown that degradation of PLGA can be employed for sustained drug release at desirable doses by implantation without surgical procedures. Additionally, it is possible to tune the overall physical properties of the polymer-drug matrix by controlling the relevant parameters such as polymer molecular weight, ratio of lactide to glycolide and drug concentration to achieve a desired dosage and release interval depending upon the drug type [4–6]. However the potential toxicity from dose dumping, inconsistent release and drug-polymer interactions require detailed evaluation. Here we present a review on the PLGA primarily as a delivery vehicle for various drugs, proteins and other macromolecules in commercial use and in research. We also present possible directions for future uses of PLGA in drug delivery applications.

2. Biodegradable Polymers

Biodegradable materials are natural or synthetic in origin and are degraded *in vivo*, either enzymatically or non-enzymatically or both, to produce biocompatible, toxicologically safe by-products which are further eliminated by the normal metabolic pathways. The number of such materials that are used in or as adjuncts in controlled drug delivery has increased dramatically over the past decade. The basic category of biomaterials used in drug delivery can be broadly classified as (1) synthetic biodegradable polymers, which includes relatively hydrophobic materials such as the α -hydroxy acids (a family that includes poly lactic-*co*-glycolic acid, PLGA), polyanhydrides, and others, and (2) naturally occurring polymers, such as complex sugars (hyaluronan, chitosan) and inorganics (hydroxyapatite) [7–9]. The breadth of materials used in drug delivery arises from the multiplicity of diseases, dosage range and special requirements that may apply. Biocompatibility is clearly important, although it is important to note that biocompatibility is not an intrinsic property of a material, but depends on the biological environment and the tolerability that exists with respect to specific drug-polymer-tissue interactions [9].

2.1. Poly Lactic-*co*-Glycolic Acid (PLGA)

Polyester PLGA is a copolymer of poly lactic acid (PLA) and poly glycolic acid (PGA). It is the best defined biomaterial available for drug delivery with respect to design and performance. Poly lactic acid contains an asymmetric α -carbon which is typically described as the D or L form in classical stereochemical terms and sometimes as R and S form, respectively. The enantiomeric forms of the polymer PLA are poly D-lactic acid (PDLA) and poly L-lactic acid (PLLA). PLGA is generally an acronym for poly D,L-lactic-*co*-glycolic acid where D- and L- lactic acid forms are in equal ratio.

2.1.1. Physico-Chemical Properties

In order to design a better controlled drug delivery device, it is essential to understand the physical, chemical and biological properties of PLGA. The physicochemical properties of optically active PDLA and PLLA are nearly the same. In general, the polymer PLA can be made in highly crystalline form

(PLLA) or completely amorphous (PDLA) due to disordered polymer chains. PGA is void of any methyl side groups and shows highly crystalline structure in contrast to PLA as shown in Figure 1. PLGA can be processed into almost any shape and size, and can encapsulate molecules of virtually any size. It is soluble in wide range of common solvents including chlorinated solvents, tetrahydrofuran, acetone or ethyl acetate [7,10]. In water, PLGA biodegrades by hydrolysis of its ester linkages (Figure 2). Presence of methyl side groups in PLA makes it more hydrophobic than PGA and hence lactide rich PLGA copolymers are less hydrophilic, absorb less water and subsequently degrade more slowly. Due to the hydrolysis of PLGA, parameters that are typically considered invariant descriptions of a solid formulation can change with time, such as the glass transition temperature (T_g), moisture content and molecular weight. The effect of these polymer properties on the rate of drug release from biodegradable polymeric matrices has been widely studied. The change in PLGA properties during polymer biodegradation influences the release and degradation rates of incorporated drug molecules. PLGA physical properties themselves have been shown to depend upon multiple factors, including the initial molecular weight, the ratio of lactide to glycolide, the size of the device, exposure to water (surface shape) and storage temperature [11]. Mechanical strength of the PLGA is affected by physical properties such as molecular weight and polydispersity index. These properties also affect the ability to be formulated as a drug delivery device and may control the device degradation rate and hydrolysis. Recent studies have found, however, that the type of drug also plays a role in setting the release rate [12]. Mechanical strength, swelling behavior, capacity to undergo hydrolysis and subsequently biodegradation rate of the polymer are directly influenced by the degree of crystallinity of the PLGA, which is further dependent on the type and molar ratio of the individual monomer components in the copolymer chain. Crystalline PGA, when co-polymerized with PLA, reduces the degree of crystallinity of PLGA and as a result increase the rate of hydration and hydrolysis. As a rule, higher content of PGA leads to quicker rates of degradation with an exception of 50:50 ratio of PLA/PGA, which exhibits the fastest degradation, with higher PGA content leading to increased degradation interval below 50%. Degree of crystallinity and melting point of the polymers are directly related to the molecular weight of the polymer. The T_g (glass transition temperature) of the PLGA copolymers are reported to be above the physiological temperature of 37 °C and hence are glassy in nature, thus exhibiting fairly rigid chain structure. It has been further reported that T_g of PLGAs decrease with a decrease of lactide content in the copolymer composition and with a decrease in molecular weight [13]. Commercially available PLGA polymers are usually characterized in terms of intrinsic viscosity, which is directly related to their molecular weights.

Figure 1. Structure of poly lactic-*co*-glycolic acid (x is the number of lactic acid units and y is number of glycolic acid units).

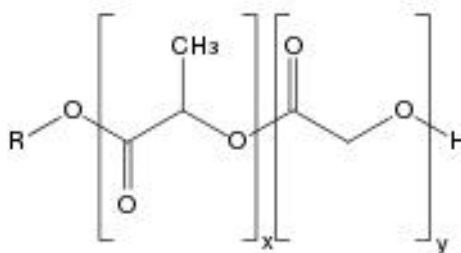
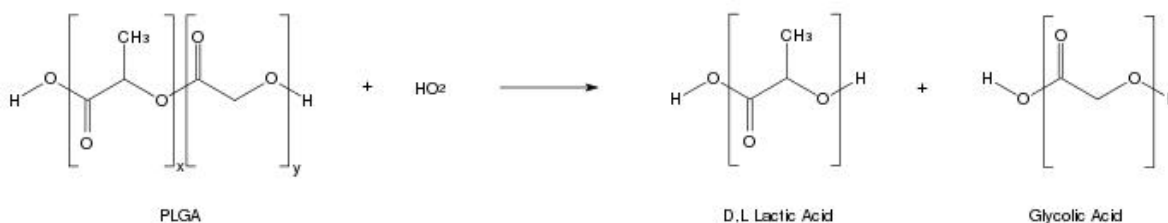


Figure 2. Hydrolysis of poly lactic-*co*-glycolic acid.

2.1.2. Pharmacokinetic and Biodistribution Profile

The drug delivery specific vehicle, *i.e.*, PLGA, must be able to deliver its payload with appropriate duration, biodistribution and concentration for the intended therapeutic effect. Therefore, design essentials, including material, geometry and location must incorporate mechanisms of degradation and clearance of the vehicle as well as active pharmaceutical ingredients (API). Biodistribution and pharmacokinetics of PLGA follows a non-linear and dose-dependent profile [14]. Furthermore, previous studies suggest that both blood clearance and uptake by the mononuclear phagocyte system (MPS) may depend on dose and composition of PLGA carrier systems [15]. Additionally whole-body autoradiography and quantitative distribution experiments indicate that some formulations of PLGA, such as nanoparticles, accumulate rapidly in liver, bone marrow, lymph nodes, spleen and peritoneal macrophages. The degradation of the PLGA carriers is quick on the initial stage (around 30%) and slows eventually to be cleared by respiration in the lung [16]. To address these limitations, studies have investigated the role of surface modification, suggesting that incorporation of surface modifying agents can significantly increase blood circulation half-life [17].

2.2. Copolymers of PLGA

The need for better delivery formulations that incorporate a variety in drugs and methods of administration has resulted in the development of various types of block copolymers of polyesters with poly ethylene glycol (PEG). PLGA/PEG block copolymers have been processed as diblock (PLGA-PEG) [18,19] or triblock molecules with both ABA (PLGA-PEG-PLGA) [20] and BAB (PEG-PLGA-PEG) [21] types. In diblock types, PEG chains orient themselves towards the external aqueous phase in micelles, thus surrounding the encapsulated species. This layer of PEG acts as a barrier and reduces the interactions with foreign molecules by steric and hydrated repulsion, giving enhanced shelf stability [22]. However, the addition of PEG to the system also results in reduction of encapsulation efficiency for drugs and proteins, even with the most appropriate fabrication techniques. The reduced drug incorporation may be due to steric interference of drug/protein-polymer interaction by the PEG chains. The precise mechanism for this effect is unclear. Better release kinetics from formulations of diblock copolymers have been demonstrated in comparison to PLGA alone. Various mechanisms of targeted delivery of drugs from diblock nanoparticles have also been reported [18,23,24].

Triblock copolymers of both ABA and BAB type can act as a thermogel with an A-block covalently coupled with a B-block via ester link. The copolymer is usually a free flowing solution at low temperature and can form a high viscosity gel at body temperature. These temperature-responsive copolymers,

PLGA-PEG-PLGA or PEG-PLGA-PEG, are a kind of block copolymers composed of hydrophobic PLGA segments and hydrophilic PEG segments. The hydrophobic PLGA segments form associative crosslinks and the hydrophilic PEG segments allow the copolymer molecules to stay in solution. At lower temperatures, hydrogen bonding between hydrophilic PEG segments and water molecules dominates the aqueous solution, resulting in their dissolution in water. As the temperature increases, the hydrogen bonding becomes weaker, while hydrophobic forces among the PLGA segments are strengthened, leading to solution-gel transition. The ease of handling during fabrication, formulation, filtration and filling makes such thermoresponsive polymers attractive candidates. Drug and/or protein release from both ABA and BAB copolymers occurs by two principal mechanisms: (i) drug diffusion from the hydrogel during the initial release phase; and (ii) release of drug by the erosion of the hydrogel matrix during the later phase. During the degradation of a PEG-PLGA-PEG gel, there is a preferential mass loss of PEG-rich components. Therefore, the remaining gel becomes more hydrophobic in an aqueous environment, resulting in less water content [20,25–28]. This motif can also be applied to other co-polymer combinations, including but not limited to various copolymers of PLGA and polycaprolactone [29,30].

3. Fabrication Techniques for PLGA Carriers

Drugs and proteins are the most rapidly growing class of pharmaceuticals for which controlled or targeted release is used to increase specificity, lower toxicity and decrease the risk associated with treatment. However, the stability and delivery challenges associated with these agents have limited the number of marketed products. Maintaining adequate shelf-life of peptide and protein drugs often requires solid-state formulation to limit hydrolytic degradation reactions [31]. Drug delivery of peptides and proteins may also require parenteral formulations to avoid degradation in the digestive tract and first pass metabolism, while the short circulating half-lives of peptides and proteins contribute to the need for parenteral formulations that will reduce dosing frequency. In order to avoid the inconvenient surgical insertion of large implants, injectable biodegradable and biocompatible PLGA particles (microspheres, microcapsules, nanocapsules, nanospheres) could be employed for controlled-release dosage forms. Drugs formulated in such polymeric devices are released either by diffusion through the polymer barrier, or by erosion of the polymer material, or by a combination of both diffusion and erosion mechanisms. In addition to its biocompatibility, drug compatibility, suitable biodegradation kinetics and mechanical properties, PLGA can be easily processed and fabricated in various forms and sizes. This section describes various fabrication techniques of PLGA controlled drug delivery devices [9].

3.1. Microparticle Preparation Techniques

3.1.1. Solvent Evaporation Method

(1) Single emulsion process

Oil-in-water emulsification processes are examples of single emulsion processes. Polymer in the appropriate amount is first dissolved in a water immiscible, volatile organic solvent (e.g., dichloromethane (DCM)) in order to prepare a single phase solution. The drug of particle size around 20–30 μm is added to the solution to produce a dispersion in the solution. This

polymer dissolved drug dispersed solution is then emulsified in large volume of water in presence of emulsifier (polyvinyl alcohol (PVA) *etc.*) in appropriate temperature with stirring. The organic solvent is then allowed to evaporate or extracted to harden the oil droplets under applicable conditions. In former case, the emulsion is maintained at reduced or atmospheric pressure with controlling the stir rate as solvent evaporates. In the latter case, the emulsion is transferred to a large quantity of water (with or without surfactant) or other quench medium to diffuse out the solvent associated with the oil droplets. The resultant solid microspheres are then washed and dried under appropriate conditions to give a final injectable microsphere formulation [32–35].

(2) Double (Multiple) emulsion process

Water-in-oil-in-water emulsion methods are best suited to encapsulate water-soluble drugs like peptides, proteins, and vaccines, unlike single emulsion methods which is ideal for water-insoluble drugs like steroids. First, an appropriate amount of drug is dissolved in aqueous phase (deionised water) and then this drug solution is added to organic phase consisting of PLGA and/or PLA solution in DCM or chloroform with vigorous stirring to yield a water-in-oil emulsion. Next, the water-in-oil primary emulsion is added to PVA aqueous solution and further emulsified for around a minute at appropriate stress mixing conditions. The organic solvent is then allowed to evaporate or is extracted in the same manner as oil-in-water emulsion techniques. In double emulsion processes, choice of solvents and stirring rate predominantly affects the encapsulation efficiency and final particle size [32,36,37].

3.1.2. Phase Separation (Coacervation)

Coacervation is a process focused on preparation of micrometer sized biodegradable polymer encapsulation formulations via liquid-liquid phase separation techniques. The process yields two liquid phases (phase separation) including the polymer containing coacervate phase and the supernatant phase depleted in polymer. The drug which is dispersed/dissolved in the polymer solution is coated by the coacervate. Thus, the coacervation process includes the following three steps as reported in literature [38–40]

- (1) Phase separation of the coating polymer solution,
- (2) Adsorption of the coacervate around the drug particles, and
- (3) Quenching of the microspheres.

Solutions are prepared by mixing polymer and solvent in appropriate ratios. Hydrophilic drugs like peptides and proteins are dissolved in water and dispersed in polymer solution (water-in-oil emulsion). Hydrophobic drugs like steroids are either solubilized or dispersed in the polymer solution (oil-in-water emulsion). Gradual addition of organic medium to the polymer-drug-solvent phase while stirring, extracts the polymer solvent resulting in phase separation of polymer by forming a soft coacervate of drug containing droplets. The size of these droplets can be controlled by varying stirring rate and temperature of the system. The system is then quickly dipped into a medium in which it is not soluble (both organic or aqueous) to quench these microdroplets. The soaking time in the quenching bath controls the coarsening

and hardness of the droplets. The final form of the microspheres is collected by washing, sieving, filtration, centrifugation or freeze drying. The processing parameters including polymer concentration, quenching temperature, quenching time and solvent composition affect the morphology and size of the microspheres [41–43].

3.1.3. Spray Drying

Emulsion techniques require precise control of processing parameters for higher encapsulation efficiency, and phase separation techniques tend to produce agglomerated particles and also require removal of large quantities of the organic phase from the microspheres. This makes the process difficult for mass production. Alternatively, spray drying is very rapid, convenient and has very few processing parameters, making it suitable for industrial scalable processing. In this process, drug/protein/peptide loaded microspheres are prepared by spraying a solid-in-oil dispersion or water-in-oil emulsion in a stream of heated air. The type of drug (hydrophobic or hydrophilic) decides the choice of solvent to be used in the process. The nature of solvent used, temperature of the solvent evaporation and feed rate affects the morphology of the microspheres. The main disadvantage of this process is the adhesion of the microparticles to the inner walls of the spray-dryer. Various spray drying techniques have been reported [44–49]. This method is known to encapsulate all kinds of drugs/peptides/proteins into microparticles without significant loss in their biological activity. Recently, coaxial capillary flows have become a preferable technique to produce monodispersed micro/nanoparticles with either simple or core-shell structure because of their precise control on mean particle size [50,51]. Using these techniques, processing parameters such as orientation of jets, material flow rates, and rate of solvent extraction can be controlled to create uniform and well-centered double-walled microspheres exhibiting a controllable shell thickness [52]. Additionally, microfluidic devices can incorporate the use of electrostatic forces to control the size and shape of particles for increased tuning of release characteristics [53].

3.2. Nanoparticle Preparation Techniques

Various groups have also reported successful preparation of PLGA nanoparticles. All the above described microparticle techniques can be employed for manufacturing PLGA nanoparticles (nanospheres and nanocapsules) by adjusting the processing parameters. These parameters usually use a small dispersed phase ratio and rate of stirring. The most common method used for the preparation of solid, polymeric nanoparticles is the emulsification-solvent evaporation technique. However, this method is primarily used in encapsulation of hydrophobic drugs. A modification on this procedure called the double or multiple emulsion technique has become the favored protocol for encapsulating hydrophilic compounds and proteins [37]. Nanoparticles can also be synthesized by nanoprecipitation methods. Polymer and drug are dissolved in acetone and added to an aqueous solution containing Pluronic F68. The acetone is evaporated at appropriate temperatures and reduced pressures leaving behind the polymer encapsulated nanoparticles with drug [54]. Salting out is another method in which a water-in-oil emulsion is first formed containing polymer, solvent (usually non chlorinated like acetone), salt (e.g., magnesium acetate tetrahydrate) and stabilizer. Water is then added to the solution until the volume is sufficient to diffuse acetone into the water, resulting in nanoparticle formulations [55–58].

3.3. *Implant Preparation Techniques*

3.3.1. Solvent-Casting and Compression Molding

Solvent casting is a method to fabricate a macroscopic millimeter size formulation which can be implanted or inserted for long term medication [59]. Large size, macroscopic formulations act as a reservoir for drug that can be delivered over a longer interval. In this method, a polymer and drug mixture is dissolved in a common solvent (e.g., acetone) in the desirable proportion, and the solvent is cast at around 60 °C until complete evaporation. Their resultant structure is a composite material of the drug together with the polymer. The solvent cast material is then compression molded into its desired geometry at around 80 °C and 25,000 psi to final density of 1 g/cc. This implant can be subcutaneously delivered in the body. The main advantage of this approach over micro/nanospheres is related to the ability to manage adverse events, since implants retain a degree of reversibility which is not available in depot mechanisms [12,59].

3.3.2. Extrusion

Solvent-casting methods are not ideal for industrial scale-up for many reasons. First, the process requires large amounts of organic solvent to dissolve PLGA and the active pharmaceutical agent (API) to combine the drug and polymer for pellet fabrication. Such systems are also open to the risk of denaturation of drugs and/or proteins during encapsulation because of the use of organic solvents. Denatured species are therapeutically inactive and can cause unpredictable side effects, such as immunogenicity or other toxicity. Second, this process requires a very long time to completely remove solvents from the resulting material. Third, solvent-casting and compression molding are not continuous processes, which may increase batch-to-batch variation in the composition of implants as well as cost of manufacturing [60].

Unlike solvent-casting, extrusion is a continuous process of drawing polymer-drug mixture through a die to create implants of fixed cross-sectional profile without any use of solvent. The process requires an extruder and polymer-drug mixture with required micron size feed material. During the process, the polymer-drug mixture is heated to semi-liquid state by a combination of heating elements and shear stress from the extrusion screw. The screw pushes the mixture through the die. The resulting extrudate is then cooled and solidified before cutting into desired lengths for implants or other applications [61]. Exposure of drug to high temperature can be disadvantageous as denaturation can take place. Therefore, the extrusion process possess a limitation on the drugs that can be used based on their melting point, polymorph stability and chemical interactions with PLGA.

3.4. *Miscellaneous Systems*

3.4.1. Multi-Drug Delivery Devices

A pulsated drug release profile is sometimes preferred over the continuous presence of the drug, which may lead to downregulation of receptors or the development of tolerance. Novel multi-pulsatile delivery devices have developed in which there is a predetermined off period followed by rapid and transient drug release in a cycle until the device is degraded. Such devices have also been shown to be capable

of releasing multiple drugs for a sequence of cycles. PLGA is also an attractive candidate for devices with multi-drug delivery and multi-pulsed delivery applications because of its desirable and tunable properties [62–65]. Such systems can be extended to achieve programmed delivery of multiple drugs in a predetermined sequence of pulses from a single device [64]. For example, a single biodegradable polymeric microchip can be constructed of PLGA and/or PLLA in combination with multiple drugs to achieve pulsatile drug delivery over a long period of time [65].

3.4.2. Supercritical CO₂

More recently, alternative methods of fabrication using supercritical CO₂ as the foaming agent have also been proposed to overcome some limitations that result from conventional methods of microporous foam formation, including solvent-casting and particulate leaching techniques. Conventional methods usually require large amounts of organic solvents and thus require additional extensive purification steps to remove the residual solvent. Using supercritical CO₂ as a foaming agent, organic solvents can be minimized or eliminated in production of PLGA foams [66]. Polymer encapsulated with drug/protein is usually manufactured using emulsion techniques. To apply this technique, a solution is placed into a CO₂ pressure cell immediately after emulsion. Under high pressure CO₂, the glass transition temperature of PLGA is reduced, resulting in a CO₂ dissolved polymer liquid. After such pressurization and rapid depressurization sequence, the thermodynamic instability of CO₂ molecules leads to their clustering inside the liquid polymer. As CO₂ leaves, the emulsion results in a porous polymer structure [66,67]. Since micro-porous foams have higher surface-to-volume ratios, more efficient drug release has been reported [68].

3.4.3. Multifunctional PLGA Micro/Nanoparticles

PLGA micro/nanoparticles have also been used for multiple applications in a single formulation. PLGA particles may be used to encapsulate absorption and fluorescence dyes in addition to a drug for multimodal imaging using fluorescence (FL), ultrasound (US), or photoacoustic tomography (PAT) [69]. Such multifunctional particles can also be formulated from a component material to reduce side effects of the encapsulated drug [70]. These particles can not only serve as a delivery system for the encapsulated drug but also reduce the harmful side effects through targeted drug delivery. However, the chemical reactivity among these adjuvants needs to be assessed before determination of a final formulation. The fabrication of such multifunctional particles is usually achieved through emulsion techniques. However, the high rate clearance of micro/nanoparticles by the body's reticuloendothelial system (RES) and the difficulty for such particles to penetrate many tissue types may limit their use to the vascular space [69–71].

4. Drug Release Behavior

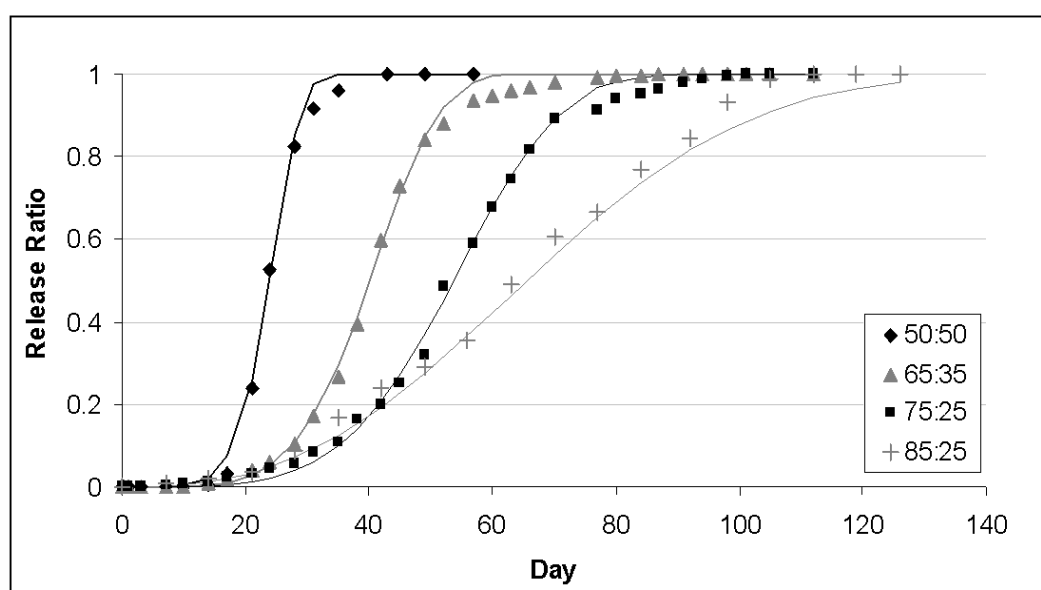
4.1. Biphasic Release

PLGA copolymer undergoes degradation by hydrolysis or biodegradation through cleavage of its backbone ester linkages into oligomers and, finally monomers. This has been demonstrated in both *in vivo* and *in vitro* for various drug types and proteins with different polymer ratios [72,73]. The

degradation process for these polymers is mainly through uniform bulk degradation of the matrix where the water penetration into the matrix is higher than the rate of polymer degradation. Furthermore, the increase of carboxylic end groups as a result of biodegradation autocatalyses the process. The degradation of PLGA copolymer is the collective process of bulk diffusion, surface diffusion, bulk erosion and surface erosion. Since there are many variables that influence the degradation process, the release rate pattern is often unpredictable. The biodegradation rate of the PLGA copolymers are dependent on the molar ratio of the lactic and glycolic acids in the polymer chain, molecular weight of the polymer, the degree of crystallinity, and the Tg of the polymer. The release of drug from the homogeneously degrading matrix is more complicated. A biphasic curve for drug release as a result of PLGA biodegradation has been shown to display following pattern: (Figure 3) [72–74]

- (1) Initial burst of drug release is related to drug type, drug concentration and polymer hydrophobicity. Drug on the surface, in contact with the medium, is released as a function of solubility as well as penetration of water into polymer matrix. Random scission of PLGA decreases molecular weight of polymer significantly, but no appreciable weight loss and no soluble monomer product are formed in this phase.
- (2) In the second phase, drug is released progressively through the thicker drug depleted layer. The water inside the matrix hydrolyzes the polymer into soluble oligomeric and monomeric products. This creates a passage for drug to be released by diffusion and erosion until complete polymer solubilization. Drug type also plays an important role here in attracting the aqueous phase into the matrix.

Figure 3. Modeled *in vivo* release profiles for 50:50, 65:35, 75:25 and 85:15 poly lactic-*co*-glycolic acid. Notation 65:35 PLGA means 65% of the copolymer is lactic acid and 35% is glycolic acid. A biphasic release profile with a initial zero release period followed by a rapid drug release has been observed. The profiles also show increase in release rate with decrease in lactide to glycolide proportion.



The role of enzymes in any PLGA biodegradation is unclear. Most literature indicate that the PLGA biodegradation does not involve any enzymatic activity and is purely through hydrolysis. However, some investigators have suggested an enzymatic role in PLGA breakdown based upon the difference in the *in vitro* and *in vivo* degradation rates. The PLGA polymer biodegrades into lactic and glycolic acids. Lactic acid enters the tricarboxylic acid cycle and is metabolized and subsequently eliminated from the body as carbon dioxide and water [75]. Glycolic acid is either excreted unchanged in the kidney or it enters the tricarboxylic acid cycle and is eventually eliminated as carbon dioxide and water. Ideally PLGA polymer systems should have considerable mechanical strength, since the drug delivery devices formulated using them are subjected to significant physical stress, which can also influence mechanical breakdown of implants and alter surface area and hydration/hydrolysis [76].

4.2. Factors Affecting Degradation

To enhance the desirable properties of PLGA, it is essential to understand the factors affecting the PLGA degradation and design a drug delivery device accommodating all these factors to make it more efficient and efficacious.

4.2.1. Effect of Composition

Polymer composition is the most important factor to determine the hydrophilicity and rate of degradation of a delivery matrix which influence the rate of degradation. A systematic study of polymer composition with its degradation has been shown by many groups [77,78]. These results show that increase in glycolic acid percentage in the oligomers accelerates the weight loss of polymer. PLGA 50:50 (PLA/PGA) exhibited a faster degradation than PLGA 65:35 due to preferential degradation of glycolic acid proportion assigned by higher hydrophilicity. Subsequently PLGA 65:35 shows faster degradation than PLGA 75:25 and PLGA 75:25 than PLGA 85:15 [79]. Thus absolute value of the degradation rate increases with the glycolic acid proportion. The amount of glycolic acid is a critical parameter in tuning the hydrophilicity of the matrix and thus the degradation and drug release rate.

4.2.2. Effect of Crystallinity (or Tg)

Copolymer composition also affects important properties such as glass transition temperature and crystallinity which have indirect effects on degradation rate. At the moment, there are conflicting reports on the effect of crystallinity on the degradation rate [80]. Few groups [81] have proposed that the crystallinity of lactic acid (PLLA) increases the degradation rate because the degradation of semi-crystalline polymer is accelerated due to an increase in hydrophilicity. In contrast, various other studies have shown a decrease of degradation rate with increase in sample crystallinity [82].

4.2.3. Effect of Weight Average Molecular Weight (M_w)

Polymers with higher molecular weight have generally exhibited lower degradation rates [83]. Molecular weight has a direct relation with the polymer chain size. Polymers having higher molecular weight have longer polymer chains, which require more time to degrade than small polymer chains.

However this is opposite for PLLA due to an inversely proportional degree of crystallinity with the molecular weight [83,84].

4.2.4. Effect of Drug Type

The mechanism of polymer-drug matrix degradation and the parameters of drug release rate vary as a function of drug type [85]. The presence of drug may change the degradation mechanism from bulk erosion to surface degradation, as well as affect the rate of matrix degradation [12]. The drug release profile, as defined by the time required for 100% release and the steady-state rate also varies significantly. However, efforts to correlate the release rate parameters to the drug chemistry (as defined by the density of OH groups) or hydrophilicity (as given by solubility in water) do not yield a strong relationship. However, it is clear that one must seriously consider the effect of the chemical properties of the drug to explain the drug-release mechanisms of a particular system using biodegradable polymers.

4.2.5. Effect of Size and Shape of the Matrix

The ratio of surface area to volume has shown to be a significant factor for degradation of large devices. Higher surface area ratio leads to higher degradation of the matrix. It has also been reported that bulk degradation is faster than pure surface degradation for PLGA, which makes the release of the drug faster from the devices with higher surface area to volume [82,86,87].

4.2.6. Effect of pH

The *in vitro* biodegradation/hydrolysis of PLGA showed that both alkaline and strongly acidic media accelerate polymer degradation [88]. However, the difference between the slightly acidic and neutral media is less pronounced due to autocatalysis by the carboxylic end groups [89].

4.2.7. Effect of Enzymes

There are conflicting results published on the effect of enzymes on degradation mechanisms (hydrolytic *versus* enzymatic cleavage) partially due to observations that degradation *in vivo* cannot be entirely correlated to *in vitro* assessment [80]. It has been proposed that PLGA degrades primarily through hydrolytic degradation but it has also been suggested that enzymatic degradation may play a role in the process. Due to a lack of uniformity in *in vivo* tests, there is difficulty in comparing and demonstrating the choice of proposed enzymes and their contribution in the degradation process [90,91].

4.2.8. Effect of Drug Load

Amount of drug loading in the drug delivery matrix plays a significant role on the rate and duration of drug release. Matrices having higher drug content possess a larger initial burst release than those having lower content because of their smaller polymer to drug ratio. However, this drug content effect is attenuated when the drug content reaches a certain level depending upon drug type [92].

4.3. Toxicology

Toxicological studies with PLGA devices suggest that local tissue reactions at the site of application may occur [93,94]. Although these reactions are generally mild and PLGA has been shown to be extremely safe as a material for macroscopic and microparticle systems, unique considerations may arise when using nanoscale applications. Several studies suggest that nanoparticles of any material may create specific biodistribution and toxicological profiles [95].

4.4. Modeling of PLGA Drug Release Profiles

PLGA degradation and drug release from a matrix is a combination of surface diffusion, bulk diffusion, and erosion of the matrix which is attributed to a variety of physical, chemical and processing parameters of that corresponding system. However, underlying mechanisms of this complex process are not clearly understood. The first stage of drug release is through random scission of the polymer without any polymer weight loss and is mainly through diffusion, while the second stage is characterized by the onset of weight loss. One proposed diffusion model of polymer degradation incorporates the effect of polymer degradation on the drug diffusivity in the polymer and the non-uniform distribution of that drug inside the formulation. The equation describing the release is the common diffusion equation: [96]

$$\frac{\partial C(r, t)}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 D(M_w) \frac{\partial C(r, t)}{\partial r} \right) \quad (1)$$

where C is the concentration of the drug, r is the radial position, t is time and $D(M_w)$ is the polymer molecular weight dependent diffusivity of the drug. Since M_w changes with time, D is parametrically dependent on time. The above equation is solved using the following boundary conditions of concentration profile (2) and initial condition (3).

$$\left. \frac{\partial C(r, t)}{\partial r} \right|_{r=0, t=0} = 0 \quad (2)$$

$$C(r, t) \Big|_{r=R, t>0} = 0 \quad (3)$$

where R is the radius of the particle (if spherical). At time t , the concentration of drug is given by the initial drug distribution.

$$C(r, t) \Big|_{t=0} = f(r)$$

The initial drug distribution within the structure $f(r)$ is usually obtained empirically. The first stage of hydrolytic degradation has been widely investigated and molecular weight as a function of time is given by Equation (4)

$$M_w(t) = M_w(t = 0) \exp(-k_{deg}t) \quad (4)$$

where $M_w(t = 0)$ is the molecular weight of the polymer at time $t = 0$ and k_{deg} is the polymer degradation constant [74,97,98].

If micro/nanoparticles are used, the effect on the drug release from the population size distribution has to be considered in the cumulative equation. From previous studies, microparticle size distribution is best modeled as a Weibull distribution or Rosin–Rammler mathematical distribution

$$\frac{1}{M_{\infty}} \frac{\partial M_{drug}}{\partial r} = f(r; \lambda, k) = \frac{k}{\lambda} \left(\frac{r}{\lambda}\right)^{k-1} \exp\left(-\left(\frac{r}{\lambda}\right)^k\right) \quad (5)$$

where M_{∞} is the total mass of the drug in the population, M_{drug} is the mass of drug in one particle and r is the radius of the particle [97].

5. Conclusions and Future Prospects

PLGA polymers have been shown to be excellent delivery carriers for controlled administration of drugs, peptides and proteins due to their biocompatibility and biodegradability. In general, the PLGA degradation and the drug release rate can be accelerated by greater hydrophilicity, increase in chemical interactions among the hydrolytic groups, less crystallinity and larger volume to surface ratio of the device. All of the these factors should be taken into consideration in order to tune the degradation and drug release mechanism for desired application. Thus, for a short-term release requirement (up to one month), an amorphous polymer with high hydrophilicity is recommended. For a longer-term release requirement (one to six months), the choice of an amorphous polymer with high molecular weight would be appropriate. Also, for very long-term release (more than six months), semi-crystalline polymer with a high degree of crystallinity can be considered. Furthermore, multiple studies demonstrate that PLGA can easily be formulated into the drug carrying devices at all scales, *i.e.*, as nanospheres, as microspheres and even as millimeter sized implants, can encapsulate a wide range of drugs, peptides or proteins and can be delivered over different periods of time with diverse routes of delivery.

Acknowledgements

This study was supported by R01MH074672.

References

1. Bouissou, C.; Rouse, J.J.; Price, R.; van der Walle, C.F. The influence of surfactant on PLGA microsphere glass transition and water sorption: Remodeling the surface morphology to attenuate the burst release. *Pharm. Res.* **2006**, *23*, 1295–1305.
2. Jain, R.A. The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices. *Biomaterials* **2000**, *21*, 2475–2490.
3. Ruhe, P.Q.; Hedberg, E.L.; Padron, N.T.; Spauwen, P.H.; Jansen, J.A.; Mikos, A.G. rhBMP-2 release from injectable poly (DL-lactic-co-glycolic acid)/calcium-phosphate cement composites. *J. Bone Jt. Surg.* **2003**, *85*, 75–81.
4. Allison, S.D. Effect of structural relaxation on the preparation and drug release behavior of poly(lactic-co-glycolic)acid microparticle drug delivery systems. *J. Pharm. Sci.* **2008**, *97*, 2022–2035.

5. Mundargi, R.; Babu, V.; Rangaswamy, V.; Patel, P.; Aminabhavi, T. Nano/micro technologies for delivering macromolecular therapeutics using poly(D,L-lactide-*co*-glycolide) and its derivatives. *J. Control. Release* **2008**, *125*, 193–209.
6. Mohamed, F.; van der Walle, C.F. Engineering biodegradable polyester particles with specific drug targeting and drug release properties. *J. Pharm. Sci.* **2008**, *97*, 71–87.
7. Uhrich, K.E.; Cannizzaro, S.M.; Langer, R.S.; Shakesheff, K.M. Polymeric systems for controlled drug release. *Chem. Rev.* **1999**, *99*, 3181–3198.
8. Nair, L.S.; Laurencin, C.T. Biodegradable polymers as biomaterials. *Prog. Polym. Sci.* **2007**, *32*, 762–798.
9. Anderson, J.M.; Shive, M.S. Biodegradation and biocompatibility of PLA and PLGA microspheres. *Adv. Drug Deliv. Rev.* **1997**, *28*, 5–24.
10. Wu, X.S.; Wang, N. Synthesis, characterization, biodegradation, and drug delivery application of biodegradable lactic/glycolic acid polymers. Part II: Biodegradation. *J. Biomater. Sci. Polym. Ed.* **2001**, *12*, 21–34.
11. Houchin, M.L.; Topp, E.M. Physical properties of PLGA films during polymer degradation. *J. Appl. Polym. Sci.* **2009**, *114*, 2848–2854.
12. Siegel, S.J.; Kahn, J.B.; Metzger, K.; Winey, K.I.; Werner, K.; Dan, N. Effect of drug type on the degradation rate of PLGA matrices. *Eur. J. Pharm. Biopharm.* **2006**, *64*, 287–293.
13. Passerini, N.; Craig, D.Q.M. An investigation into the effects of residual water on the glass transition temperature of polylactide microspheres using modulated temperature DSC. *J. Control. Release* **2001**, *73*, 111–115.
14. Yang, Y.Y.; Chung, T.S.; Ng, N.P. Morphology, drug distribution, and *in vitro* release profiles of biodegradable polymeric microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method. *Biomaterials* **2001**, *22*, 231–241.
15. Panagi, Z.; Beletsi, A.; Evangelatos, G.; Livaniou, E.; Ithakissios, D.S.; Avgoustakis, K. Effect of dose on the biodistribution and pharmacokinetics of PLGA and PLGA-mPEG nanoparticles. *Int. J. Pharm.* **2001**, *221*, 143–152.
16. Bazile, D.V.; Ropert, C.; Huve, P.; Verrecchia, T.; Marlard, M.; Frydman, A.; Veillard, M.; Spenlehauer, G. Body distribution of fully biodegradable [¹⁴C]-poly(lactic acid) nanoparticles coated with albumin after parenteral administration to rats. *Biomaterials* **1992**, *13*, 1093–1102.
17. Esmaeili, F.; Ghahremani, M.H.; Esmaeili, B.; Khoshayand, M.R.; Atyabi, F.; Dinarvand, R. PLGA nanoparticles of different surface properties: Preparation and evaluation of their body distribution. *Int. J. Pharm.* **2008**, *349*, 249–255.
18. Cheng, J.; Teply, B.A.; Sherifi, I.; Sung, J.; Luther, G.; Gu, F.X.; Levy-Nissenbaum, E.; Radovic-Moreno, A.F.; Langer, R.; Farokhzad, O.C. Formulation of functionalized PLGA-PEG Nanoparticles for *in vivo* targeted drug delivery. *Biomaterials* **2007**, *28*, 869–876.
19. Li, Y.; Pei, Y.; Zhang, X.; Gu, Z.; Zhou, Z.; Yuan, W.; Zhou, J.; Zhu, J.; Gao, X. PEGylated PLGA nanoparticles as protein carriers: Synthesis, preparation and biodistribution in rats. *J. Control. Release* **2001**, *71*, 203–211.
20. Ghahremankhani, A.A.; Dorkoosh, F.; Dinarvand, R. PLGA-PEG-PLGA tri-block copolymers as an *in-situ* gel forming system for calcitonin delivery. *Polym. Bull.* **2007**, *59*, 637–646.

21. Jeong, B.; Bae, Y.H.; Kim, S.W. *In situ* gelation of PEGPLGAPEG triblock copolymer aqueous solutions and degradation thereof. *J. Biomed. Mater. Res.* **2000**, *50*, 171–177.
22. Tobio, M.; Gref, R.; Sanchez, A.; Langer, R.; Alonso, M.J. Stealth PLA-PEG nanoparticles as protein carriers for nasal administration. *Pharm. Res.* **1998**, *15*, 270–275.
23. Dhar, S.; Gu, F.X.; Langer, R.; Farokhzad, O.C.; Lippard, S.J. Targeted delivery of cisplatin to prostate cancer cells by aptamer functionalized Pt(IV) prodrug-PLGA–PEG nanoparticles. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 17356–17361.
24. Yoo, H.S.; Park, T.G. Folate receptor targeted biodegradable polymeric doxorubicin micelles. *J. Control. Release* **2004**, *96*, 273–283.
25. Duvvuri, S.; Janoria, K.G.; Mitra, A.K. Development of a novel formulation containing poly (D,L-lactide-co-glycolide) microspheres dispersed in PLGA-PEG-PLGA gel for sustained delivery of ganciclovir. *J. Control. Release* **2005**, *108*, 282–293.
26. Garinot, M.; Fievez, V.; Pourcelle, V.; Stoffelbach, F.; des Rieux, A.; Plapied, L.; Theate, I.; Freichels, H.; Jerome, C.; Marchand-Brynaert, J.; Schneider, Y.; Preat, V. PEGylated PLGA-based nanoparticles targeting M cells for oral vaccination. *J. Control. Release* **2007**, *120*, 195–204.
27. Danhier, F.; Lecouturier, N.; Vroman, B.; Jerome, C.; Marchand-Brynaert, J.; Feron, O.; Preat, V. Paclitaxel-loaded PEGylated PLGA-based nanoparticles: *In vitro* and *in vivo* evaluation. *J. Control. Release* **2009**, *133*, 11–17.
28. Pai, S.S.; Tilton, R.D.; Przybycien, T.M. Poly(ethylene glycol)-modified proteins: Implications for poly(lactide-co-glycolide)-based microsphere delivery. *AAPS J.* **2009**, *11*, 88–98.
29. Choi, S.H.; Park, T.G. Synthesis and characterization of elastic PLGA/PCL/PLGA tri-block copolymers. *J. Biomater. Sci. Polym. Ed.* **2002**, *13*, 1163–1173.
30. Dong, C.M.; Guo, Y.Z.; Qiu, K.Y.; Gu, Z.W.; Feng, X.D. *In vitro* degradation and controlled release behavior of D, L-PLGA50 and PCL-bD, L-PLGA50 copolymer microspheres. *J. Control. Release* **2005**, *107*, 53–64.
31. Houchin, M.L.; Topp, E.M. Chemical degradation of peptides and proteins in PLGA: A review of reactions and mechanisms. *J. Pharm. Sci.* **2008**, *97*, 2395–2404.
32. Arshady, R. Preparation of biodegradable microspheres and microcapsules: 2. Polyactides and related polyesters. *J. Control. Release* **1991**, *17*, 1–21.
33. King, T.W.; Patrick, C.W., Jr. Development and *in vitro* characterization of vascular endothelial growth factor (VEGF)-loaded poly (D,L-lactic-co-glycolic acid)/poly (ethylene glycol) microspheres using a solid encapsulation/single emulsion/solvent extraction technique. *J. Biomed. Mater. Res. Part A* **2000**, *51*, 383–390.
34. Rosca, I.D.; Watari, F.; Uo, M. Microparticle formation and its mechanism in single and double emulsion solvent evaporation. *J. Control. Release* **2004**, *99*, 271–280.
35. Sah, H. Microencapsulation techniques using ethyl acetate as a dispersed solvent: Effects of its extraction rate on the characteristics of PLGA microspheres. *J. Control. Release* **1997**, *47*, 233–245.
36. Chaisri, W.; Hennink, W.E.; Okonogi, S. Preparation and characterization of cephalexin loaded PLGA microspheres. *Curr. Drug Deliv.* **2009**, *6*, 69–75.

37. Mao, S.; Xu, J.; Cai, C.; Germershaus, O.; Schaper, A.; Kissel, T. Effect of WOW process parameters on morphology and burst release of FITC-dextran loaded PLGA microspheres. *Int. J. Pharm.* **2007**, *334*, 137–148.
38. Thomasin, C.; Nam-Trân, H.; Merkle, H.P.; Gander, B. Drug microencapsulation by PLA/PLGA coacervation in the light of thermodynamics. 1. Overview and theoretical considerations. *J. Pharm. Sci.* **1998**, *87*, 259–268.
39. Thomasin, C.; Merkle, H.P.; Gander, B. Drug microencapsulation by PLA/PLGA coacervation in the light of thermodynamics. 2. Parameters determining microsphere formation. *J. Pharm. Sci.* **1998**, *87*, 269–275.
40. Edelman, R.; Russell, R.G.; Losonsky, G.; Tall, B.D.; Tacket, C.O.; Levine, M.M.; Lewis, D.H. Immunization of rabbits with enterotoxigenic *E. coli* colonization factor antigen (CFA/I) encapsulated in biodegradable microspheres of poly (lactide-co-glycolide). *Vaccine* **1993**, *11*, 155–158.
41. Hua, F.J.; Kim, G.E.; Lee, J.D.; Son, Y.K.; Lee, D.S. Macroporous poly(L-lactide) scaffold 1. Preparation of a macroporous scaffold by liquid–liquid phase separation of a PLLA-dioxane-water system. *J. Biomed. Mater. Res.* **2002**, *63*, 161–167.
42. Hua, F.J.; Park, T.G.; Lee, D.S. A facile preparation of highly interconnected macroporous poly(D,L-lactic acid-co-glycolic acid) (PLGA) scaffolds by liquid-liquid phase separation of a PLGA-dioxane-water ternary system. *Polymer* **2003**, *44*, 1911–1920.
43. Graham, P.D.; Brodbeck, K.J.; McHugh, A.J. Phase inversion dynamics of PLGA solutions related to drug delivery. *J. Control. Release* **1999**, *58*, 233–245.
44. Mu, L.; Feng, S.S. Fabrication, characterization and *in vitro* release of paclitaxel (Taxol®) loaded poly (lactic-co-glycolic acid) microspheres prepared by spray drying technique with lipid/cholesterol emulsifiers. *J. Control. Release* **2001**, *76*, 239–254.
45. Gavini, E.; Chetoni, P.; Cossu, M.; Alvarez, M.G.; Saettone, M.F.; Giunchedi, P. PLGA microspheres for the ocular delivery of a peptide drug, vancomycin using emulsification/spray-drying as the preparation method: *In vitro/in vivo* studies. *Eur. J. Pharm. Biopharm.* **2004**, *57*, 207–212.
46. Nie, H.; Lee, L.Y.; Tong, H.; Wang, C. PLGA/chitosan composites from a combination of spray drying and supercritical fluid foaming techniques: New carriers for DNA delivery. *J. Control. Release* **2008**, *129*, 207–214.
47. Wagenaar, B.; Muller, B. Piroxicam release from spray-dried biodegradable microspheres. *Biomaterials* **1994**, *15*, 49–54.
48. Sastre, R.L.; Olmo, R.; Teijón, C.; Muñiz, E.; Teijón, J.M.; Blanco, M.D. 5-Fluorouracil plasma levels and biodegradation of subcutaneously injected drug-loaded microspheres prepared by spray-drying poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) polymers. *Int. J. Pharm.* **2007**, *338*, 180–190.
49. Castelli, F.; Conti, B.; Conte, U.; Puglisi, G. Effect of molecular weight and storage times on tolmetin release from poly-lactide microspheres to lipid model membrane. A calorimetric study. *J. Control. Release* **1996**, *40*, 277–284.
50. Barrero, A.; Loscertales, I.G. Micro- and nanoparticles via capillary flows. *Annu. Rev. Fluid Mech.* **2007**, *39*, 89–106.

51. Freitas, S.; Merkle, H.P.; Gander, B. Microencapsulation by solvent extraction/evaporation: Reviewing the state of the art of microsphere preparation process technology. *J. Control. Release* **2005**, *102*, 313–332.
52. Berkland, C.; Pollauf, E.; Pack, D.W.; Kim, K.K. Uniform double-walled polymer microspheres of controllable shell thickness. *J. Control. Release* **2004**, *96*, 101–111.
53. Loscertales, I.G.; Barrero, A.; Guerrero, I.; Cortijo, R.; Marquez, M.; Ganan-Calvo, A.M. Micro/Nano encapsulation via electrified coaxial liquid jets. *Science* **2002**, *295*, 1695–1698.
54. Hans, M.L.; Lowman, A.M. Biodegradable nanoparticles for drug delivery and targeting. *Curr. Opin. Solid State Mater. Sci.* **2002**, *6*, 319–327.
55. Lamprecht, A.; Ubrich, N.; Perez, M.H.; Lehr, C.M.; Hoffman, M.; Maincent, P. Influences of process parameters on nanoparticle preparation performed by a double emulsion pressure homogenization technique. *Int. J. Pharm.* **2000**, *196*, 177–182.
56. Murakami, H.; Kobayashi, M.; Takeuchi, H.; Kawashima, Y. Preparation of poly(D,L-lactide-co-glycolide) nanoparticles by modified spontaneous emulsification solvent diffusion method. *Int. J. Pharm.* **1999**, *187*, 143–152.
57. Konan, Y.N.; Cerny, R.; Favet, J.; Berton, M.; Gurny, R.; Allemann, E. Preparation and characterization of sterile sub-200 nm meso-tetra(4-hydroxyphenyl)porphyrin-loaded nanoparticles for photodynamic therapy. *Eur. J. Pharm. Biopharm.* **2003**, *55*, 115–124.
58. Kwon, H.Y.; Lee, J.Y.; Choi, S.W.; Jang, Y.S.; Kim, J.H. Preparation of PLGA nanoparticles containing estrogen by emulsification-diffusion method. *Colloids Surf. A Physicochem. Eng. Asp.* **2001**, *182*, 123–130.
59. Rabin, C.; Liang, Y.; Ehrlichman, R.S.; Budhian, A.; Metzger, K.L.; Majewski-Tiedeken, C.; Winey, K.I.; Siegel, S.J. *In vitro* and *in vivo* demonstration of risperidone implants in mice. *Schizophr. Res.* **2008**, *98*, 66–78.
60. Widmer, M. Manufacture of porous biodegradable polymer conduits by an extrusion process for guided tissue regeneration. *Biomaterials* **1998**, *19*, 1945–1955.
61. Wang, C.; Wang, W.; Meyer, R.F.; Liang, Y.; Winey, K.I.; Siegel, S.J. A rapid method for creating drug implants: Translating laboratory-based methods into a scalable manufacturing process. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2010**, *93*, 562–572.
62. Yang, R.; Chen, T.; Chen, H.; Wang, W. Microfabrication of biodegradable (PLGA) honeycomb-structures and potential applications in implantable drug delivery. *Sens. Actuat. B Chem.* **2005**, *106*, 506–511.
63. Grayson, A.C.R.; Cima, M.J.; Langer, R. Size and temperature effects on poly(lactic-co-glycolic acid) degradation and microreservoir device performance. *Biomaterials* **2005**, *26*, 2137–2145.
64. Stubbe, B.G.; Smedt, S.C.D.; Demeester, J. “Programmed polymeric devices” for pulsed drug delivery. *Pharm. Res.* **2004**, *21*, 1732–1740.
65. Grayson, A.C.R.; Choi, I.S.; Tyler, B.M.; Wang, P.P.; Brem, H.; Cima, M.J.; Langer, R. Multi-pulse drug delivery from a resorbable polymeric microchip device. *Nat. Mater.* **2003**, *2*, 767–772.

66. Koushik, K.; Kompella, U.B. Preparation of large porous Deslorelin-PLGA microparticles with reduced residual solvent and cellular uptake using a supercritical carbon dioxide process. *Pharm. Res.* **2004**, *21*, 524–535.
67. Davies, O.R.; Lewis, A.L.; Whitaker, M.J.; Tai, H.; Shakesheff, K.M.; Howdle, S.M. Applications of supercritical CO₂ in the fabrication of polymer systems for drug delivery and tissue engineering. *Adv. Drug Deliv. Rev.* **2008**, *60*, 373–387.
68. Hile, D.D.; Amirpour, M.L.; Akgerman, A.; Pishko, M.V. Active growth factor delivery from poly (D,L-lactide-co-glycolide) foams prepared in supercritical CO₂. *J. Control. Release* **2000**, *66*, 177–185.
69. Xu, J.S.; Huang, J.; Qin, R.; Hinkle, G.H.; Povoski, S.P.; Martin, E.W.; Xu, R.X. Synthesizing and binding dual-mode poly (lactic-co-glycolic acid) (PLGA) nanobubbles for cancer targeting and imaging. *Biomaterials* **2010**, *31*, 1716–1722.
70. Zhang, L.; Xu, J.S.; Sanders, V.M.; Letson, A.D.; Roberts, C.J.; Xu, R.X. Multifunctional microbubbles for image-guided antivasular endothelial growth factor therapy. *J. Biomed. Opt.* **2010**, *15*, 030515.
71. Sun, B.; Ranganathan, B.; Feng, S. Multifunctional poly(D,L-lactide-co-glycolide)/montmorillonite (PLGA/MMT) nanoparticles decorated by Trastuzumab for targeted chemotherapy of breast cancer. *Biomaterials* **2008**, *29*, 475–486.
72. Ramchandani, M.; Robinson, D. *In vitro* and *in vivo* release of ciprofloxacin from PLGA 50:50 implants. *J. Control. Release* **1998**, *54*, 167–175.
73. Amann, L.C.; Gandal, M.J.; Lin, R.; Liang, Y.; Siegel, S.J. *In vitro-in vivo* correlations of scalable PLGA-risperidone implants for the treatment of schizophrenia. *Pharm. Res.* **2010**, *27*, 1730–1737.
74. Faisant, N.; Siepmann, J.; Benoit, J.P. PLGA-based microparticles: Elucidation of mechanisms and a new, simple mathematical model quantifying drug release. *Eur. J. Pharm. Sci.* **2002**, *15*, 355–366.
75. Crotts, G.; Park, T.G. Protein delivery from poly (lactic-co-glycolic acid) biodegradable microspheres: Release kinetics and stability issues. *J. Microencapsul.* **1998**, *15*, 699–713.
76. Kranz, H.; Ubrich, N.; Maincent, P.; Bodmeier, R. Physicomechanical properties of biodegradable poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) films in the dry and wet states. *J. Pharm. Sci.* **2000**, *89*, 1558–1566.
77. Lu, L.; Peter, S.J.; Lyman, M.D.; Lai, H.; Leite, S.M.; Tamada, J.A.; Uyama, S.; Vacanti, J.P.; Langer, R.; Mikos, A.G. *In vitro* and *in vivo* degradation of porous poly(-lactic-co-glycolic acid) foams. *Biomaterials* **2000**, *21*, 1837–1845.
78. Lu, L.; Garcia, C.A.; Mikos, A.G. *In vitro* degradation of thin poly(D,L-lactic-co-glycolic acid) films. *J. Biomed. Mater. Res.* **1999**, *46*, 236–244.
79. Park, T.G. Degradation of poly(lactic-co-glycolic acid) microspheres: Effect of copolymer composition. *Biomaterials* **1995**, *16*, 1123–1130.
80. 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.
81. Tsuji, H.; Mizuno, A.; Ikada, Y. Properties and morphology of poly(L-lactide). III. Effects of initial crystallinity on long-term *in vitro* hydrolysis of high molecular weight poly(L-lactide) film in phosphate-buffered solution. *J. Appl. Polym. Sci.* **2000**, *77*, 1452–1464.

82. 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. Pharm.* **2003**, *266*, 39–49.
83. Park, T.G. Degradation of poly (D,L-lactic acid) microspheres: Effect of molecular weight. *J. Control. Release* **1994**, *30*, 161–173.
84. Liggins, R. Paclitaxel loaded poly(L-lactic acid) microspheres: Properties of microspheres made with low molecular weight polymers. *Int. J. Pharm.* **2001**, *222*, 19–33.
85. Frank, A.; Rath, S.K.; Venkatraman, S.S. Controlled release from bioerodible polymers: Effect of drug type and polymer composition. *J. Control. Release* **2005**, *102*, 333–344.
86. Witt, C. 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.
87. 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.
88. Holy, C. *In vitro* degradation of a novel poly(lactide-*co*-glycolide) 75/25 foam. *Biomaterials* **1999**, *20*, 1177–1185.
89. Zolnik, B.S.; Burgess, D.J. Effect of acidic pH on PLGA microsphere degradation and release. *J. Control. Release* **2007**, *122*, 338–344.
90. Cai, Q.; Shi, G.; Bei, J.; Wang, S. Enzymatic degradation behavior and mechanism of poly(lactide-*co*-glycolide) foams by trypsin. *Biomaterials* **2003**, *24*, 629–638.
91. Li, S.; Girard, A.; Garreau, H.; Vert, M. Enzymatic degradation of polylactide stereocopolymers with predominant -lactyl contents. *Polym. Degrad. Stab.* **2000**, *71*, 61–67.
92. Eniola, A.O.; Hammer, D.A. Characterization of biodegradable drug delivery vehicles with the adhesive properties of leukocytes II: Effect of degradation on targeting activity. *Biomaterials* **2005**, *26*, 661–670.
93. Dailey, L.; Jekel, N.; Fink, L.; Gessler, T.; Schmehl, T.; Wittmar, M.; Kissel, T.; Seeger, W. Investigation of the proinflammatory potential of biodegradable nanoparticle drug delivery systems in the lung. *Toxicol. Appl. Pharmacol.* **2006**, *215*, 100–108.
94. Sundback, C.A.; Shyu, J.Y.; Wang, Y.; Faquin, W.C.; Langer, R.S.; Vacanti, J.P.; Hadlock, T.A. Biocompatibility analysis of poly(glycerol sebacate) as a nerve guide material. *Biomaterials* **2005**, *26*, 5454–5464.
95. Olivier, J.C.; Fenart, L.; Chauvet, R.; Pariat, C.; Cecchelli, R.; Couet, W. Indirect evidence that drug brain targeting using polysorbate 80-coated polybutylcyanoacrylate nanoparticles is related to toxicity. *Pharm. Res.* **1999**, *16*, 1836–1842.
96. Berchane, N.S.; Carson, K.H.; Rice-Ficht, A.C.; Andrews, M.J. Effect of mean diameter and polydispersity of PLG microspheres on drug release: Experiment and theory. *Int. J. Pharm.* **2007**, *337*, 118–126.
97. Raman, C.; Berkland, C.; Kim, K.; Pack, D.W. Modeling small-molecule release from PLG microspheres: Effects of polymer degradation and nonuniform drug distribution. *J. Control. Release* **2005**, *103*, 149–158.

98. Siepmann, J.; Göpferich, A. Mathematical modeling of bioerodible, polymeric drug delivery systems. *Adv. Drug Deliv. Rev.* **2001**, *48*, 229–247.

© 2011 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>.)