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PLGA – A versatile copolymer for design and development of nanoparticles for drug delivery

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Introduction

Poly (lactic-co-glycolic acid) or PLGA, a highly hydrophobic copolymer comprised of lactic acid and glycolic acid, has been approved in many drug products and medical devices.[1] Over the years since the first approved in 1997, PLGA has been widely studied polymer in the industry because of its compatibility and safety, especially in oncology.[2] As a homopolymer of two polymerized acidic moieties, one relatively hydrophobic lactic acid and other hydrophilic glycolic acid. PLGA with its unique LA/GA composition ratios and molecular weight provides a good barrier to protect the premature release and degradation of drugs encapsulated in the microspheres or nanoparticles. Because of its biocompatibility and biodegradability in nature, it has also been used in several oncology drugs.[3]

This article will focus on the chemistry, properties, applications and the regulatory aspects of PLGA and the future trends in the industry especially those requiring the development of long acting injectable of treatment for varieties of rare diseases and for life cycle management.

Structure of PLGA

It is synthesized by ring opening chemistry that follows the copolymerization of monomer of lactic acid and glycolic acid moieties. PLGA is polyester where these moieties are linked together by ester linkages to a linear aliphatic polymer as shown in Figure 1.

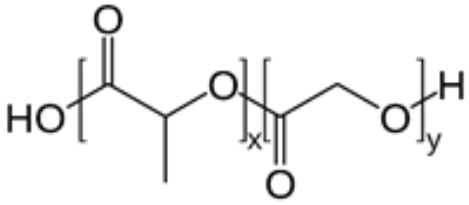

Figure 1 Structure of PLGA: Poly (lactic acid-co-glycolic acid (x= lactic acid and y = glycolic acid units).

Different grades of PLGA are commercially available for pharmaceutical applications as microspheres, nanoparticle and medical devices.

Depending upon the molar ratios of lactic acid and glycolic acid used in the synthesis, the PLGAs used for pharmaceutical applications are comprised of 75% lactic acid and 25% glycolic acid and/or 50% each of lactic acid and glycolic acid. PLGA with its lactic acid and glycolic acids molar ratios of 75:25 or 50:50 or 85:15, exists in an amorphous state.[4] PLGA with higher GL accelerates the degradation as compared to lower GA and higher LA moieties. For example, PLGA with 50:50 shows faster degradation than PLGA with 65:35, 75:25 and 85:15 GA/LA due to inherent hydrophilicity of glycolic acid.[5]

The glass transition temperature (T_g) ranges 40 °C to 60 °C depending upon the molecular weight (MW), and its solubility in organic solvents depends upon the lactic acid/glycolic acid ratios. PLGA is typically soluble in a wide range of chlorinated methylene chloride. chloroform, and hexafluoro isopropanol (HFIP) and non-chlorinated solvents such as THF, acetone, DMSO, glycofural, ethyl acetate, ethanol, N-methyl pyrrolidone, methyl ethyl ketone, acetonitrile, isosorbid dimethyl ether, dioxane among others.[6] In water, PLGA biodegrades by hydrolysis of its ester linkages. The methyl side group in poly lactic acid moiety makes it relatively more hydrophobic than polyglycolic acid and hence lactide rich PLGA copolymers are less hydrophilic and susceptible to degradation by hydrolysis.[5] Faster degradation depends on the ratios of the 2 acids; higher the lactic acid, slower the degradation and vice versa. In LA/GA 1:1 copolymer, the degradation is fast, leading to formation of lactic acid and glycolic acid within 3 months. Lactic acid is metabolized in tricarboxylic acid cycle and gets excreted via carbon dioxide and water, whereas, glycolic acid metabolized the same pathway as lactic acid, and it gets excreted through kidney. Glycolic acid is also metabolized into oxalic acid, which may lead to systemic toxicity in body during implant or longer circulation of PLGA microsphere.

Characteristic and drug delivery of PLGA microspheres

Physicochemical properties of PLGA such as molecular weight, LA:GA copolymer ratios, crystallinity, nature of drug and its loading as well as the particle size, morphology, porosity of the nanoparticles may affect the *in vitro* drug release characteristics.[7] The challenges in utilizing PLGA stems from encapsulating hydrophilic drugs into hydrophobic PLGA. The challenges with reducing burst release and increasing encapsulation efficiency of hydrophilic drugs in PLGA require additional functional hydrophilic layers. To overcome this issue, additional functional layers, like hydrophilic gels/hydrogels around the PLGA core–shell microspheres for sustained release. Yu et al. demonstrated losartan loaded PLGA microspheres with gel cores along the exteriors yielded high encapsulation efficiency of water-

soluble drugs.[8] By selecting 5% gelatin in the inner core, release was over 30 days as compared to 16 days release with water in the inner cores. With 25% Poloxamer 407 as hydrogel, it formed showed initial slower release but as P407 swelled, microcapsules cracked that resulted in faster release of drugs. In other cases where Poloxamer 407 hydrogel can encapsulate the small molecules like goserelin, a hydrophilic peptide, and acts as hydrogel depot at the exterior PLGA depot encapsulated with the same drug prepared by double emulsion solvent evaporation method with combined encapsulation efficiency of >94%. The resulting di-depot structure with PLGA and Poloxamer 407 showed 2-weeks controlled release, first diffusion of drug through PLGA core followed by diffusion of drug through Poloxamer 407 core.[8]

Porosity of PLGA microspheres

The single layer core is dense and non-porous for delivery of hydrophilic or hydrophobic drugs, it may lead to slower release due, in part, to slower erosion of polymer via hydrolysis. These challenges can be alleviated by reducing the polymer concentration and varying polymeric chain lengths of LA and GA moieties with different molecular weight and/or by selecting the appropriate preparation methods designed with different outer surfaces. Those modifications include hydrophilic shell comprised of exterior polyethylene glycol moieties exposed to water, and a lecithin layer is sand-witched between the two, that prevents the degradation of polymer chain and controls the erosion from water, whereas, the exterior PEG layer help stabilize the structures by creating the electrostatic charges with zeta potential of 40 mV to -60 mV around the microspheres ranging between 60 nm and 70 nm in size. An example includes, docetaxel prepared with PLGA-lecithin-PEG core with 62% encapsulation efficiency, and release kinetics was controlled by diffusion of drug through lipid layer.[9]

As compared with tradition PLGA single layered core, the porous microspheres have also been used as a reservoir for extended release of drugs. Mahboubian et al. for instance, evaluated an anti-cancer drug triptorelin from porous PLGA microspheres prepared by double emulsion process prepared with 2% Poloxamer 407 in first emulsion solution (w/o) containing drug and PLGA in methylene chloride that was emulsified by homogenization before mixing with 0.5% polyvinyl alcohol to form w/o/w double emulsions.[10] The release kinetics from porous PLGA microspheres (130µ in size) were about twice faster as compared to PLGA without Poloxamer 407 (110µ in size). The encapsulation efficiency with Poloxamer 407 decreased by 7% because of its ability to occupy the hydrophilic surface and competing with drug, hence, allowing a lesser degree of encapsulation in PLGA microspheres. [11] Varga et al. also observed the impediment of higher loading of vitamin E due to competing Poloxamer 407 stabilizer at the non-porous, smooth PLGA microsphere with hydrophilic surface prepared by nano-precipitation in acetone followed by lyophilization. Increasing amounts of Poloxamer 407 resulted in larger particle size (ca. 212 nm) with drug loading (DL) of 9% and encapsulation efficiency (ee) of 41% as compared to ee of 98% ee and DL of 20% DL with smaller particle size (ca. 178 nm) at 0.05% Poloxamer 407 as stabilizer.[12]

PLGA microsphere's core shells are distinct in nature, and depending upon the usage of these nanoparticles, they may have varying core shapes, internal structures, shell thicknesses and morphologies and porosities.[13] The latter is most explored for designing and increasing drug loading in PLGA microspheres for controlling the delivery by changing the porosity of the PLGA cores. Pore size and porosity of PLGA microspheres with broader surface area and lower density play an important role in faster releasing of drugs.[14] A number of porogen agents such as sodium chloride, ammonium bicarbonate, a tri-block copolymer Poloxamer 407, sodium oleate, gelatin, bovine serum albumin, cyclodextrins and mineral oils have been investigated for creating porous PLGA microspheres.[6] Porosity can be modified by solvents and polymer concentrations. For instance, solvents with lower boiling points, the pores are larger and vice versa.[15] Likewise, increasing the polymer concentrations from 1% to 5%, the porosity decreases about 25%.[16] Other porogen agents have also been studied. For instance, Qutachi et al. prepared the porous PLGA microspheres with average size of 84 microns and pore size of 8µ to 15µ by treatment for 2 min with ethanolic sodium hydroxide (EtOH/NaOH) and used as injectable cell carriers.[17] Ni et al., while investigated PVP as porogen agent and stabilizer for higher drug (e.g. cinaciguat) loading to prepare the porous PLGA by o/w emulsion solvent evaporation method for treatment of pulmonary hypertension via inhalation.[18] Mylonaki et al reported that the internal structure of atorvastatin (ATV)-loaded PLGA microspheres is dependent upon the MW, glass transition temperature (T_g) and most importantly on porosity on drug release kinetics, which in turn dependent upon drug characteristics such as melting point, logP and its concentration in the formulation.[19] The hydrophobic drugs release through diffusion PLGA matrix whereas, the hydrophilic drugs release through porous route. Shen et al. investigate the drug release from porous risperidone loaded microspheres and compared with regular microspheres.[20] For instance, porous microspheres were prepared by dissolving risperidone in benzyl alcohol at 24% and dissolving 16.7% PLGA in ethyl acetate. Both solutions (polymer and drug) were mixed and transferred to 1% PVA solution to form oil-in-water (o/w) emulsions by vortex mixing or homogenization (3,400 rpm). The resulting emulsions were extracted with ethyl acetate to yield the porous microspheres, which were allowed to dry under vacuum at room temperature to remove any residual solvent. In contrast, the regular microspheres were prepared by dissolving polymer/drug (4:3) in methylene chloride which was homogenized in 1% polyvinyl alcohol solution to an o/w emulsion. Methylene chloride was removed by extraction that resulted in hardening of microspheres, which were further dried under vacuum. The dried microspheres were then washed with water and sieved through 25 microns and 212 microns sieves and lyophilized as powder cake. Chitkara and Kumar evaluated PLGA nanoparticles loaded with a highly hydrophilic drug, gemcitabine and coated with bovine serum albumin at the exterior layer.[21] The nanoparticles with 243 nm in size and encapsulation efficiency was 40% and loading was 8.8%, showed a controlled release over 12 hours *in vitro* and cellular uptake within 2 hour *in vivo*.

These elements contribute to drug loading and release kinetics. Furthermore, the size of these microspheres typically ranged between 10-200 microns. With particle size 20 microns or lower, they are engulfed by immune cells; whereas, the large particles >200 microns cause inflammations. There are several techniques to produce these particles but the top down microfluidic method allows fabrication of microspheres with uniform size, shape and thickness, with higher encapsulation efficiency for hydrophilic and hydrophobic molecules.[22]

Preparation of PLGA Microspheres and Devices

There are several methods to prepare the PLGA nano/microspheres. There are some tradition methods and others are more new technologies based. Those methods are illustrated in Figure 2 and their details of preparations are summarized below. Ruirui et al. describe some of these methods used for delivery of a number of drugs encapsulated in PLGA micros/nano-spheres.[23]

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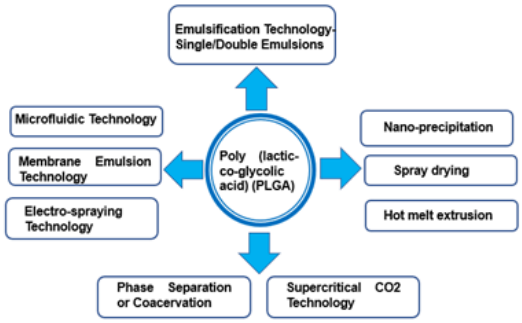

Figure 2 Processing methods for fabricating PLGA microspheres and devices.

Table 1 Brain uptake of surface modified PLGA

NPs	Size, nm	Admin.	Dose (μg/ml)	Drug	Animal model	Brain uptake, %					
						0.5h	1 h	1.5h	3 h	6 h	12 h
1% PS80/PLGA	138	oral	100/200/400	estradiol	Rats	-					
4% PS80/PLGA	157	oral	100/200/400	estradiol	Rats						
PS80/PLGA	194	i.v.	20	EF	Rats			4.3			
TPGS/PLGA	165	i.v.	20	EF	Rats			4.2			
P407/PLGA	188	i.v.	20	EF	Rats			5.5			
P188/PLGA	196	i.v.	20	EF	Rats			6.2			
P188/PLGA	252	c.a.	5000	EF	Rats		3.2				
PS80/PLGA	231	c.a.	5000	EF	Rats		6.4				

c.a. carotid artery; EF entrapped fluorescence marker; PS 80- Polysorbate 80, TPGS- Vitamin E-TPGS; P188 – Poloxamer 188; P407 – Poloxamer 407; iv. Intravenous route,

1. **Emulsion and double emulsion solvent evaporation process** (W/O/W) – this process is simple and requires the drug to dissolved in an aqueous solution (W) with or without excipients, and the PLGA is dissolved in organic solvents, preferably in methylene chloride or ethyl acetate (O). First W/O/ emulsions are formed by adding and mixing of aq. solution of drug in PLGA dissolved in organic solvent. The first emulsions (W/O) are then mixed with a second continuous aqueous solution containing a surfactant such as polyvinyl alcohol (PVA) to yield W/O/W emulsions. Following removal of organic solvent through diffusion or extraction or evaporation, it leads to solidification of the PLGA microspheres. The process limitations include solubility of drug in organic solvent used, and presence of residual solvents, and necessity for aseptic processing. Example of double emulsion process includes Lupron® Depot, see in Table 2.
2. **Phase separation or coacervation method:** This requires the preparation of first emulsions by addition of aq. drug into PLGA dissolved in methylene chloride. A coacervation agent, such as silicon oil is gradually added into primary emulsions to promote phase separation. As methylene chloride is extracted into the silicon oil, PLGA microspheres get precipitated, which are further hardened by washing with apolar solvents such as heptane or hexane. The process limitations include residual solvents, larger particles and necessity for aseptic processing. The approved drug Bydureon® is manufactured by this process, see Table 2. Arestin®, as shown in Table 2, was also prepared by dissolving PLGA in dichloromethane and suspending the micronized minocycline hydrochloride in PLGA emulsion. Silicon oil was added as coacervate solvent and resulting dispersion was then solidified by discharging in hexane.[24]
3. **Spray drying process:** This atomization based process requires the spray drying of W/O emulsions prepared by aq. drug mixing with PLGA dissolved in methylene chloride. The resulting spray dried powder of PLGA microspheres entrapped with drug are dried to remove the residual solvents. The process limitations include thermal stress, residual solvents, and necessity for aseptic processing. The approved drug Supercure® MP is manufactured by this process and marketed in Japan, see Table 2. This is a rapid process, however, a low yield could be obtained due to adherence of the product along sidewall of drying chamber.
4. **Hot melt extrusion (HME):** Hot melt extrusion is an ideal solvent free method for creating implants by processing of PLGA at temperatures higher than glass transition temperature (T_g) of polymers, PLGA/PLA. The resulting extrudates or rods can be used as implants. The limitations of process include the thermal stress on drugs and low drug loading. The approved drug Zoladex® is manufactured by HME.
5. **Nano-precipitation method:** This process requires dissolving of drug and PLGA in water miscible organic solvents and injecting into an aqueous phase water, that leads to solvent exchange by diffusion and nanoprecipitation of drug into PLGA depots, ideally suited as reservoirs for in situ delivery. This method is simple and forms the nanoparticles in one step, and is more effective than emulsification method to encapsulate drugs. The limitation includes use of organic solvents and residual solvents. The approved drugs Eligard® is marketed using this method.
6. **Supercritical CO_2 method:** It involves the injection of drug dissolved in methanol into SC-CO_2 as an anti-solvent, which acts as an extractant for methanol, and instantaneously lead to precipitation of drug nanoparticles, which is encapsulated in PLGA with well dispersed drug in microsphere by use of the anhydrous technique.[25]
7. **Electro-spraying process**: It is based on atomization of drug and PLGA in an organic solvent, which is subjected to electric voltage to produce the particles. It is commonly used in preparation of solid dispersions of poorly soluble drugs. This process has advantages of producing narrow particle size distribution with high drug loading efficiency and significantly less agglomeration challenges.
8. **Microfluidics technology:** It offers good controls over particle size distribution and is amenable to low volumes. Microfluidic systems fitted with 1 mm channels have shown to be suitable for

large scale production of PLGA nanoparticles and allows creating microspheres with uniform size and thickness with advantages of higher loading of hydrophilic and hydrophobic drug molecules.

9. **Membrane emulsification technology:** It is relatively a new technology that employs a combination of emulsification methods and porous membranes in which the dispersed phase is pressed through a membrane and the droplets formed are carried away with the continuous phase, that results in uniform and controlled particle size with narrow distribution and high drug encapsulation efficiency than emulsification solvent evaporation technology.

Purification of PLGA nanoparticles

Several methods are used for purification of PLGA encapsulated NPs.[26] For instance, at lab scale, centrifugation and dialysis are commonly used but for large scale manufacturing and especially, for continuous manufacturing (CM), the tangential flow filtration (TFF) is preferred. TFF method requires a continuous filtration of fluid that runs through surface of a filter membrane cartridge rather than passing through it. This allows the filter cake to flush away during washing process. TFF is highly effective in removing >90% of stabilizers with no impact on particle size, yield, and stability of product. This TFF could be challenging for highly viscous liquids due to partial pressure difference between two sides of the membrane cartridges, causing to compromise the filtration efficiency during large scale manufacturing.

The TFF cartridges are membranes derived form cellulose ester (CE), regenerated cellulose (RC), mixed cellulose (MC), polysulfone (PS), polyethersulfone (PES) and most preferably, the modified PES which are hydrophilic and can reduce the fouling odors.

PLGA is typically dissolved in methylene chloride, ethyl acetate, dimethyl sulfoxide, among others, so careful selection of organic solvent compatible to membrane cartridge is highly critical during purification of PLGA nanoparticles. For instance, RC filters are recommended for purification of PLGA in methylene chloride. In addition, the molecular cut off of the membrane and its surface area should be taken in account when purifying the nanoparticles.

The storage of PLGA nanoparticles could be challenging as the polymer is susceptible degradation by hydrolysis, light, air, heat and moisture. The degradation into lactic acid and glycolic acid can lead to change in particle morphology of particles, lower potency of drugs, and could render the toxicity of formulation.[27] Therefore, an efficient method to remove water is important to improve the stability of nanoparticles. That leads to options of utilizing the spray drying and lyophilization to alleviate the degradation and improve the stability of nanoparticles. It also helps to improve the stability of moisture sensitive drugs encapsulated in PLGA nanoparticles.

In vitro release of drug from PLGA Nanoparticles

There are some challenges to find an accurate release test method to measure the drug from PLGA microspheres. This is due, in part, to complexity of PLGA structure and methods used in fabricating the microspheres owing to its biodegradability and biocompatibility in nature. Therefore, several attempts have been made to identify the appropriate *in vitro* test method able to discriminate and help support *in vivo* characteristics, that could be reproducible to meet the product's critical quality attributes.[28] Accelerated stability of product can lead to erroneous release profiles if the *in vitro* test method is not fully validated. The lack of compendial method also makes more challenging to quantify the release drugs from PLGA formulations.

Clark et al. evaluated the release of minocycline hydrochloride microspheres in-house method so called sample-and-separate method as reported previously.[29] Briefly, 4 mg of sample was dispersed in phosphate buffer pH 7.4 containing 0.02% polysorbate 20 in a screw capped tube and rotated at 100 rpm while incubated at 37 °C. The tubes were centrifuged at 3000 rpm for 3 minutes and drug was analyzed by HPLC in the supernatant following filtration though 0.22 micron Nylon filter. Shen et al. evaluated both sample-and-separate method and flow through (USP Type 4) test methods to differentiate risperidone microspheres with differences in porosity under real-time (37°C) and accelerated (45 °C) testing conditions which were in comparable to only the accelerated USP Type 4 for highly porous risperidone microspheres, suggesting that accelerated Type 4 method is most appropriate for long acting PLGA microspheres.[20] Though there might some challenges with particle aggregation over extended dissolution period, but that can be prevented by addition of beads that in turn facilitate laminar flow of dissolution media throughout the cells.[30]

Shen et al. used sample-and-separate method for *in vitro* release risperidone PLGA microspheres. Briefly, 10 mg of microspheres were dispersed in 250 mL of phosphate buffer pH 7.4 and incubated in a shaker water bath at 100 rpm at either 37 °C or 45 °C. One mL samples were withdrawn and centrifuged at 3,000 rpm for 3 minutes and drug was analyzed by HPLC in supernatants following filtration through 0.22 μm Nylon filters. The release profiles by sample-and separate method at elevated temperature showed poorer reproducibility for porous microspheres, caused by challenges with floating microspheres on the surface of the media couple with inconsistent sampling process. It can be taken to suggest that flow through method (USP Type 4) is more reliable for differentiating the release profiles at elevated temperature (ca. 45 °C) of the porous vs regular microspheres due to lack in floating and inconsistent in sampling.[20] Tomic et al. used flow through *in vitro* test method (USP Type 4) to study the release of cyclic somatostatin analog (MW ~ 1kD) in PBS 0.02 M at pH 2 and 45 °C.[31] It was found that drug release was influenced by composition of dissolution media since the osmotic effect controls the erosion and diffusion processes. In other cases, Janich et al. used dialysis method to investigate the *in vitro* release of risperidone encapsulated PLGA at 37 °C at 50 rpm.[32] Briefly, the PLGA formulation sample was suspended in 1 mL of PBS at pH 7.4 and transferred into a dialysis membrane tube with molecular cut off of 1000 kD and was placed in 60 ml PBS. The drug release was quantity was spectrophotometer. Likewise, Varga et al. quantified vitamin E at 268 nm by dialysis using cellulose membrane in PBS pH 7.4 containing 0.01% Poloxamer 407.[12]

PLGA Nanoparticles in drug delivery of blood brain barriers

Blood brain barriers (BBB) protect central nervous systems (CNS) from unnecessary entry of unwanted substances, which also pose challenges in delivery of molecules for treatment of glioblastoma and other diseases in the brain. These tight junctions (TJs) formed by a complex network of proteins and linked with the cytoskeleton can restrict the passage of substances from the bloodstream to the brain as a result many of the therapeutic agents can't overcome the BBB. Kabanov et al. have shown that poloxamer micelles with hydrophobic in nature can penetrate the BBB and delivery the drugs.[33] PLGA nanoparticle with hydrophobic in nature can penetrate the BBB and can be used as carries for delivery of drugs.[34] PLGA NPs with surface modified using surfactants also improved the cellular uptake by permeation of BBB. For instance, PLGA NPs coated with vitamin E-TPGS, poloxamer 188 and polysorbate 80 improved the cellular uptake due, in part, to changes in surface hydrophilicity and surface charge.[35] The MDCK cellular uptake of TPGS coated PLGA (222 nm) was 1.5-fold higher as compared to PVA emulsified PLGA NPs

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following 4 hours of incubation. Likewise, Poloxamer 188 and PS80 coated loperamide encapsulated PLGA nanoparticles, the *in vitro* cellular uptake was 21% and 14.5%, respectively, as compared to 4.5% uptake with unmodified PLGA nanoparticles with respect to free drug (ca. 0.4%).[36] *In vivo* uptake differed considerably as compared to *in vitro* cellular uptakes. Table 1 list the brain uptake surface modified PLGA nanoparticles in animal models.[34]

It is evident from Table 1 that carotid administration showed relatively higher brain uptake than intravenous route of administration. For instance, PS80 coated PLGA (231 nm) was delivered relatively higher than P188 coated PLGA nanoparticles (3.2%) at the same dose level by carotid route of administration in an hour. In other studies, P188 surface modified PLGA nanoparticles were found to be better BBB targeting than PS80 following intravenous administration. [37]

Sterilization of PLGA nanoparticles

Several methods have been used for sterilization of nanoparticles depending upon the drug and polymers in formulations, For PLGA formulation, autoclaving and gamma irradiation would be detrimental as it could lead to degradation of drugs as well as the polymer, and hence, the compromised activities of nanoparticles.[27] Fraguas-Sanchez et al. used gamma sterilization for CBD encapsulated PLGA microparticles placed in dry ice to avoid excessive heating at 25 kGy radiation exposure.[38] The authors compared the sterilized and non-sterilized formulations and did not observe any difference in particle morphology and particle size distribution, and particles remained spherical in shape and smooth surface with average diameter of 25 nm in size. In such cases, sterile filtration is highly preferred for the nanoparticles with particle size distribution falls within 0.22 microns. Aseptic manufacturing is also viable but it brings risks for contamination if multiple steps are used in the formulation, and could be expensive to implement. However, aseptic manufacturing fits well with the continuous production in scale up under enclosed systems to prevent from any microbial or bacterial or human cross contamination.

Regulatory Information about PLGA and drugs approved by FDA

PLGA regulatory status is well established.[39] It has been approved in many drug products. Table 2 shows the list of approved drugs.[40]

PLGA is also listed in FDA's inactive ingredient database. Table 3 shows the PLGA (free acid terminal) has been approved as implants, and also in injectable solutions and suspensions for intravitreal, subcutaneous, and intramuscular drug products with maximum potency per unit and/or maximum daily exposure (MDE) limits. Evidently, the amounts of polymer could range from 135 mg to 533 mg per unit depending upon the formulation dosages to 11 mg-145 mg to MDE as injection suspension powders.[41]

Ascendia's capabilities in PLGA Nanoparticle Formulations

PLGA has been investigated in long acting injectable formulations of a number of drug products from early phase to clinical phases of development. Ascendia's in-house capabilities in upstream and downstream cGMP manufacturing of injectable lipid based LipidSol and polymeric based PLGA have been well utilized within our state-of-the art sterile facility with ISO certified cleanrooms. Table 4 shows the preparation of carvedilol loaded PLGA nanoparticles from PLGA (50:50 LA/GA).[42]

Table 2 PLGA based approved drugs.

Drug	Active	Indication	Duration/Dose
Lupron® Depot	Leuprolide acetate	Prostate cancer	1-m to 6-m/ 7.5 - 45 mg
Eligard®	Leuprolide acetate	Prostate acetate	1-m to 6-m, /7.5-45 mg
Bydureon®	Exenatide	Type 2 Diabetes	1-w/2.0 mg
Trelstar®	Triprorelin pamoate	Prostate cancer	1-m to 3-m/3.75-22.5 mg
Sandostatin® LAR	Octreotide acetate	Neuroendocrine tumor	1-m/20-30 mg
Signifor® LAR	Pasireotide pamoate	Acromegaly/cushing disease	1-m, 10-60 mg
Zoladex®	Goserelin acetate	Prostate, breast cancer	1-m, 3-m/3.6 mg, 10.8 mg
Superfact® Depot	Buserelin acetate	Prostate cancer	2-m, 3-m/6.3 mg, 9.5 mg
Arestin®	Minocycline HCl	Antibiotic	1 mg

Table 3 PLGA listed in IID database (as of May 2023)

Inactive Ingredient	Route	Dosage Form	Max. potency/unit	Max. daily exposure
DL-Lactide and Glycolide (50:50) copolymer 12000 Acid	Endosinusial	Implant	1.35 mg	
DL-Lactide and Glycolide (50:50) copolymer 12000 Acid	Intravitreal	Implant	116 mg	
DL-Lactide and Glycolide (50:50) copolymer 12000 Acid	Intravitreal	Injection	116 mg	
DL-Lactide and Glycolide (50:50) copolymer 12000 Acid	Subcutaneous	Injection, Solution	533 mg	
DL-Lactide and Glycolide (75:25) copolymer 20000 Acid	Intramuscular	Injection		145 mg
DL-Lactide and Glycolide (75:25) copolymer 20000 Acid	Intramuscular	Injection, powder, for suspension		11 mg

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Table 4 PLGA vs PLA nanoparticles: Physico-chemical properties

Polymer	MW, D	Viscosity, dL/g	T_g, °C	Half life	Surfactant	Particle size, nm	Zeta potential, mv
PLGA/50:50	7000-17,000	0.16-0.24	42-46	< 3 mo.	2% PVA	128 nm	-13.4
PLA (Reference)	18,000-24,000	0.25-0.35	48-52	< 6 mo.	2% PVA	135 nm	-11.4

Method for preparation of carvedilol encapsulated PLGA nanoparticles involves dissolving the drug and polymer (1:10) in methylene chloride by thorough mixing as an oil phase. An aqueous solution containing 2% polyvinyl alcohol (PVA) with MW 9,000-10,000 D was used as a surfactant. API/polymer oil phase was added slowly in PVA aqueous solution dropwise and mixed thoroughly, keeping the oil/water phase ratio 1:7. The entire solution was mixed thoroughly in ice cold water to emulsify by sonication (Fisher Scientific Sonic Dismembrator Model 500) to achieve the desired particle size (Malvern Nano-ZS zeta sizer). The resulting nanoparticles were poured and mixed in 2% PVA aqueous solution for 3 hours, and collected following the centrifugation for 30 min at 14,000xg. The drug/PLGA nanoparticles were collected by discarding the supernatant, washed repeatedly with water. The resulting pure concentrated drug/PLGA nanoparticle suspension once again was passed through filter (Amicon® Ultra Centrifugal filter with MW 50 kD cut off), and centrifuged again for 10 min at 14,000xg to remove any free drug. It was lyophilized with sucrose (10-30%) as cryo-protectant or used freshly or stored at 4 °C for weeks, and drug loading was determined by HPLC. Figure 3 show the PSD of PLGA (A) and PLA (B).

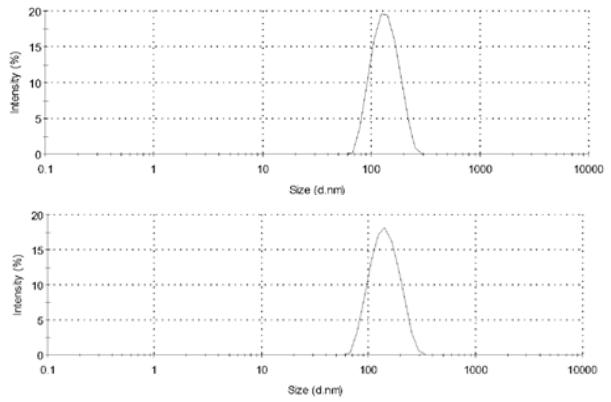

Figure 3 PSD of PLGA (A) and PLA (B) nanoparticles encapsulated with 10% carvedilol.

Conclusion

PLGA is widely used as an alternative drug-delivery system (DDS) for injectable drugs, as long acting excipient. It forms microspheres that allows slow or control release of drugs. It is biocompatible and biodegradable, that make attractive for pharmaceutical drugs and medical devices. It is hydrophobic in nature with ability to hydrophobic drugs with limited ability for encapsulation of hydrophilic molecules. But co-encapsulation with hydrophilic and hydrophobic drugs with high encapsulation efficiency is possible by changing the composition of microsphere core-shell. Surface modification of PLGA with PEG or receptors can lead to longer circulation and targeting of certain diseases tissues, respectively. PLGA microspheres can increase drug loading and avoid phagocytosis by macrophages, thus achieving a longer-lasting drug release effect. Because of their smaller particle size and targeting characteristics they are easier to accumulate in tumor cells through the enhanced permeability and retention (EPR) effect. In addition to therapeutic molecules, imaging agents can also be encapsulated in w/o/w double emulsions to help improve cancer cells targeting and bioavailability of hydrophobic molecules. Choice of selecting the non-toxic solvents also add another significant step forward to select the PLGA for designing a safe vehicle for encapsulating and delivery of drugs across all modalities. For designing PLGA micro/nanospheres require smarter selection of fabricating process. For example, membrane emulsion and microfluidics methods yield the PLGA microspheres with higher drug encapsulation efficiency and with low polydispersity index, for example, PDI of 0.048 with carvedilol encapsulated PLGA.[42] Take collectively, Ascendia's capabilities in down stream and upstream manufacturing process can lead to development of PLGA based nanoparticles encapsulated drugs for life threatening ailments. With state of the art cGMP manufacturing suites designed to handle organic solvents, including methylene chloride are well in place for future generation polymeric and lipid based nanoparticles for unmet medical needs.

Conflicts of interest

Authors declare that there is no conflict of interest

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