CHAPTER

Poly(lactic-*co*-glycolic acid) (PLGA) matrix implants

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CHAPTER OUTLINE

10.1 INTRODUCTION

Matrix implants are solid, rigid structures, usually cylindrical rods measuring millimeters in length, and with a diameter of less than a millimeter made essentially from polymers that allow a wide variety of drugs to be incorporated, usually entrapped, in the polymer matrix. They are dosage forms that allow controlled release of a drug for an extended period of time of months or even years, depending on the type of polymer used in their production (Markland and Yang, 2002). They are usually are placed subcutaneously in the patient, requiring a hypodermic needle or an easy surgery. If the polymer chosen is biodegradable, no additional surgery is required to remove the implant at the end of the therapeutic period (Iyer et al., 2006).

For the past four decades, there has been a proliferation of academic and industrial research on implantable delivery systems (Langer and Folkman, 1976; Furra and Hutchinsonb, 1992; Kleiner et al., 2014; Kamaly et al., 2016). Injectable implants from poly(lactic-*co*-glycolic acid) (PLGA) have been successfully prepared to deliver small drugs and therapeutic peptides, but there has been also substantial research to deliver therapeutic proteins and vaccines over a period of days, weeks, and even months at a constant release rate, depending on the degradation behavior of the PLGA employed.

With the topic being so vast in scope, the authors felt the need to address a chapter only on PLGA matrix implants and leave behind other modalities often included when addressing the topic of biodegradable implantable drug delivery systems (IDDS).

10.2 IMPLANTABLE DRUG DELIVERY SYSTEMS

IDDS, using polymers as delivery vehicles, started being developed in the 1960s, introducing a new concept in drug delivery (Kleiner et al., 2014; Kamaly et al., 2016). Since then, major efforts have been made to improve their formulation and release characteristics. Using these systems, drugs could be delivered in a sustained, continuous, and predictable way, especially useful to control chronic diseases that require repeated treatments (Fung and Saltzman, 1997). The systems were based on biocompatible polymers with appropriate physical properties; in the beginning they were developed to deliver hormones, among other therapeutics, (Fung and Saltzman, 1997; Kamaly et al., 2016) using nondegradable polymers.

The term IDDS refers to both nondegradable and degradable systems. The first controlled-release systems were based on nondegradable polymeric materials such as silicone elastomers (Fung and Saltzman, 1997; Folkman and Long, 1964). This led to the development of reservoir drug delivery systems that released the drug by controlled diffusion, through the polymer wall of the delivery device (Brown et al., 1986). The release was exceptionally controlled; however, after releasing the drug at the end of the therapeutic period, the empty reservoir needed to be extracted from the body by a health professional. Following the reservoir IDDS,

solid matrices of nondegradable polymers appeared and were used for long-term drug release. They differ from the previous ones by being simple in production and in safety. Being homogeneous matrices, they were also potentially safer because, unlike a reservoir device, a mechanical defect in a matrix has a reduced possibility of dose dumping and thereby to produce adverse effects or even drug-induced toxicity. Unfortunately, solid matrices can't achieve the idealized zero order constant drug release, like nondegradable reservoir ones (Fung and Saltzman, 1997) and require challenging formulation study.

There has been a major stimulus to develop biodegradable IDDS that can degrade in biologically compatible components under physiological conditions (Kleiner et al., 2014; Markland and Yang, 2002). Among the advantages is the unnecessary removal of the implant at the end of the therapeutic period, which improves patient compliance, especially when managing chronic illnesses that require long therapeutic periods and repeated treatments to control the disease (usually by frequent injections).

These systems are made of natural or synthetic biodegradable materials, usually polymers that can be degraded in vivo, enzymatically, nonenzymatically, or both, to produce biocompatible, endogenous metabolites that can be eliminated by the normal metabolic pathways of the body without associated toxicity (Makadia and Siegel, 2011). In the case of matrix implants, biodegradable polymers are generally used to form delivery devices by physically entrapping drug molecules into matrices. Because biodegradable polymers dissolve after implantation and drug release, they undergo degradation at the same time as they are releasing the drug, allowing certain aspects of device degradation and erosion to be controlled by careful selection of the appropriate polymer properties (Fung and Saltzman, 1997).

The main advantage of this approach over micro and nanoparticulates is related to the ability to be extracted when in the presence of undesirable adverse events, since the matrix implants retain a degree of reversibility which is not available in depot injections (Makadia and Siegel, 2011; Rabin et al., 2008; Siegel et al., 2006).

10.3 ABILITY TO SUSTAIN AND TO CONTROL DRUG DELIVERY

By definition, a controlled release system provides slow release of a drug over an extended period of time. This is usually achieved by using polymeric materials where drugs are incorporated. During this period of time, the system is capable of providing control at a constant drug level, also known, as zero-order drug release (Stevenson et al., 2012; Alexis, 2005). A sustained release system is able to prolong the release of a drug over a period of time, but unlike the former, not necessarily at a constant drug level (Stevenson et al., 2012). Nevertheless, both systems provide long-term delivery.

The effective half-lives of drugs administered by implants, where they are entrapped in a polymer, is much longer than when compared to the free drug

administered by the same route. This leads to a potentially reducing of the amount of drug and longer periods of drug release (Fung and Saltzman, 1997; Desai et al., 2010). Keeping constant therapeutic drug blood levels is important, especially for drugs with a low therapeutic window that need maintenance of the effective dose at precise therapeutic levels for the desired duration of the treatment, usually extensively prolonged. This prolonged systemic delivery approach is particularly useful for hormonal anticancer therapies that require therapeutic peptides as drugs. Many of the developed therapeutic agents to combat cancer are proteins that have short half-lives, and cross biological barriers poorly, which makes them almost ineffective when delivered as free drugs in a bolus injection (Fung and Saltzman, 1997). Hormone-responsive cancers, such as carcinomas of the breast, prostate, and endometrium, require frequent injections of hormone agonists, usually synthetic agonistic analogs of luteinizing hormone−releasing hormone (LH-RH), as conventional treatments to inhibit tumor growth by lowering plasma testosterone levels in the body. However, these agonists have short plasma half-lives. Treatment with these therapeutic peptides requires daily injections, necessary to maintain therapeutic concentrations. This can be a burden for patients, due to their inconvenience and due to their concentration fluctuation, which can produce undesirable testosterone release responses in patients, leading sometimes to the withdrawal of therapy (Fung and Saltzman, 1997). Polymer drug delivery systems provide an opportunity to deliver high, localized doses of chemotherapy for a prolonged period, as shown in Fig. 10.1.
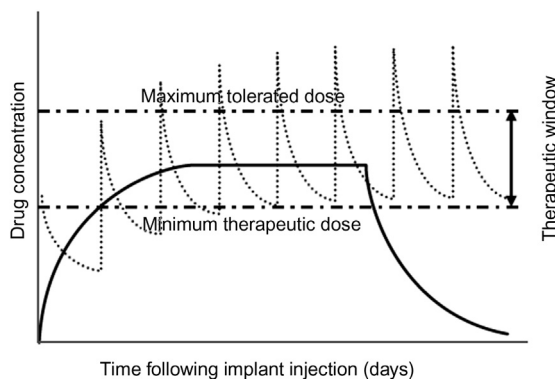
FIGURE 10.1

Drug concentration in plasma following subcutaneous injection of a drug-loaded matrix implant (solid lines) or daily subcutaneous injections of free drug (dotted line). When the implant is administered, drug therapeutic concentrations are maintained for over a longer period. In contrast, following an injection of free drug, most of the drug is eliminated in 1 day, and repeated injections are necessary to maintain the desire drug concentration along the therapeutic period of time.

One of the advantages of controlled delivery system specifically IDDS is the possibility of protecting drugs that are inherently unstable, such as therapeutic proteins and peptides, once stabilized, allowing their continuous delivery at consistent rates for several months. (Langer, 1998).

10.4 THE ISSUE OF BIOCOMPATIBILITY

When an implant is administered, scarring of the tissue usually occurs to a greater or lesser extent even if a needle is used to made the insertion, instead of a surgical procedure. Once inside, it is considered a foreign body by the organism and the immunological system is going to react to it; after implantation a response to injury is initiated (Anderson and Shive, 1997). The foreign body physiological response is initiated, not so much due to the nature of the material, which in the case of PLGA is considered well tolerated and with time is metabolized, but due to the size and necessity of scarring tissue after implantation (Morais et al., 2010) Scarring of the tissue will originate a tissue response, such as inflammation, followed usually by fibrous encapsulation isolating the implant (Oviedo Socarrás et al., 2014; Anderson et al., 1993). Table 10.1 shows the sequence of events that usually take place. Each event leads to the next. In a sequence, from injury to acute inflammation, to chronic inflammation, granulation tissue formation, foreign body reaction, and fibrous encapsulation (Anderson and Shive, 1997). The body tends to completely isolate foreign implants like a foreign body by forming a sheath-like, relatively avascular, densely fibrous membrane capsule around the implant within a few weeks after implantation that effectively walls off the implant from its environment (A. Rothen-Weinhold et al., 1999a,b; Iyer et al., 2006). It is surrounded by fatty tissue, mainly composed of lipid-laden macrophages, which in a long-acting device, can lead to overall variability of drug release (Anderson et al., 1993). This could impair the function of the matrix implant and, in the end, lose the capacity of control-releasing the concentration of drug necessary to treat or manage the disease.

Table 10.1 Sequence of Tissue Response to an Implantable Delivery System

Tissue injury: Implantation
Acute inflammation: Polymorphonuclear leukocytes
Chronic inflammation: Monocytes and lymphocytes
Granulation tissue: Fibroblasts and new blood capillaries
Foreign body reaction: Macrophages and foreign body giant cells at Tissue: implant interface
Fibrosis: Fibrous capsule

Adapted with permission from Anderson, J.M., Shive, M.S., 1997. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv. Drug Delivery Rev. 28(1), 5–24.

10.5 POLY(LACTIDE-*CO*-GLYCOLIC ACID) (PLGA)

Aliphatic poly(esters) are the best-characterized and most widely studied biodegradable synthetic materials (Uhrich et al., 1999). Polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymer PLGA, poly(ε-caprolactone), poly(3-Hydroxybutyrates) (Uhrich et al., 1999) and poly(alkyl cyanoacrylates) (Kamaly et al., 2016) are included in this family of polymers.

Among them, polyesters based upon lactic and glycolic acids are currently the most used biodegradable synthetic polymer for controlled release applications in research academia and in industrial research. They have been in focus since the 1970s, with regulatory approval first as sutures, then as excipients for drug delivery, and finally as IDDS (Kamaly et al., 2016). They are currently the most investigated with available clinical and toxicological data (Witt et al., 2000). Their chemical structure is represented in Fig. 10.2.

PLA can exist in an optically active stereoregular semicrystaline form (L-PLA), due to the high regularity of the polymer chain, and in an optically inactive racemic amorphous form (D,L-PLA), due to the irregularities of the polymer chain structure. PGA exists as a high crystalline polymer, due to the lack of methyl side groups that are present in PLA (Jain, 2000). Poly(lactic-*co*-glycolic acids), which contain L-PLA and PGA, are crystalline copolymers, while those with (D,L-PLA) and PGA are amorphous (Jain, 2000). Commercially available PLGAs are usually
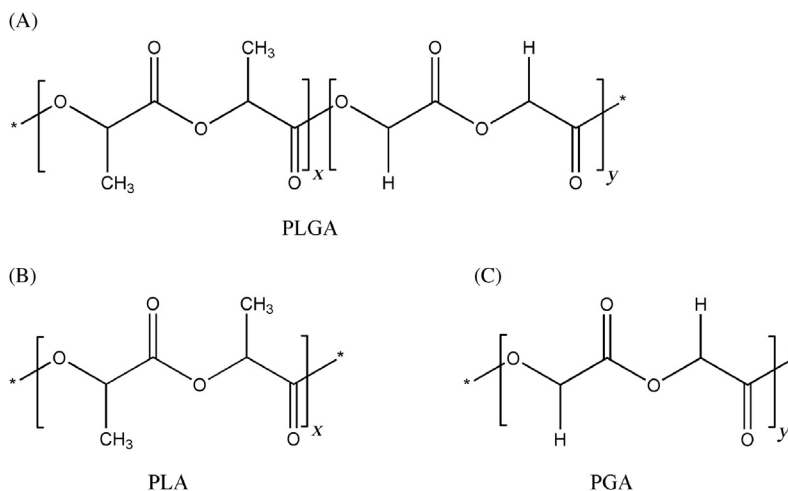

FIGURE 10.2

Chemical structures of: (A) copolymer of lactide (*x*) and glycolide (*y*);(B) homopolymer of lactide, and (C) homopolymer of glycolide; "*x*" and "*y*" refer to the relative amounts of lactide and glycolide units.

presented with intrinsic viscosity as a form of characterization, which is directly related to their molecular weights helping when choosing the PLGA of interest (Yeo and Park, 2004; Kapoor et al., 2015). PLGAs are glassy, but have a fairly rigid chain structure, with considerable mechanical strength that allow them to be formulated as drug delivery devices. Their T_g is usually above 37°C, but it decreases with the decrease of lactide content and molecular weight (Jain, 2000). Furthermore, mechanical strength is also a reflection of the molecular weight, copolymer composition in terms of PLA-PGA ratio, crystallinity, and geometric regularity of the polymer chains (Jain, 2000).

Lactic acid is more hydrophobic than glycolic acid. PLGA copolymers with high ratio of lactic acid in their composition are expected to be less hydrophilic, absorb less water and degrade slower (Jain, 2000; Kapoor et al., 2015). As one can already notice, PLGAs with a wide range of physicochemical properties, so a wide range of erosion times, are commercially available. It is possible to tailor the release profile of a drug by the choice of the PLGA with the right physical chemical characteristics or blend different PLGAs to achieve the best characteristics of both (Fredenberg et al., 2011; Hines and Kaplan, 2013).

10.6 BIODEGRADABILITY

PLGAs are relatively stable when in a dry state but degrade by hydrolysis of the polymer backbone when exposed to moisture or an aqueous environment, such as the in vivo environment (Stevenson et al., 2012; Jain, 2000). They degrade by a process of hydrolytic chain scission, where polymer chains are first broken down to small oligomers and then to monomers (Alexis, 2005; Lao et al., 2011). The scission of the chains occurs through cleavage of the backbone ester linkages and can be seen in Fig. 10.3.

The two monomers lactic acid and glycolic acid are endogenous acid metabolites, they are going to enter the Krebs cycle and be cleared from the body as carbon dioxide and water (Houchin and Topp, 2008; Danhier et al., 2012) with only minimal systemic toxicity associated leaving no trace in the end and only increased local acidity due to the degradation can lead to irritation at the site of where the polymer is implanted (Uhrich et al., 1999).

10.7 PLGA MATRIX IMPLANTS

A monolithic implant, also known as millirod or injectable monolith (Mitragotri et al., 2014), is a unitary structure, typically having dimensions greater than about 0.5 mm, more preferably from 1 to 30 mm (Booth et al.,
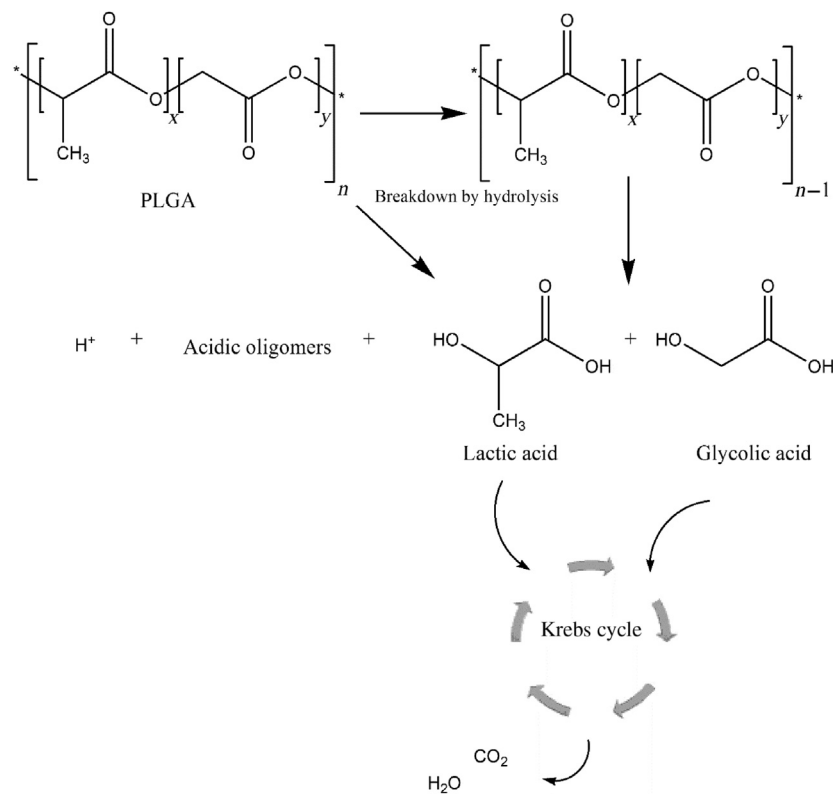
FIGURE 10.3

PLGA hydrolysis when in moisture or aqueous environment. PLGA is biologically hydrolyzed into lactic and glycolic acid. These hydrolysis products are metabolized via endogenous body mechanisms with very minimal systemic toxicity associated.

2003). PLGA matrix implants can be considered monolith implants, where a drug is homogeneously distributed throughout the PLGA matrix (Markland and Yang, 2002). A blend or composite material is formed between a drug and the polymer, or even with more components, and the drug is entrapped mainly by the polymer chains (Weinberg et al., 2007). The system does not require extraction because of PLGA biodegradability.

10.7.1 PLGA MATRICES AS SUSTAINED DRUG DELIVERY SYSTEMS

As previously mentioned, PLGA degrades through hydrolytic cleavage of its poly (ester) backbone (Houchin and Topp, 2008), as seen in Fig. 10.3. Chains of

polymer are cleaved into shorter chains or oligomers (Lao et al., 2011). Then, due to the transformation of the latter in CO_2 and water, the mass of the matrix is reduced, this mass loss process being erosion (Lao et al., 2011). PLGA is considered to be a bulk-eroding polymer (Lao et al., 2011; Kapoor et al., 2015). Bulk degradation is a homogenous process in which degradation occurs throughout the polymer matrix and can be described as consisting of four consecutive steps (Lao et al., 2011). First, a polymer absorbs water and undergoes some swelling. The water penetrates, and secondary or tertiary structures, previously stabilized by van der Waals forces and hydrogen bonds, are broken. Second, hydrolysis of the covalent ester bonds in the polymer backbone begins generating more and more carboxylic end groups, which can autocatalyze the hydrolysis, improving the breakdown rate of the polymer backbone. This step marks the beginning of a molecular mass decrease and loss of mechanical strength. Third, massive cleavage of the backbone covalent bonds continues. At some critical value of molecular weight, significant mass loss begins to occur. Loss of physical and mechanical integrity occurs at the same time this process is taking place. Fourth, the polymer loses substantial mass, due to solubilization of oligomers into the surrounding medium. The polymer breaks down to many small fragments, which will be further hydrolyzed into free acids (Lao et al., 2011; Hines and Kaplan, 2013).

In spite of degradation by bulk-eroding being a characteristic of the PLGA-type polymers, and being that this process is what allows a drug entrapped in a matrix to be released, drugs are usually released from macroscale PLGA-matrix implants via a combination of three mechanisms: diffusion-controlled release, drug-carrier affinity, and degradation of the matrix material (Kamaly et al., 2016; Kearney and Mooney, 2013). The drug release is diffusion-driven and can be affected by concentration gradients, matrix swelling, and diffusion distance, related to the shape of the implant (Kamaly et al., 2016). That is why the size of the matrix also plays an important role in the release. The presence of pores on the matrix could lead to differences in the release. Other processes may also contribute to the release mechanism, including: water penetration and solubilization after the device is first submerged in an aqueous environment, erosion and diffusion of PLGA polymer fragments, and the rate of diffusion of the releasing drug. Because these processes can occur at the same time, the release mechanism may be complex (Hines and Kaplan, 2013).

The release profile for a macroscopic PLGA matrix implant usually has three different phases, due to the heterogeneous degradation that usually takes place. It is often called tri-phasic profile. Phase I is usually described as a burst release and has been attributed to drug particles on the surface of the matrix that are easily solubilized by the exterior aqueous environment on the implantation site. Phase II is often a slow-release phase, usually referred to as lag-phase. During this phase, the drug diffuses slowly, either through the few existing pores, or through the relatively dense polymer. Polymer chains still have enough length and still entrap the drug, while polymer degradation and hydration is already

taking place. The lag-phase may not necessarily be caused by a dense polymer with low porosity, but by pore closure, polymer—drug interactions, or drug—drug interactions that inhibit the release of the drug. Phase III is usually a period of faster release, often attributed to the onset of erosion. This phase is sometimes called the second burst and usually, most of the drug is released rapidly in this phase. It can also be due to crack formation in the matrix. Most of the time, the initial burst release is not desired and formulation optimization can allow changes to the classic tri-phasic release profile. PLGA degradation is a dynamic process; the properties and behavior change while the degradation is ongoing. As the pH and other characteristics inside the matrix are changing during degradation, the conditions that caused slow release are also changing; a pore formation process can dominate over pore closure. The choice of type of PLGA used will also influence drug rapid release. This rapid release could start in Phase II instead of at Phase III, since the onset of rapid drug release was found to be correlated with swelling, erosion, and deformation of the device, and, accordingly, the easier hydration of the PLGA matrix. Phases may also be superimposed and one cannot draw conclusions and predict the drug release by only analyzing the release profile (Fredenberg et al., 2011).

Many mathematical models have been developed to try and describe drug release from PLGA matrix implants (Siepmann and Siepmann, 2012). Mathematical modeling is a useful tool that can be used to identify release mechanisms, characterize the significant transport processes involved, estimate unknown parameters such as the diffusion coefficient when diffusion is involved, reduce experimentation, and provide predictive capabilities (Hines and Kaplan, 2013). These models help to elucidate the governing release mechanisms and provide predictive power on the release behavior of a particular formulation. There are comprehensive reviews and several excellent articles that outline mathematical models developed to predict the release kinetics of drug controlled release from bulk-degrading systems (Lao et al., 2011; Siepmann and Siepmann, 2012).

10.7.2 MANUFACTURING TECHNIQUES

PLGAs have characteristics of low-melting thermoplastics that soften and melt when heated above their T_g. They can be shaped as macroscopic (or even microscopic) millirods relatively easily with the aid of pressure and mild to high temperature, allowing the manufacturing of devices of several morphologies (Hines and Kaplan, 2013; Jain, 2000).

Different implant manufacturing techniques leads to different PLGA processing conditions. Differences in the molding operation, in generated shearing forces, and thermal treatments in the end may change the final molecular weight, crystallinity, or microporous structures of the polymer, leading to differences in degradation of the final implant (a. Rothen-Weinhold et al., 1999a,b). Those macro or microscopic differences make it essential to individually evaluate,

in vitro and in vivo, each implant produced (a. Rothen-Weinhold et al., 1999a,b). The degradation properties of the polymers, the manufacturing technology, as well as the relative drug-loading of the device determine the in vivo performance of the PLGA matrix implant delivery system (a. Rothen-Weinhold et al., 1999a,b; Rothen-Weinhold et al., 1997). Most of the properties that characterize the final matrix implant are a consequence of the manufacturing technique chosen to produce it.

Common manufacturing techniques for the preparation of biodegradable implants are listed below:

Solvent casting: Solvent casting is used to fabricate large sized, macroscopic matrix formulations with millimeter size which can be implanted or inserted subcutaneously in the body. When applied to PLGA, this technique depends on the dissolution of the polymer in an appropriate organic volatile solvent such as acetone. The polymer solution is then cast in a mold with the desired size and shape, and the solvent allowed to evaporate, resulting in a composite material (Rabin et al., 2008; Makadia and Siegel, 2011). Usually, this method is chosen to produce films and laminar implants as simple monolithic discs or even multilayer discs (Umeki et al., 2011; Dorta et al., 2002). It is not the ideal technique for industrial scale-up; it requires large amounts of organic solvent to dissolve PLGA and the drug, in order to blend them. The use of solvents can introduce the risk of denaturation of drugs, especially if they are proteins. After the blending step, the solvent need to be removed, which requires a very long time to completely remove all solvents from the resulting material. Lastly, it is not a continuous process. The fact that a technique is not a continuous process leads to possible increases in batch-to-batch variation in the composition of the implants, as well as cost increase of manufacturing (Widmer et al., 1998; Makadia and Siegel, 2011).

Compression molding: This is a technique with similarities to solvent casting. After a previous solvent casting step, the mixture material is also compressed in a mold, using both high temperature and pressure, producing an implant with higher density (Makadia and Siegel, 2011). With this technique, the use of heat and solvents is avoided, and compression force is used instead. A mixture of the powders is compressed using punches on a punch press at room temperature, in a similar process to the one used to produce tablets (Santoveña et al., 2009). Implants prepared by this technique are reported to release the drug quickly and in a short time (Negrin et al., 2004; Onishi et al., 2005). To delay the release, using a coating layer is a useful approach, however, here the use of solvents is introduced (Schliecker et al., 2004).

Ram extrusion: An easy manufacturing technique that could or not use solvents and offers some advantages, such as requiring only a small amount of raw material and low temperatures for preparation. There are reports for the production of implants by ram extrusion that result in almost no peptide drug

degradation (a. Rothen-Weinhold et al., 1999a,b). A previously made mixture of the chosen polymer and drug is made requiring or not a solvent, then the blend is introduced into a barrel, where an inserted piston rod will move the blend under appropriate pressure and temperature. Briefly, the blend is forced through a small orifice and, because it has viscoelastic properties, an extrudate is produced. Then the extrudate will pass in a die creating long rods with the desired width. As a final step, the produced rods are cut into implants with the desire length (a. Rothen-Weinhold et al., 1999a,b). This technique requires the use of force, high pressure, and temperatures above the T_g of the chosen PLGA to made it soft enough to be forced through the die. Again, stability of the drug needs to be accessed. Because this technique requires the use of high temperature, a decrease in M_w of the PLGA is often reported (a. Rothen-Weinhold et al., 1999a,b). There are also reports that relate an increase of impurities formed during this process, when high temperatures and long extrusion times are applied (a. Rothen-Weinhold et al., 1999a,b; Rothen-Weinhold et al., 1999a,b; Rothen-Weinhold et al., 2000). However, extrusion is a continuous process, able to allow scale-up suitable for industrial production.

Hot melt extrusion: Following its introduction in the plastic industry, hot-melt extrusion has now been applied in the pharmaceutical field with success. It is a continuous process, where a mixture of polymer and drug circulate through a die to create implants with fixed diameter, without the use of solvents (Makadia and Siegel, 2011; Wang et al., 2010). The blend is melted above the T_g and forced through a die at that temperature. If necessary, previous premixing can be made to help achieve a homogenous extrudate. It is the most appropriate technique to produce matrix systems, with the drug uniformly distributed throughout the implant. A change in the used temperature could have consequences on the drug-loading and M_W of the polymer. 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 (Makadia and Siegel, 2011). Surprisingly, negligible loss of biological activity has been reported for some peptides (Ghalanbor et al., 2010; Bhardwaj and Blanchard, 1997).

Injection-molding: Injection-molding is a technique also more appropriate for large scale industrial production. This manufacturing technique ensures a good mixing treatment between polymer and drug, and allows the manufacture of implants of various shapes. A special adapted injection molding machine is usually used, with a mold of the desired shape and size for the final desire form. The mixture of the polymer and drug is previously subjected to an appropriate temperature to plasticize the polymeric blend, then to an injection temperature and pressure to mold the blend to the desire form. The cast implants are allowed to cool at a much lower temperature (a. Rothen-Weinhold et al., 1999a,b). Besides being a continuous process, it can be

automatized and is very reproducible. Again, this technique requires the use of high temperature and a decrease in M_w of the PLGA is often reported. As previously explained, this might lead to some degradation of the active compound (a. Rothen-Weinhold et al., 1999a,b). A partial material sterilization is also possible in some cases, with the disadvantages of the higher temperatures used for preparation being deleterious when formulating peptides and proteins. Radiation sterilization seems to be the method of choice to implant matrices for clinical uses (Rothen-Weinhold et al., 1999a,b; Alexis, 2005).

There are reports that compare implants produced with different manufacturing techniques (a. Rothen-Weinhold et al., 1999a,b). According to the production technique, authors reported differences related to appearance, color uniformity, smoothness, and small differences in diameter even if the die of the extruder has the same diameter as the mold of an injection-molder. Extruded implants are shown to acquire a slightly bigger diameter than the diameter of the die (a. Rothen-Weinhold et al., 1999a,b). There are also reported differences in the brittle characteristics, in the density of the matrix, resulting higher for injection-molded implants when compared to implants with the same formulation produced by extrusion, and in the weight average molecular weight (M_w) of the polymer. A decrease in M_w and polydispersity of the polymer has also been reported after melt manufacturing techniques, where relative high temperatures are used such as injection molding and extrusion (a. Rothen-Weinhold et al., 1999a,b; Rothen-Weinhold et al., 1997); a more pronounced M_w drops when the implant is produced by injection molding. In injection-molding, the polymer is exposed to higher temperatures, to high pressures, and to greater shearing forces. In contrast, during the extrusion process, the matrix is exposed to lower temperatures but also to high pressures. Rothen-Weinhold et al. compared PLA implants made by extrusion and injection-molding and noticed that implants extruded were extremely porous and extensively fragmented, whereas the injection-molded ones showed numerous cracks throughout the matrix, but no porosity. Injection-molded samples appear to be denser than the extruded ones, which may lead to increased water uptake in the extruded implants, which may consequently accelerate the degradation process. They concluded that elevated temperatures and a slow rate of cooling allows polymer chains to move and to realign themselves in a more regular structure, becoming the more crystalline polymer, depending on the cooling rate during solidification after melting (a. Rothen-Weinhold et al., 1999a,b).

10.7.3 DRUG RELEASE

10.7.3.1 Mechanism of Drug Release From the Implant

One of the most important steps when developing PLGA formulations is foreshadowing the release process, which could be achieved by understanding the erosion

process that is going to take place (Alexis, 2005). Several authors state that the release of the drug confined in a PLGA matrix is complex (Fredenberg et al., 2011) and mainly a direct consequence of the erosion process that takes place when exposed to hydrolytic chain scission (Alexis, 2005).

PLGA matrix implants are usually administrated subcutaneously or placed directly in specific areas of the body. Following implantation, the drug is expected to slowly be released from the implant to the immediate vicinity tissue fluids via complex release mechanisms that involve diffusion, polymer erosion, or a combination of both (Alexis, 2005). The drug is subsequently transported into the systemic blood circulation via diffusion and/or convective processes (Iyer et al., 2006; Larsen et al., 2009; Shen and Burgess, 2015).

The degradation properties of the polymers, the manufacturing technology, as well as the relative drug-loading of the device, determine the in vivo performance of the delivery system, as stated previously.

10.7.3.2 Biodistribution

After subcutaneous implantation, the drug is released in the immediate vicinity of the implant, comprising cells and interstitial fluid of the extracellular space (ECS) (Iyer et al., 2006). The fluid, with the consistency of a gel, consists of fibrous collagen, proteoglycans, salt solution at pH 7.4, and proteins derived from plasma in less concentration (Iyer et al., 2006). After being exposed to this aqueous environment, the drug released from the implant migrates away from the polymer/tissue site interface via the ECS. It moves by passive diffusion and fluid convection or facilitated transport to reach cells, blood capillary, and the lymphatic vessels to be subsequently transported into the systemic blood circulation via diffusion and/or convective processes (Fung and Saltzman, 1997; Iyer et al., 2006; Larsen et al., 2009). If the drug is sufficiently lipophilic, it may penetrate cell membranes rapidly enough to move through a transcellular path (Fung and Saltzman, 1997). The size exclusion−like properties of the ECS significantly reduce diffusion of plasma proteins and other macromolecules. Drug molecules with molecular masses below 2 kDa after leaving the implant can enter blood and lymph capillaries and will be cleared predominantly by the blood vessels (Porter and Charman, 2000; Larsen et al., 2009). The degree of uptake by the lymphatics increase directly with the size of the drug molecule (Porter and Charman, 2000). If the drugs are macromolecules above 16 kDa instead of small peptides and particulates of PLGA from the implant, they will be preferentially removed from the tissue by the lymphatic system (Iyer et al., 2006). The presence of blood and lymphatic capillary is the reason for observed variability in absorption rates following subcutaneous administration of therapeutic proteins at different administration sited in the body (Larsen et al., 2009).

As previously mentioned, following implantation, normal subcutaneous wound healing is going to take place, due to the macroscopic size of these types of milli-rods and the necessity to scar in more or less extent the tissue. This can smooth

the implant surface and chemically inert the implant, due to fibrous encapsulation. This tissue scarring and wound healing process is dependent on the size and shape of the device, as well as the biocompatibility of the PLGA (Larsen et al., 2009). The formation of the capsule could limit drug diffusion and perfusion transport, leading to a less effective implant. Contributing to the reduced effectiveness is also the infiltration of scleroprotein, formed as a result of the tissue reaction to the presence of a foreign body in the pores of the surface of the matrix, also known as ghost formation (Iyer et al., 2006).

The fate of drug molecules released and delivered to tissues in the end is a combination of the rates of transport (via diffusion and fluid convection), elimination (by degradation, metabolism, transcapillary permeation and internalization (Fung and Saltzman, 1997), maintenance of implant integrity, and administration location in the body. However, the rate-limiting step in the absorption of a drug released by a PLGA matrix implant will be the controlled release, provided by the device (Larsen et al., 2009).

10.7.4 FACTORS AFFECTING DEGRADATION AND ALSO DRUG RELEASE FROM DEGRADABLE PLGA MATRICES

Being an IDDS, a major factor affecting the degradation and, consequently, the drug-release mechanism of a matrix implant is the type of polymer used, among other important factors (Fredenberg et al., 2011). Some polymer properties could be tailored to achieve a specific drug release behaviour (Hines and Kaplan, 2013).

Polymer composition: Polymer composition, in terms of PLA-PGA ratio is recognized as the most important factor that influences the degradation rate (Alexis, 2005; Washington et al., 2017). A ratio increase in more hydrophilic glycolic acid in PLGA composition accelerates weight loss, due to specific chain scission of glycolic linkages, leading to preferential degradation of those units instead of lactic acid units (Makadia and Siegel, 2011). The higher the amount of PGA in the copolymer, the higher the hydrophilicity of the PLGA matrix, increasing the rate of degradation of PLGA backbone due to hydrolytic scission and subsequently faster drug release (Makadia and Siegel, 2011). Conversely, a ratio increase in lactic acid residues increases the crystallinity of PLGA, resulting in higher degradation rate of the backbone. Reports suggest that the rate of decrease in M_w, when subject to hydrolysis, was higher for PLGA with high initial crystallinity, meaning a high content of L-PLA not subject to any process that could result in loss of crystallinity like compressing molding or quenching processes (Alexis, 2005).

Crystallinity: Crystallinity can be correlated with T_g. It is affected by the percentage of PGA and PLA units (Makadia and Siegel, 2011). If the PLGA has more L-PLA or PGA, it is more crystalline.

Weight average molecular weight (M_w*):* PLGAs with higher M_w have bigger polymer chains, therefore require more time to undergo full hydrolysis and degrade (Makadia and Siegel, 2011). The opposite occurs with L-PLA, due to their high crystallinity that increases with M_w (Makadia and Siegel, 2011). PLGA chains with low M_w are known to have higher biodegradation rates and to release drugs faster than PLGA chains with high M_w (Alexis, 2005). This behavior is accompanied by a reduction of the glass transition temperature. The opposite behavior is seen in L-PLA, due to the high degree of crystallinity that is present as the M_w decreases.

Low M_w, low PLA-PGA ratio and uncapped end groups result in a less hydrophobic PLGA, with increased rates of water absorption, hydrolysis and erosion (Tracy, 1999; Fredenberg et al., 2011). However, as earlier revealed, those properties change along the degradation and drug release period. During these processes, PLGA has a dynamic nature, as its properties and behavior change with degradation. Hydrophobic, high M_w and slow-degrading PLGA will eventually become more-hydrophilic, low M_w and fast-degrading PLGA (Fredenberg et al., 2011).

Morphology of the matrix: Especially for large devices, the higher the ratio of surface area-to-volume, the higher the degradation of the matrix (Grizzi et al., 1995; Kapoor et al., 2015). Bulk degradation will be faster and subsequently faster drug release (Makadia and Siegel, 2011). The presence of pores in the matrix can anticipate drug release if the initial pores had sufficient size to allow drug molecules to be released by diffusion when water fills the pores after implantation.

Manufacturing technique: As discussed earlier, the choice of technique to manufacture the implant will have consequences in the final PLGA characteristics, due to the processing variables used and this will have an impact on the degradation (Hines and Kaplan, 2013).

Drug type: The type of drug entrapped could change the mechanism of the matrix degradation and affect the rate of degradation (Siegel et al., 2006; Makadia and Siegel, 2011). The choice of the drug, due to its chemical properties, can tremendously affect the release mechanism. The behavior of the release mechanism would vary greatly, depending on the chemical properties of the drug of choice. In general, lower drug loadings, salts, and drugs that aided hydrolysis process led to faster degradation of the matrix. Interactions between the polymer and drug may occur, affecting the rate of release (Hines and Kaplan, 2013). When dispersed in a PLGA matrix, some drugs can also decrease the T_g (such as caffeine and salicylic acid) and others can interact with the carboxyl groups generated during the process of PLGA degradation itself (as reported for quinidine) (Alexis, 2005). When the drug entrapped is a protein or peptide, additives like protein stabilizers which are salts (basic anions and divalent cations) are commonly found in the formulations (Milacic and Schwendeman, 2014). They can neutralize acids but also be pore forming, catalyzing even more the hydrolysis and having the opposite effect (Fredenberg et al., 2011).

pH: Alkaline and strongly acidic media accelerate PLGA degradation. When the degradation of PLGA is taking place, the accumulation of carboxylic end groups is going to autocatalyze the degradation by hydrolysis of the ester linkages (Makadia and Siegel, 2011).

Drug load: When entrapping drugs in a PLGA matrix, polymer-to-drug ratio has an influence on the rate and duration of release. Higher polymer-to-drug ratio leads to higher rate and duration of release; however, this will lead to a higher burst release if present in the mechanism of release (Makadia and Siegel, 2011). When the drug is released, the space left will be probably a pore in the matrix. As the medium enters the pore, it will facilitate more drug to be released by diffusion (Fredenberg et al., 2011).

Other factors: Other factors affecting the degradation and, as a consequence, the drug-release mechanism of PLGA also include: flow rate, sterilization of the final pharmaceutical form, strain, presence of plasticizers, and the presence of enzymes, although there are contradictory reports linking a correlation between the role of body enzymes and the degradation of PLGA (Alexis, 2005).

10.7.5 THERAPEUTIC PEPTIDES AND PROTEINS INCORPORATED IN PLGA MATRIX IMPLANTS

When the drug is a therapeutic peptide or protein, which are extremely unstable molecules, the difficulty to formulate and to deliver them without some loss of purity is usually reported (Frokjaer and Otzen, 2005). Proteins are highly organized, complex and unstable macromolecules, most of them with short half-lives (Vaishya et al., 2015). Maintaining their three-dimensional structure with their chemical integrity during and after manufacturing of the implant is a major concern (Fu et al., 2000). Once degraded, they are likely to cause immunogenicity and an impact on its release behaviour and bioactivity.

Their complexity and fragile nature imposes certain restrictions on the process parameters that may be employed to formulate these drugs in PLGA matrix implants. Depending on the manufacturing technique chosen, if the drug is a peptide or protein the exposure to the use of organic solvents, elevated temperature shear, and high pressure in processing might jeopardize their function, due to a loss of stability (Ghalanbor et al., 2010). Each protein is unique and so is likely to have a unique set of conditions that would maintain their stability during the manufacturing technique of implant production. Nonetheless, the possibility of denaturation needs to be consider when developing these types of pharmaceutical forms. When producing implants with those type of drugs, peptide purity should to be evaluated right after the implant manufacturing, to assess the feasibility of the technique employed. There are strategies to reduce peptide degradation, which are based on an understanding of the effect of the changes in the manufacturing chosen conditions (Rothen-Weinhold et al., 1999a,b).

PLGA can also contribute to physical and chemical protein degradation (Zhu et al., 2000). After implant administration, the protein entrapped in PLGA comes in contact with moisture and the ambient temperature of the body for the total degradation period of the implant, which is often months. It is known that water plays a role in protein degradation (Fu et al., 2000). PLGA degradation will produce an acidic micro environment inside the implant and in the surroundings of the implant location. The products of implant degradation are going to contribute to jeopardizing the stability of the protein released. Several reactions between chemical groups of the protein entrapped and the groups of PLGA can take place after the implantation on the body, as soon as the degradation reaction of the matrix implant starts (Fu et al., 2000).

Production of acylation products are dependent on the type of protein entrapped. Proteins like calcitonin and parathyroid analog have been reported to undergo this kind of acylation reaction, whereas leuprolide peptides are known to maintain stability in this situation (Brown, 2005). This usually has to do with the peptide primary chemical sequence. It is a common practice to add salts, such as basic anions and divalent cations like $Mg(OH)_2$, to reverse the acidity. These are usually referred to as stabilizers or additives (Fredenberg et al., 2011). Acid labile proteins, such as bovine serum albumin (BSA), fibroblast growth hormone, and bone morphogenic protein-2, can be stabilized by adding base salts that retard acidity.

The common degradative pathways are mostly identified; several processing and formulation strategies, namely the use of certain excipients, can prevent or reduce deleterious chemical reactions (Fu et al., 2000; Manning et al., 2010). During implant manufacturing, impurities may form. A thorough study on the formation of impurities in the protein during implant manufacturing is fundamental to try to figure out how the polymer matrix affects the stability of the incorporated protein. Implants of PLA and the peptide vapreotide were extruded under harsh conditions of high temperature and shear, deliberately, in order to identify the impurities formed and access the influence of the PLA matrix on their formation (Rothen-Weinhold et al., 2000). A high percentage of an impurity resulting from the addition of lactide from the PLA on the peptide phe-terminal amino group was found (Rothen-Weinhold et al., 2000). In another study, BSA-PLGA implants were produced by hot-melt extrusion. After being submitted to an in vitro release study, it was noticed that the protein was not completely released from the implant, due to the formation of insoluble covalent adducts that BSA formed with PLGA by thioester linkages (Ghalanbor et al., 2012).

Even if the manufacturing technique chosen is less deleterious to their stability, the biggest issue with formulations for proteins controlled-release systems is the instability of proteins themselves (Fu et al., 2000). A rigorous analysis of protein conformation using techniques like circular dichroism, enzyme-linked immunosorbent assays (ELISAs), and chemical state using high-performance liquid chromatography (HPLC) should be performed over the entire life of the implant, starting in the formulation phase, release in vivo, and during stability studies.

Table 10.2 Commercial Controlled-Released PLGA Matrix Implants

Drug	Trade Name	PLGA Type /Technology	Company	References
Goserelin	Zoladex	PLGA 50:50	AstraZeneca	Furr and Hutchinson (1992)
Buserelin	Suprefact Depot	PLGA 75:25	Sanofi-Aventis	products.sanofi.ca (2015)
Dexamethasone	Ozurdex	Novadur technology Blend of PLGA 50:50 uncapped and capped	Allergan, Inc.	EMA.europa.eu (2015)

10.8 SUCCESSFUL CASE STUDIES

There are several patents which indicate the potential and amount of work put into this type of formulation, especially for the delivery of peptide and protein drugs (Booth et al., 2003; Deghenghi, 2000). However, only three examples are present in the market currently sold for use in humans (Table 10.2). They include two formulations based on LH-RH agonists, which are peptides with a large therapeutic window, and dexamethasone, a corticosteroid.

10.8.1 ZOLADEX

In order to increase the circulation half-life of LH-RH from minutes to hours, several LH-RH analogs (LH-RHa) have been developed. However, there was not enough half-live duration to treat chronic conditions, such as hormone-responsive cancers. Long-acting injections with a duration of several months was required (Stevenson et al., 2012). To fulfill that need, formulations that can last for months, taking advantage of PLGA-based systems, have been present in the market since the late 1980s; Zoladex being the first product to appear in the form of a matrix implant (Brown, 2005; Stevenson et al., 2012).

Zoladex, marketed by AstraZeneca, provides a subcutaneous depot formulation of LH-RH analog goserelin. Goserelin, a synthetic peptide blocker of LH-RH receptor, works by reducing testosterone or oestradiol production (Kleiner et al., 2014). It is administered in a relatively large 1.5 mm subcutaneous implant (Brown, 2005) millirod, in which the drug is dispersed in a PLGA matrix, using a preloaded single-use syringe device and packaged in sealed, light, and moisture-protected aluminium foil pouch. After subcutaneous implantation into the skin of

the patient's upper stomach, the encapsulated goserelin is released by a combination of a controlled diffusion and erosion mechanisms (Kleiner et al., 2014).

The Zoladex product line consists of implants of bioerodible PLGA rods for 1 month or 3 month delivery of 3.6 and 10.8 mg of goserelin, respectively. They can be used for the palliative treatment of prostate and breast cancer, as hormone ablation therapy due to advanced carcinoma (Stevenson et al., 2012; Kleiner et al., 2014), and treating endometriosis, fibroid tumors, and precocious puberty (Brown, 2005).

First launched in 1987, Zoladex is now available and widely prescribed in more than 100 countries, with indications in prostate and breast cancer. According to AstraZeneca, it is an important oncology product, with annual sales of approximately $1 billion and one of AstraZeneca's leading cancer drugs, offering therapy for prostate cancer, with proven survival data, and similar overall survival benefits and improvements in quality of life, compared to surgical castration (orchidectomy) (AstraZeneca.com, 2013).

10.8.2 SUPREFACT DEPOT

Another LH-RHa is buserelin acetate. It has a greatly enhanced LH-RH effect and longer duration of action than natural LH-RH. When administered for periods greater than 1−3 months, it results in clinical inhibition of gonadotropin release, and when used in large pharmacologic doses of 50−500 μg SC/day or 300−1200 μg IN/day, induces reduction of serum testosterone or estradiol to castration levels. Unfortunately, buserelin is rapidly inactivated by enzymes from liver, kidney, and anterior pituitary. The main buserelin-degrading enzyme is pyroglutamyl-amino-peptidase (PGP) found in the mammalian liver and anterior pituitary, and chymotrypsin-like enzymes, such as neutral endopeptidase from the pituitary (products.sanofi.ca, 2015).

Suprefact Depot, also known as Profact Depot and Trigonist, marketed by Sanofi-Aventis, are implants that contain 6.6 mg (buserelin acetate implant equivalent to 6.3 mg of buserelin base) or 9.9 mg of buserelin acetate (buserelin acetate implant equivalent to 9.45 mg of buserelin base) in a matrix of 26.4 or 39.4 mg PLGA 75:25 molar ratio. They are administered every 2 or 3 months as a subcutaneous injection in the abdomen to help diminish the size of cancer in patients with advanced prostate cancer, by reducing the levels of testosterone to the desired level for managing this condition (products.sanofi.ca, 2015).

Suprefact Depot comes in a prefilled disposable ready-to-use sterile syringe/applicator with an integrated safety-engineered needle (internal needle diameter of 1.4 mm). It contains two or three cream-color implants, biodegradable and biocompatible rods that deliver 6.3 or 9.45 mg of buserelin in total per administration (Schliecker et al., 2004). The administration needs to be made by a doctor or nurse (products.sanofi.ca, 2015). However, chronic administration of the implant every 2 months or 3 months by a healthcare professional ensures continuous

suppression of testosterone secretion with no accumulation of buserelin release after repeated dosing, ensuring therapeutically effective systemic concentrations and palliative treatment for hormone-dependent advanced carcinoma of the prostate gland.

10.8.3 OZURDEX

Allergan, Inc. developed Ozurdex, an intravitreal biodegradable implant containing 0.7 mg of dexamethasone for the treatment of macular edema related to branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and noninfectious uveitis. This implant uses the Novadur technology and has been approved by Food and Drug Administration since 2009 (Kleiner et al., 2014). Novadur is a solid, cylindrical implant sustained-release drug delivery system that used ester-terminated 50:50 and acid-terminated 50:50 PLGA. Ozurdex is used for the controlled delivery of 700 micrograms of dexamethasone. Ozurdex is presented in a specially designed injector with a 22-gauge needle sealed in a foil pouch containing desiccant. It should be administered by an health professional in the vitreous cavity of the eye in a sterile ambient (EMA.europa.eu, 2015; allergan.com, 2014).

A 12-month clinical study to evaluate the safety and efficacy of one or two treatments showed that reinjection with Ozurdex implant was safe and well tolerated over the entire period of the study; improvements in BCVA and central retinal thickness were also observed after the second treatment, without serious treatment-related incidence of adverse events (Haller et al., 2011).

10.9 PROBLEMS TO OVERCOME AND OPPORTUNITIES

Biocompatible and biodegradable PLGA matrix implants possess the capability of delivering a variety of drugs in a controlled manner over periods of weeks to several months taking advantage of the physical chemical characteristics of the copolymer. They have been known for 40 years and they present a huge market potential, if several important issues are resolved. Among them are the assurance of product performance and safety through in vitro quality control tests design specifically for the product in question that, unfortunately, are lacking (Shen and Burgess, 2015). To obtain a reliable, robust correlation of both the rate of drug release obtained in a laboratory using in vitro assays and the real rate of drug release in the body is still difficult.

A faster drug release in vivo, when comparing to in vitro release, suggest differences in drug absorption and drug dissolution. The acidic products that result from PLGA degradation process may accumulate at the local sites, lowering the pH in the interstitial space immediately surrounding the implant, and could

accelerate polymer degradation with subsequent increased drug release in vivo when compared to in vitro (Shen and Burgess, 2015). Furthermore, chronic inflammation in response to the presence of the implant as a foreign body in the interstitial site could lead to fibrosis isolating the implant, slowing drug absorption or drug release (Anderson et al., 1993).

Observed differences are likely to be due to local transport and metabolism of drugs in tissues, as well as to differences in the rate of polymer degradation after implantation (Fung and Saltzman, 1997) as previously explained.

An in vitro−in vivo correlation (IVIVC) is a predictive mathematical model describing the relationship between an in vitro property and a relevant in vivo response of a drug product, one of the most important issues in the field of drug development. IVIVCs are categorized into five different levels: A, B, C, D, and multiple Level C. Level A IVIVC being the most desired, since the in vitro release method can be used as a surrogate for bioequivalence studies, if pre-approval and postapproval changes are required throughout the process of development of the drug (Shen and Burgess, 2015).

The successful development and application of a meaningful IVIVC allows for an accurate prediction of the in vivo performance of a developed drug product and could minimize human or animal studies, also reducing the regulatory burden with the final goal of less money spend in research and development (Shen and Burgess, 2015). A meaningful IVIVC can be used to guide formulation and/or process development changes in the various stages of drug product development and can be used to support and/or validate the use of an in vitro dissolution method, helping set clinically relevant dissolution specifications to ensure product quality (Shen and Burgess, 2015). Establishing an IVIVC for nonoral dosage forms, such as parenteral polymeric implants, has remained extremely challenging, due to their complex characteristics and the lack of standardized, compendial in vitro release testing methods, capable of mimicking in vivo drug release conditions (Shen and Burgess, 2015). Besides the lack of suitable in vitro release testing methods, the development of IVIVCs for nonoral drug products is even more complicated, due to their complex multiphasic release. This issue has been thoroughly addressed by Burgess and colleagues since the beginning of 2000s (Burgess et al., 2004; Martinez et al., 2008, 2010; Shen and Burgess, 2015). Regulatory guidance to aid stablishing an IVIVC is only available for extended-release oral dosage forms and, to date, this guidance is being adapted to the development of many parenteral polymeric microspheres and implants, transdermal patches/gels, as well as ocular inserts (Shen and Burgess, 2015).

During the last two decades, considerable progress has been achieved with "proof-of-concept" research that could only demonstrate the possibility of developing point-to-point linear correlations, or Level B correlations, based on one formulation. Although a Level A IVIVC is the most informative and recommended, other levels of IVIVC, such as multiple Level C and Level B, can be helpful to assure product quality and to assist in formulation development (Schliecker et al.,

2004; Shen and Burgess, 2015). Designing in vitro release studies that reflect, as much as possible, the in vivo behavior of these products is still a challenge to overcome. Even now, one could see in the available literature several in vitro release methods used, such as sample-and-separate (Schliecker et al., 2004), membrane dialysis, and flow through to determine in vitro drug release characteristics and to develop IVIVCs. Those methods are not able to adequately mimic different in vivo drug release conditions and so there is still a dearth of biorelevant in vitro dissolution methods that are capable of reflecting the complex and dynamic in vivo environment these dosage forms encounter (Shen and Burgess, 2015). In vivo drug release can usually be determined through analyzing drug content in the plasma or blood fluid. Noninvasive techniques, such as micropositron emission tomography (PET/Micro-PET) imaging are reported as a possible useful technique to determine in vivo drug release and facilitate the development of IVIVCs (Hühn et al., 2010) for those kind of formulations. This will allow a reduction in animal testing, due to unnecessary drug content in the plasma or blood fluid analysis. This requires frequent sampling, followed by complicated procedures to extract the drug from biological samples, high sensitive analytical instruments, as well as extensive animal/human experiments. New nondestructive biomedical imaging techniques that can be used to study implants in situ are highly desirable in the evaluation of IDDS (Zhou et al., 2015) and could help achieving relevant data. Recent data suggest the evaluation of formulations that have a dissolution rate of the drug, on a lower, medium and higher scale, in order to obtain the best possible correlation, A, B or C, which decreases the number of extremely expensive in vivo studies (Shen and Burgess, 2015).

10.10 CONCLUSIONS

Despite the continuous improvements in the field of controlled drug release with the trend to go nanoscale instead of staying macro, matrix implants are still playmakers in the controlled-delivering arena. Taking into account that nanoscale manufacturing involves high costs, PLGA matrix implants should be consider. The added value of PLGA in terms of how well characterized it is, biocompatible, clinical tested and approved for human use and the use of drugs in solid state important when dealing with proteins, as well as, the straight forward implant manufacturing techniques without complicated apparatus and mostly suited for continuous processes easy to scale up for industrial production are desirable when developing and producing a new pharmaceutical product.

More emphasis needs to be placed on the problem of IVIVC for non-oral drug products, such as polymeric implants, and on development of innovative in vitro models that allow accurate prediction of in vivo drug release as well as mathematical methods and simulation techniques. Regulatory approval, high cost of

preclinical to clinical translation of these systems (in particular for biological drugs) and patient compliance are among the matters still need to be improved. Nevertheless, those drawbacks are the same that arise when developing a formulation based in micro- or nanoparticles so PLGA matrix implants came with advantages as a controlled release form even nowadays.

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