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REVIEW

Biocompatibility, biodegradation and biomedical applications of poly(lactic acid)/poly(lactic-co-glycolic acid) micro and nanoparticles

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Abstract

Background Poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) are among the well-documented FDA-approved polymers used for the preparation of safe and effective vaccine, drug and gene delivery systems using well-described reproducible methods of fabrication. Various nano and microparticulates are fabricated using these polymers. Their successful performance relies on PLA and PLGA biocompatibility and degradability characteristics.

Area covered This review provides an overview of the biocompatibility and biodegradation of PLA, PLGA and their copolymers, with a special emphasis on tissue responses for these polymers as well as their degradation pathways and drug release models. Moreover, the potential of PLA and PLGA based nano and microparticulates in various advanced biomedical applications is highlighted.

Expert opinion PLA and PLGA based delivery systems show promises of releasing different drugs, proteins and nucleic acids in a stable and controlled manner and greatly ameliorating their therapeutic efficacy. In addition, advancement in surface modification and targeting of nanoparticles has extended the scope of their utility.

Keywords Biocompatibility · Biodegradation · PLA · PLGA · Microparticles · Nanoparticles

Introduction

Extensive studies have shown the importance of using biocompatible and biodegradable polymers for drug delivery applications (Hughes 2017). Broadly speaking, many natural, viz., polysaccharides and proteins, and synthetic, viz. poly(α-hydroxy esters) polymers play a pivotal role in this respect, by virtue of their biocompatibility and biodegradability. However, the use of natural polymers in certain delivery applications can be disadvantageous from degradation perspective, exhibiting heightened, uncontrolled and inconsistent degradation (Abedalwafa et al. 2013). In contrast, uniqueness of synthetic polymers lies in the feasibility to tailor their chemical, physical and mechanical features, controlling their degradation rate (Dhandayuthapani et al. 2011; Gentile et al. 2014).

Specifically, synthetic polyesters show great promises, including polymers such as Poly-epsiloncaprolactone (PCL), poly(glycolic acid) (PGA),poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA). By comparison with other polyesters, PCL degradation is exclusively very slow, limiting its utilization in some specific biomedical fields and necessitating its modification such as surface decoration or forming composite systems with other natural and synthetic polymers (Abedalwafa et al. 2013). PGA, on the other hand, exhibited faster degradation rate despite its structural similarity with PLA, and hence, this polymer cannot meet up with the requirements of advanced delivery systems (Gentile et al. 2014; Vroman and Tighzert 2009).

In the family of polyesters, PLA and PLGA, also known as polylactide and polylactide-co-glycolide respectively, have been the most used for drug delivery applications, owing to their attractive mechanical and processing characteristics (Martins et al. 2018; Reis et al. 2017). In addition,

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contrary to others biodegradable polyesters which are synthesized from petrochemical sources such as polyhydroxyalkanoates (PHA) and poly(butylene succinate) (PBS), PLA and PLGA polymers are produced by lactic and glycolic acid fermentation from sugars which make them more green and eco-friendly (Dischert and Soucaille 2015; Juturu and Wu 2016; Koivistoinen et al. 2013).

Several systems based on PLA or PLGA have been prepared to deliver different payloads ranging from small drug molecules to large proteins and nucleic acids in a sustained release manner (Sun et al. 2014). The rate of drug release and cellular uptake from such systems could be easily tunable by changing several factors such as particle size, polymer crystallinity, polymer molecular weight (M_{wt}), polymer chemical composition, drug loading and drug-polymer interaction (Kamaly et al. 2016).

Being biocompatible, PLA and PLGA produce safe and non-toxic degradation products which made them good candidates for many medical and pharmaceutical applications (Alsaheb et al. 2015). The biodegradation of PLA and PLGA-based homo and copolymers involve their hydrolytic degradation to lactic and glycolic acids which are finally eliminated from the body as CO_2 and water (Tačić et al. 2017). The biodegradation of PLA and PLGA based drug delivery systems (DDS) is very important with regard to controlling the release of loaded cargos (Kamaly et al. 2016). As the polymer degrades and erodes, the drug release kinetics is a function of polymer degradation as well as drug diffusion through polymer matrix (Xu et al. 2017).

Various microparticles (MPs) and nanoparticles (NPs) can be designed using FDA-approved biodegradable and biocompatible PLA and PLGA. These particulate systems possess excellent biocompatibility, controllable biodegradability and erosion and high safety profiles (Agrahari et al. 2016). Therapeutic agents and biologics can be encapsulated within such polymeric particulates for localized and systemic delivery (Yan et al. 2012). Many multifaceted merits are realized in PLA and PLGA based DDS such as sustainment of drug release, targeted delivery, improving the bioavailability, and enhancement of the stability of encapsulated biopharmaceuticals towards enzymatic degradation (Moghimi et al. 2001; Mundargi et al. 2008). With great effort, in the last years, different PLA and PLGA based drugs delivery systems have been developed, in particular for the delivery of anticancer drugs (Haggag et al. 2019; Jain et al. 2011, 2016; Shao et al. 2018) and for a specific organ targeting such as brain or liver targeting (Bao et al. 2015; Gao et al. 2015; Jose et al. 2014; Patel et al. 2018; Xia et al. 2012; Zhu et al. 2016). Moreover, these delivery systems have been tested with great results for pulmonary administration of different drugs (Feng et al. 2014; Gaspar et al. 2019; Takami and Murakami 2011). Furthermore, therapeutic gene delivery based on these systems has been explored especially loading pDNA, mRNA, siRNA and microRNA (Gomes dos Reis et al. 2019; Matta and Maalouf 2019; Nishio et al. 2018; Terry et al. 2019; Xu et al. 2018; Zhao et al. 2018).

We aim in this manuscript to briefly review the most popular biodegradable polymers, PLA and PLGA, as well as micro- and nanoparticle systems with regard to their biocompatibility and biodegradation and their impact as delivery systems for vaccines, drugs and genes with optimal efficacy.

Poly (lactic acid) (PLA) and poly (lactic-co-glycolic acid) (PLGA)

PLA and PLGA are among the most highly studied polymers used in medical applications for drug delivery (Brown et al. 2015; Ramot et al. 2016). PLA present asymmetric centers in its backbone resulting in the formation of either D or L forms (PDLA or PLLA), while PLGA is the copolymer of D,L-lactic acid with glycolic acid (Silva et al. 2015). Figure 1 depicts the chemical structures of PLA and PLGA polymers. It is worth to say that PLLA acquires crystalline form while PDLA with disordered polymer chains is amorphous (Müller et al. 2013). Moreover, the absence of side chain in case of glycolic acid in PLGA enhance chain packing and hence polymer crystallinity when compared to PLLA of similar molecular weight (Tesfamariam 2016).

PLA and PLGA are easily shaped to DDS of various architectures, being soluble in many solvents including chloroform, dichloromethane, tetrahydrofuran (THF), acetone and ethyl acetate (Mohammadi-Samani and Taghipour 2015). They are insoluble in water; however, they absorb water and degrade by hydrolysis of their ester linkage. The

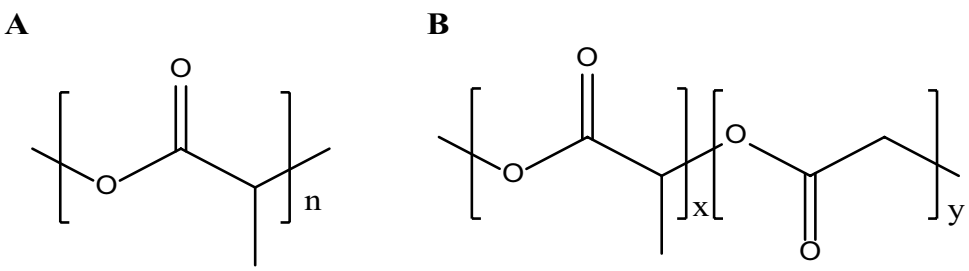

Fig. 1 Chemical structure of **A** PLA and **B** PLGA

hydrophobic side chain (methyl groups) of PLA renders the polymer with lower water uptake properties and slower degradation compared to PLGA (Fig. 1). Therefore, the drug release from PLGA would be much faster than that from PLA (Makadia and Siegel 2011). Many polymeric DDS, including MPs and NPs, were developed using PLA, PLGA and their copolymers for delivering various drugs (Kapoor et al. 2015; Mohammadi-Samani and Taghipour 2015; Tyler et al. 2016).

Biocompatibility of PLA and PLGA

The biocompatibility of PLA and PLGA was tested and proofed both in vitro and in vivo (Mir et al. 2017). The ultimate biocompatibility of polymers is influenced, not only by polymers but also by their nature of degradation products and degradation rate (Engineer et al. 2011). As mentioned above, PLA and PLGA polymers degrade by esterase enzyme, forming lactic and glycolic acids that enter Kreb`s cycle to be eliminated as CO_2 and water through respiration, feces, and urine (Silva et al. 2015). Accumulation of these polymers, when used in low concentration, in the human body organs has never been reported. Nevertheless, in some cases due to failure on the elimination of degradation by-products, the in situ accumulation of acidic (lactic and glycolic acids) degradation products become dangerous, altering biological response when in contact with tissues at high local concentrations (Ramot et al. 2016).

Also, the release of small non-degraded fragments and particulates during polymer erosion process could activate different unexpected immune responses by macrophages (Lyu and Untereker 2009). Moreover, particulates type of PLA and PLGA based systems is of prime importance, when considering toxicological issues. Due to their enhanced cellular uptake and biodistribution, NPs might have affected cell growth, viability and tissue responses (Dailey et al. 2006; Makadia and Siegel 2011). Thus, investigation of particles safety profile, on a cellular or tissue level is highly warranted.

Although larger polymeric microparticles cannot be taken up by macrophages (Champion et al. 2008; Gustafson et al. 2015), macrophages in proximity to polymer surface secretes polymer damaging agents that help MPs erosion process and help starting phagocytosis process (Ronneberger et al. 1996). Furthermore, the interior of macrophage lysosomal vesicles has highly acidic pH (~3) (Galloway et al. 1983), compared to the extracellular environment, that can accelerate the process of PLA and PLGA degradation (Zhou and Deng 2002).

It is worthy to mention that biocompatibility is not only the polymer's intrinsic property-dependent or particulate type-dependent, but also, biological environment-dependent and hence, intensity and length of specific polymer-tissue interactions can be varied greatly in different organs, tissues and species (Makadia and Siegel 2011; Ramot et al. 2016, 2015). Thus, site of administration of PLA and PLGA based DDS greatly impacted foreign body responses. The prolonged tissues/particulates interface and their continual presence inside the tissues can elicit intolerable inflammation, injury and immunological rejection (Ramot et al. 2016). For example, implantation of PLA and PLGA based DDS, with a high surface area and low injection volume via subcutaneous (SC) or intramuscular (IM) routes may increase the risk of a persistent local foreign body reaction over the duration time of polymer degradation.

PLA and PLGA local tissue responses involve three steps: (i) Organization of the inflammatory responses; (ii) Monocytes migration to DDS injection site which differentiate into macrophages and fibrous capsule development; (iii) Rapid degradation of the polymer and enhanced formation of fibrous tissues generated in second step (KyungáKim 2016). A diagrammatic illustration of tissue response steps to PLA and PLGA DDS is presented in Fig. 2.

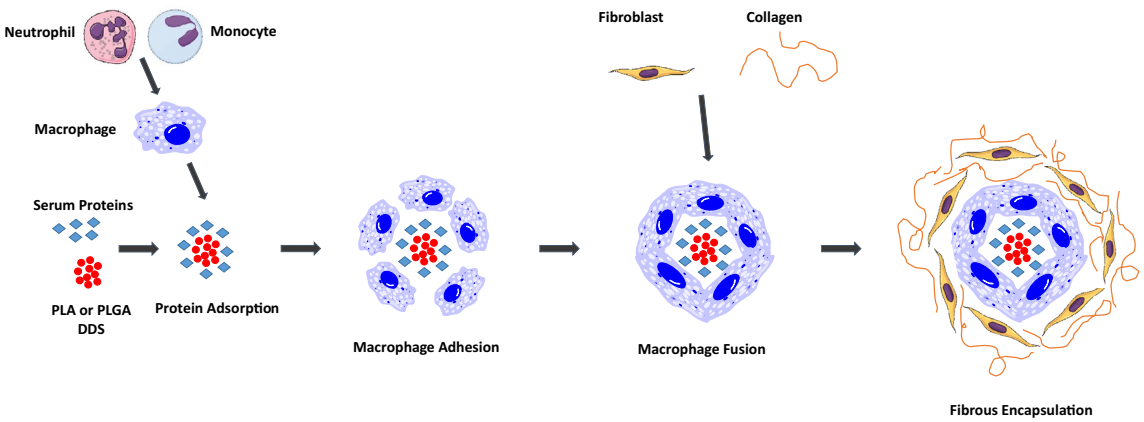

Fig. 2 Tissue response steps to PLA and PLGA drug delivery systems

Specifically, recognition of the intravenous (IV) NPs by the reticuloendothelial system (RES) is heightened, resulting in their phagocytosis. However, the rationale design of functional long-circulating PLGA NPs via surface modification with hydrophilic polymers such as polyethylene glycol (PEG), poloxamers and polysaccharides greatly stabilizes NPs against opsonization (Gref et al. 2000; Mahapatro and Singh 2011; Yoo et al. 2010). Interestingly, the alleviating influence of incorporated therapeutic agents insides PLA and PLGA DDS must be considered as such tissue responses can be greatly diminished due to drug encapsulation (Ramot et al. 2016). For instance, loading PLGA MPs with anti-inflammatory drugs such as dexamethasone has been demonstrated to provide long term control over inflammation and fibrosis, improving their performance following SC implantation (Bhardwaj et al. 2010; Dang et al. 2011).

Concerning utilization of PLA and PLGA based DDS to other administration sites such as intravitreal, intraparenchymal "for brain delivery", intratracheal and intracochlear implantations, previous studies evidenced that they meet the biocompatibility requirements. Mild tissue responses have been shown, if any with the absence of histological alterations or cell ultrastructure modification (Ensari et al. 2015; Kim et al. 2011; Lewitus et al. 2011; Rong et al. 2014).

Biodegradation of PLA and PLGA

PLA and PLGA belong to the large family of biodegradable aliphatic polyesters (Vroman and Tighzert 2009). PLA and PLGA polymers, prepared with different isomer composition and polymer molecular weight, have variable melting points and crystallinity (Ahmed and Varshney 2011). Moreover, the biodegradation of these polymers in the human body can be controlled (i.e. retarded) by the incorporation of D-lactide isomer in their backbones. The fact that our bodies do not produce enzymes that can utilize D-lactic acid results in reduced degradability of polymers containing D-lactide monomer (Gorrasi and Pantani 2013).

The biodegradation of polyesters including PLA and PLGA mainly occurs by hydrolytic degradation which may be enzyme catalyzed (Elsawy et al. 2017). Several factors can affect hydrolytic degradation process including (i) water permeability and solubility, (ii) chemical composition and molecular weight and molecular weight distribution, (iii) the mechanism of hydrolysis (noncatalytic, autocatalytic, enzymatic), (iv) additives (acidic, basic, monomers, solvents, drugs), (v) polymer crystallinity, (vi) glass transition temperature (glassy, rubbery) and other physicochemical factors (e.g. ionic strength, pH) (Antheunis et al. 2009; Frank et al. 2005; Makadia and Siegel 2011; Xu et al. 2017; Zolnik and Burgess 2007).

The most important factor affecting the degradation of PLA and PLGA and particles prepared by them is polymer molecular weight (Anderson and Shive 1997) and degree of crystallization (Mitchell and Hirt 2015). Crystalline parts of the polymer show more resistance to degradation when compared to amorphous regions (Göpferich 1996). The crystallinity of the polymer depends on its composition i.e. increasing the percentage of glycolide monomer in PLGA backbones decreases polymer crystallinity as it decreases chain rearrangement to produce crystalline structures (Keles et al. 2015; Xu et al. 2017).Moreover, it was found that increasing PLA and PLGA molecular weights, their degradation rate decreases because of the high chain–chain crossing between long polymer backbones which lead to the resistance of chain cleavage (Makadia and Siegel 2011).

The extent of water uptake affects the hydrolytic degradation of PLA and PLGA as water reacts with polyesters, resulting in reverse polycondensation (Alexis 2005). Various factors affect water uptake of these polymers including; molecular weight, purity, morphology, and the polymer processing techniques (Antheunis et al. 2010; Dorati et al. 2007; Keles et al. 2015). The abundance of water is critical to start ester bond degradation to oligomers and monomers, especially for high molecular weight polymers. Furthermore, polymer porosity helps in increasing polymer biodegradation by increasing water uptake as well as cellular migration through polymer macropores (Rodriguez et al. 2016).

PLA and PLGA degradation was found to increase in acidic (Zolnik and Burgess 2007) and basic (Wang et al. 1998) conditions, hence, the incorporation of large amounts of acid and basic drugs (D'Souza et al. 2015) and/or additives (Yoo et al. 2005) to them enhances degradation kinetics. It is also worth to note that phagolysosomal vacuoles of macrophages have acidic content (pH ~3) which, when secreted on the interface with the polymers, facilitate their biodegradation (Anderson and Shive 1997).

Methods used for the characterization of polymer degradation

Many techniques have been used to investigate the process of PLA and PLGA degradation through tracking the physical or chemical changes that happen during polymer breakdown to oligomers and monomers (Engineer et al. 2011; Keles et al. 2015). Figure 3 shows different techniques used to probe polymers degradation. The different techniques usually involve either direct investigation of the variations in polymer molecular weight with time (e.g. gel permeation chromatography (GPC) (Bawa et al. 2018) and time-of-Flight secondary ion mass spectrometry (TOF–SIMS) (Marchany et al. 2015)) or testing the changes in different physical properties which are correlated to polymer size (e.g.

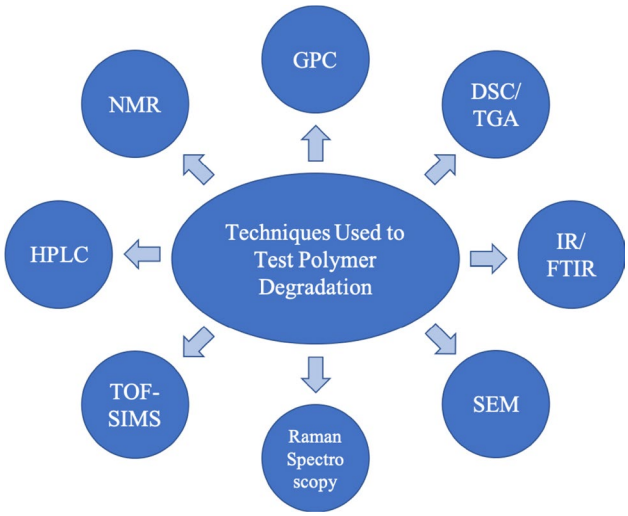

Fig. 3 Different techniques used to probe degradation of polymers

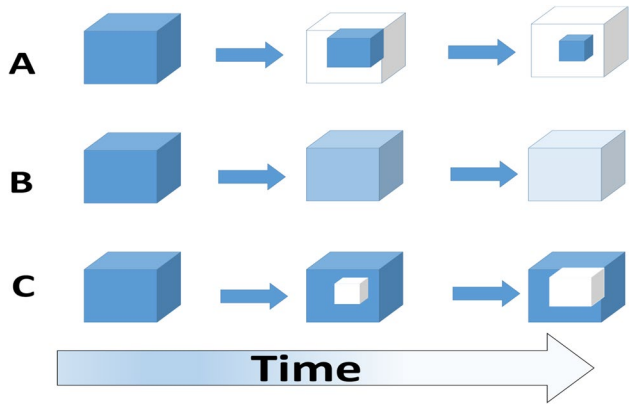

Fig. 4 Degradation pathways for PLA and its copolymers: **A** surface degradation, **B** bulk degradation, **C** bulk degradation with autocatalysis

crystallinity and thermal properties i.e. differential scanning calorimetry (DSC) and thermo gravimetric analysis (TGA)) (Turek et al. 2015). Moreover, degradation can be assessed by tracing properties of the *polymer* such as loss of molecular mass which can be demonstrated using GPC and changing of polymer crystallinity which can be assessed by studying changes in its thermal properties.

Other techniques involve following the buildup of monomer molecules during degradation and this could be followed using pH changes for acidic and basic monomers, high performance liquid chromatography (HPLC) (Giunchedi et al. 1998), Fourier transform infrared spectroscopy (FTIR) (Leroy et al. 2017), nuclear magnetic resonance (NMR) and Raman spectroscopy (Kasyapi et al. 2015). Qualitative methods by imaging polymer using scanning electron microscopy (SEM) (Liu et al. 2006) and atomic force microscopy (AFM) (Giannouli et al. 2018) have been used to check polymer degradation by probing morphological changes with time.

Degradation pathways and drug release models

The degradation of PLA and its copolymers occur by three hydrolytic pathways: (i) surface degradation, (ii) bulk degradation and (iii) bulk degradation with autocatalysis (Gajjar and King 2014) (Fig. 4). For the *surface* degradation or erosion, the cleavage of ester bonds of polymers occurs mainly on the surface, resulting in the formation of monomers and oligomers that diffuse to the degradation medium faster than those produced in the polymer bulk. *Bulk* erosion happens when degradation medium penetrates polymer matrix and random hydrolysis occurs throughout the polymer bulk, reducing its backbone molecular weight. During the gradual bulk erosion process, as long as the degradation medium diffuses throughout the hydrolyzing matrix, monomers and oligomers diffuse to the degradation medium and the polymer density decrease (von Burkersroda et al. 2002). When the bulk degradation results in the formation of a higher concentration of acidic degradation products in the polymer interior compared to the polymer surface, *autocatalysis* may happen, accelerating the internal degradation. As the polymer interior degradation increases, monomers and oligomers diffuse rapidly, producing polymer matrix with hollowed core (Antheunis et al. 2010).

PLA and PLGA degrade with second order (2nd) order kinetics depending on both ester bond and water concentration (Lyu and Untereker 2009). As hydrolysis or autocatalysis proceeds, the number average molecular weight (M_n) of polymers decreases with the increase in chain end concentration (CE) and this could be quantified by the following equation:

$$CE = \frac{X}{V} = \frac{\rho}{Mn} = \frac{\rho}{N \cdot M_0} \tag{1}$$

where X, V, and ρ: total number of chains, volume, and density of the samples; N: degree of polymerization; M_0: monomer molecular weight.2nd order hydrolysis reaction can be described as follows:

$$\frac{dCE}{dt} = k_2 C_e C_w \tag{2}$$

where k_2: rate constant; C_e: ester bond concentration; C_w: water concentration.

By combining Eqs. (1, 2), the number average molecular weight (M_n) can be calculated from 2nd order hydrolysis equation:

$$\frac{1}{Mn} = \frac{1}{Mn_0} + \frac{1}{M_0} k_2 C_e t \tag{3}$$

where M_n: number average molecular weight at time t; M_{n0}: initial number average molecular weight before starting hydrolysis reaction. In the case of auto-accelerated degradation or autocatalysis, the degradation rate is proportional to the chain bond concentration as well as water and hydrolytic bond concentrations as follows:

$$\log Mn = \log Mn_0 - k_3 C_e C_w t \quad (4)$$

where k_3: autocatalysis rate constant.

The release of different drugs from PLA or PLGA matrix is the sum of surface and bulk diffusion as well as matrix erosion mechanisms (Makadia and Siegel 2011). The drug release occurs mainly by diffusion when the polymer weight loss is minimal. This could be described by the following equation:

$$\frac{\partial C(r,t)}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(M_w)\frac{\partial C(r,t)}{\partial r}\right) \quad (5)$$

where C: drug concentration; r: radial position; t: time; $D(M_w)$: polymer molecular weight dependent diffusivity of the drug.

When polymers are formulated into MPs or NPs, the effect of population size distribution on drug release can be described by the following equation:

$$\frac{1}{M_\infty}\frac{\partial M_{drug}}{\partial r} = f(r;\lambda,k) = \frac{k}{\lambda}\left(\frac{r}{\lambda}\right)^{k-1}\exp\left(-\left(\frac{r}{\lambda}\right)^{k}\right) \quad (6)$$

where M_∞: drug total mass in the population; M_{drug}: drug mass in one particle and r is the particle radius.

Biomedical applications of PLA and PLGA nano- and microsystems

During the last decade, several research groups have prepared nano- and microsystems using PLA and PLGA for many therapeutic applications. They aimed to use these biodegradable and biocompatible polyesters to modify drug release and enhance its activity and optimal therapeutic effectiveness (Lee et al. 2016; Sharma et al. 2016). In the following sections, we will discuss part of extensive applications of the currently developed PLA and PLGA based nano and microsystems with emphasis on their beneficial effect in the delivery of biopharmaceuticals, viz., drugs, vaccines and gene delivery (Tables 1, 2 and 3). Examples of recent research studies in the last ten years which deal with biodegradation and biocompatibility of PLA and PLGA nano- and microparticulate delivery systems and their main achievements are covered in this review.

PLA and PLGA based MPs and NPs delivery systems for vaccine delivery

The potential of polyesters to produce delivery platforms adequate for vaccination for preventive and therapeutic purposes has been increasingly explored. Their attractiveness in protein and peptide delivery stemmed from their ability to act as safe and efficacious vaccines adjuvants and to co-encapsulate antigens and/or immunomodulators and other vaccine adjuvants (Ahmed and Varshney 2011; Demento et al. 2012; Kasturi et al. 2011; Mundargi et al. 2008; Schlosser et al. 2008; Wischke et al. 2009). Antigen-containing polymeric particulates get due recognition of strong and long lasting T-lymphocytes responses as compared to the soluble antigens (Cruz et al. 2017). Other striking features include protection of their payload from proteolytic degradation, sustained antigen availability, peptide dosage reduction, minimized immunization times and reduced toxicity (Demento et al. 2012; Getts et al. 2014; Tam et al. 2016).

As a consequence, the coordination of more robust optimal humoral and cellular arms of the immune response, mimicking the natural infection influence, could be achieved (Demento et al. 2012; Kasturi et al. 2011). The mechanism behind such stimulatory capacity is the phagocytosis of the particles by dendritic cells (DCs), the most professional cellular target, leading to the maturation markers up-regulation (such as CD40 and CD80) and antibody and T-lymphocytes activation and proliferative response to different antigens (Anderson et al. 2008; Clawson et al. 2010; Danhier et al. 2012; Luzardo-Alvarez et al. 2005; Rosas et al. 2001; Waeckerle-Men and Groettrup 2005). Interestingly, anti-cancer immunotherapy could be realized by such immune system alerts, through their capability to encapsulate ligands for Toll-like receptors (TLRs) (Hamdy et al. 2011; Kranz et al. 2016; Pinzon-Charry et al. 2007; Seth et al. 2017; Zhang et al. 2011).

The utilization of particulate formulated vaccines with controlled size (preferentially in the micron range), charge, polymer composition, molecular weight, degradation rate and, hydrophobicity could guarantee non-specific long lasting DCs targeting (Feng et al. 2006; Kanchan and Panda 2007; Kazzaz et al. 2006). In particular, degradability governed the second phase of the mechanism behind the release of peptides/proteins, following the initial phase of diffusion, and hence, their immunization response and the proposed regimen (Taha et al. 2012). In addition, nature of co-adjuvants and delivery route play a critical role in the efficacy of these protective immunity generators (Ashhurst et al. 2018; Newman et al. 2002; Renukuntla et al. 2013). A selection of some examples on the application of PLA and PLGA based MPs and NPs delivery systems for vaccine delivery is reviewed in Table 1, with

Table 1 Applications of PLA and PLGA based MPs and NPs delivery systems for vaccine delivery

Type of carrier	Polyester type	Vaccine	Limitations of vaccine	Stabilizing excipients/adjuvants/surface decoration	Particle size	Route	Status of investigation	Observations/outcome	References
NPs	PLGA85:15 (Mw 50,000-75,000)	Recombinant peptide of Chlamydia trachomatis major outer membrane protein (MOMP) (rMOMP-187)	Rapid degradation by proteases and poor cellular uptake and immunogenicity	–	~ 200 nm	–	In vitro	Noticeable dose-dependent triggering of high levels of inflammatory cytokines and nitric oxide (NO) in macrophages > 95% eukaryotic cell viability	Taha et al. (2012)
MPs	PLGA 65:25	Mycobacterium tuberculosis lipoprotein, MPT83	Poor immunogenicity	Trehalose-dibehenate (TDB) Monophosphoryl lipid A (MPLA).	~ 0.5–2 µm	Nasal-SC	In vivo (mice)	Modest antigen-specific Th1 and Th17 responses and infection control following SC peripheral delivery Antigen-specific Th17 responses in the lungs with no infection protection following mucosal delivery	Ashhurst et al. (2018)

Table 1 (continued)

Type of carrier	Polyester type	Vaccine	Limitations of vaccine	Stabilizing excipients/adjuvants/surface decoration	Particle size	Route	Status of investigation	Observations/outcome	References
NPs	PLGA	MART-127–35 peptide	Low stability and lack of dendritic cells (DCs) targeting (cross-presentation)	Biotinylated anti-human DEC-205 "DC surface receptor" monoclonal antibody	~ 200 nm	–	In vitro	Enhanced NPs internalization by immature DCs, as well as enhanced levels of antigen (Ag.) potentiated antigen cross-presentation Survival of > 90% of the human CD8 + T cell receptor transgenic cell line DMF5 Proven degradation of DEC-205 labelled NPs within DCs in different subcellular compartments	Saluja et al. (2014)
NPs	PLGA 50:50 (Mw—38–54 kDa)	Canine parvovirus (CPV) peptide	Rapid degradation by proteases and poor cellular uptake and immunogenicity	–	~ 221.7 ± 15.8 nm	–	In vitro	High immunogenic features in terms of phagocytosis by macrophages and induction of nitric oxide (NO) production. Promising biocompatibility (non-toxic on J774 macrophage cells).	Derman et al. (2015)

Table 1 (continued)

Type of carrier	Polyester type	Vaccine	Limitations of vaccine	Stabilizing excipients/adjuvants/surface decoration	Particle size	Route	Status of investigation	Observations/outcome	References
NPs	PLA (M w 50 kDa)	Pachyman	Rapid release and low immune response	–	245 nm	–	In vitro	Low cytotoxicity against lymphocytes Noticeable greater stimulation of immunological competence of the lymphocytes by NPs encapsulating pachyman in comparison with free drug and blank PLA	Zheng et al. (2016)
NPs	PLGA (RG 504-H)/mPEG-PLA (67: 33 W/W): mPEG-PLA (100%)		Systemic dose-limiting toxicity and tolerance with immune unresponsiveness for repetitive application	Resiquimod, a Toll-like receptor 7 ligand	154–278 nm)	SC	In vivo (mice)	Anti-cancer immune response in terms of uptake by dendritic cells and macrophages, confirming lymph node targeting Non-toxic and non-inflammatory effects of the formed NPs	Widmer et al. (2018)

Table 1 (continued)

Type of carrier	Polyester type	Vaccine	Limitations of vaccine	Stabilizing excipients/adjuvants/surface decoration	Particle size	Route	Status of investigation	Observations/outcome	References
MPs	PLGA 75:25 (Mw 84.7 kDa)	Recombinant tuberculosis (TB) antigen, TB10.4-Ag85B	Low immunidenicity and lack of alveolar macrophage uptake	MDP (adjuvant)	Aerodynamic diameter (3.3 µm)	Pulmonary	In vitro	In vitro induction of strong immune response by PLGA-MDP-TB10.4-Ag85B at much lower concentration compared to that of soluble antigen Safety and cytocompatibility of MPs on antigen presenting cells (THP-1)	Shi and Hickey (2010)
MPs	PLGA-PEG Resomer RG 502 Mw 12,000) and Mw of PEG 6000	Yersinia pestis F1 antigen	Low immunigenecity and short term protection	–	3.8 µm	Intraperitoneal-SC	In vivo (mice)	Enhanced immune response (steady-state IgG immune protection) High survival rates and noticeable reduction in morbidity	Huang et al. (2014)
MPs	PLGA 50:50 (Mw 40,000–75.000& 75:25 (Mw 66,000–107.000	Hepatitis B surface antigen (HBsAg)	Poor vaccine coverage and destabilization and degradation during microencapsulation	Cetyl trimethyl ammonium bromide (CTAB) (cationic surfactant)	For PLGA 50.50: 7.35 µm For PLGA 75:25: 5.08 µm	SC	In vivo (mice)	Superior long-lasting induction of cellular proliferative as well as humoral responses against hepatitis B after single shot as compared to multiple alum-adsorbed vaccine	Saini et al. (2011)

Table 1 (continued)

Type of carrier	Polyester type	Vaccine	Limitations of vaccine	Stabilizing excipients/adjuvants/surface decoration	Particle size	Route	Status of investigation	Observations/outcome	References
MPs (composite system)	PLGA Resomer-RG503 (50:50) (MW 40,600 Da)	Bovine serum albumin (BSA) (model protein)	Low immunogenicity and cellular response	Co-adjuvants (monophosphoryl lipid A "MPLA", polyinosinic-polycytidylic acid, galactosylceramide and alginate)	~ 1 µm	Intradermal (ID)	In vivo (mice)	Superior humoral immune response balanced IgG1/IgG2a response Effective triggering of a higher mixed immune response by using MPLA and galactosylceramide combination	Salvador et al. (2012)
MPs	PLGA 50:50 (Mw 17 kDa)	Lipoprotein of B. Hyodysenteriae (bmpb)	Degradation in the gastrointestinal tract, low bioavalability and inefficient targeting	M cell homing peptide coupled chitosan (form mucoadhesive MPs)	~ 3 µm	Oral	In vivo	Oral immunization of mucoadhesive BmpB PLGA MPs enhanced mucosal and systemic immune responses (due to higher retention of BmpB in the intestine and maximized interactions with M cells in Peyer's patches of the gut).	Jiang et al. (2014)
MPs	PLA (Mw 17 kDa)	Brugia malayi F6 molecules (filarial antigens)	Degradation during microencapsulation and low immune response		8.42 µm	SC	In vitro/in vivo (mice)	Better immune responses of the host due to PLA-MP-F6 formulation over plain F6 molecules.	Saini et al. (2014)

Table 1 (continued)

Type of carrier	Polyester type	Vaccine	Limitations of vaccine	Stabilizing excipients/adjuvants/surface decoration	Particle size	Route	Status of investigation	Observations/outcome	References
MPs	PLA (Mw 103 kDa)	Recombinant Fusion protein (TV) and Filarial epitope protein (FEP) (filarial vaccine candidate antigens)	Low and short-lasting immune response		1.67–7.78 µm	SC	In vitro/in vivo (mice)	Excellent long-lasting immunogenicity, both humoral and cellular, of PLA MPs through triggering significantly elevated antibody titer, splenocyte proliferative response and cytokine concentrations as compared to alum-adsorbed TV/FEP and the single dose of TV/FEP	Anugraha et al. (2015)
MPs	PLGA 50:50 (Mw 12 kDa)	Inactivated Polio, serotypes 1,2 and 3	Thermal instability and repeated injections for protective immunity	Eudragit E, poly(L-lysine) (PLL), and branched polyethylenimine (bPEI)		IM	In vivo (rat)	Strong neutralizing immune response of stabilized single injection Avoidance of systemic or local toxicity	Tzeng et al. (2018)
MPs	PLGA 50:50 (Mw 53.4 kDa)	Ovalbumin (model antigen)	Instability and loss of antigenicity during production	Calcium phosphate ($CaHPO_4$) adjuvant gel (protein-trapping agent) and trehalose (porosigen)	7.05 ± 0.31 µm	Nasal	In vivo (mice)	Potential systemic and local mucosal immunostimulation in terms of induction of a robust Th2-type antibody response	Bailey et al. (2017)

a focus on the biocompatibility of the prepared systems and their therapeutic outcomes.

PLA and PLGA based MPs and NPs systems for drug delivery

Past efforts have realized great achievements in therapeutic strategies using drugs, both small molecules and macromolecules, in combination with PLA and PLGA biomaterials (Makadia and Siegel 2011). In particular, polyesters based therapeutics gain success in improving chemotherapeutic efficacy, both in vitro and in vivo, and anti-inflammatory response for treatment of cancer (Hu and Zhang 2012) and inflammatory diseases (Danhier et al. 2012) respectively in various administration routes.

Bioinert and biodegradable PLA and PLGA drug carrier materials hold outstanding advantages, including (i) sustainable delivery (Mansor et al. 2018), (ii) proper control of drug release kinetics (iii) diminished fluctuations of blood drug concentrations (Makadia and Siegel 2011), (iv) augmented cellular uptake of NPs via endocytosis (Bi et al. 2016; Priemel et al. 2018), (v) enhanced stability (Xiong et al. 2016), (vi) optimal clinical utility (Lü et al. 2009) and (vii) improved medication adherence (Liu et al. 2006).

In recent years, researchers have become more focused on designing surface modified PLA and PLGA particulates, possessing prolonged systemic circulation time (Meng et al. 2018). The most relevant way to avoid RES recognition is the PEGylation, via masking hydrophobicity of the particles and imparting stealth characteristics by hydrophilic PEG brush (Mansor et al. 2018). Experimental research has also proved other favorable properties of PEGylated particles such as reducing aggregation while enhancing stability and biological potency (Goudarzi et al. 2018). Moreover, considerable interest has been conducted in the development of ligand coupled NPs like peptide, antibodies, and nucleotides ligands for enhanced localization and active targeting capabilities to specific organs or cells (Dinarvand et al. 2011). Examples of recent publications that have shown promising results towards effective sustained PLA and PLGA based MPs and NPs for drug delivery are listed in Table 2. An emphasis is placed on findings of investigations done to assess degradation and/or toxicity issues of the prepared DDS.

PLA and PLGA based MPs and NPs systems for gene delivery

Gene therapy interests the researchers of the scientific community by its potential in fighting diseases from their genetic source providing personalized medicine to the patients (Naldini 2015). This specific therapy is therefore promising for the treatment of complex diseases such as chronic infections, cancer and inherited diseases, especially in substitution of standard treatments when they fail to cure the disease.

Many achievements have been reached in the field of gene delivery of a variety of nucleic acids such as pDNA (Baoum et al. 2010), mRNA (Yasar et al. 2018), siRNA, and microRNA. These nucleic acids can both introduce genes that encode a functional protein that is vital in preventing disease progression or block the translation of specific mRNAs to prevent a toxic effect. Multiple obstacles are present after the administration of nucleic acids such as the presence of nuclease, the nucleic acid instability, biological membrane and endocytosis. The overcome of these obstacles can be achieved by the use of nanotechnology and the incorporation of nucleic acid in different nano and microparticles (Wong et al. 2017; Xiao et al. 2019).

Biodegradable polyesters including PLA and PLGA were highly investigated for preparing gene delivery vectors (Kumari et al. 2010). However, for delivery of therapeutic genes, there is a great challenge of formulating PLA and PLGA particles containing a high payload, owing to their negatively charged backbone. The loading of nucleic acids to PLA and PLGA NPs could be done by either direct encapsulation using double emulsion solvent evaporation technique (Mok and Park 2008) or by the pre cationization (adding cationic polymers) of polyester NPs to enhance the encapsulation efficiency of nucleic acids and accelerate their release (Luten et al. 2008). Cationization of polyester NPs can be done by incorporating cationic molecules such as polyethylenimine (PEI) (Frede et al. 2016; Kolte et al. 2017), chitosan (Tahara et al. 2011), polyarginine (Zhao et al. 2012), poly(2-dimethylaminoethyl methacrylate (pDMAEMA) (Qian et al. 2014), cationic lipids (Dioleyltrimethylammonium propane "DOTAP"–Dioctadecenyltrimethylammoniumpropane "DOTMA") (Yasar et al. 2018; Zhu et al. 2015), Dimethylaminoethane carbamoyl cholesterol (DC-Chol) (Baoum et al. 2010; Gwak et al. 2016) and cationic cell-penetrating peptide (CCCP) (Jain et al. 2015).

It is well known that the smaller the particle size, the more efficient the gene delivery, however, PLGA particles are easily phagocytosed by immune cells when prepared in size less than 10 µm (Oyewumi et al. 2010). Several trials have been done to modify or sustain the release of nucleic acids from PLA and PLGA based systems. However, their hydrophobic nature renders extended nucleic acid release not feasible being rapidly removed from circulation after parenteral administration (Dinarvand et al. 2011). In order to solve the previously mentioned obstacle, many strategies have been explored including PEGylation, copolymerization with hydrophilic polymers, NPs coating with a surfactant, lipid and targeting ligands (Jain et al. 2015).

Table 2 Application of PLA and PLGA based MPs and NPs systems for drug delivery

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
NPs	PLGA/PEG–PLGA "PLGA 75:25 with uncapped terminals (Resomer® RG752H) (Mw 9850 Da)"	Stromal cell-derived factor-1α (SDF-1α)	Solubility and rapid diffusion in physiological media	Lysozyme (model protein for encapsulation optimization)	~ 200 nm		Cancer cell trapping	In vitro (cytotoxicity)	Gradual biphasic sustained release of SDF-1α in its bioactive conformation Excellent biosafety on NIH3T3 mouse embryonic fibroblasts	Mansor et al. (2018)
NPs	mPEG–PLGA 50:50 (MW 2000–20,000 Da)	Rotigotine	Lack of brain selectivity and Cytotoxicity	Lactoferrin (targeting ligand)	122 nm (coated) 58 nm (uncoated)	Nasal	Parkinson's disease (brain targeting)	In vitro (cytotoxicity)/in vivo	High viability of 16HBE and SH-SY5Y cells that were not compromised by drug and lactoferrin, lowering cytotoxicity of free drug Superior cellular accumulation and targeted nose-to-brain delivery	Bi et al. (2016)

Table 2 (continued)

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
MPs	PLA "PURASORB PDL 02" (Mw 20KDa)	Rifampicin	High dose, systemic side effects and reduced systemic efficacy	poly(ethylene carbonate) (PEC) (Mw 100–250 kDa) "increasing drug release and degradation"	6–8 μm for PLA		Lung infections (macrophage targeting)	In vitro (cytotoxicity)	Promising macrophages uptake and proven intracellular localization, indicating macrophages targeting of PEC containing PLA MPs as compared to drug solution Dose-dependent higher cytotoxicity on THP-1 and A549 in comparison to drug solution, indicating the high cellular uptake Higher release rates form PEC containing PLA MPs, suggesting optimal cell-triggered drug release And higher activity against *Pseudomonas aeruginosa* and *Escherichia coli*	Priemel et al. (2018)

Table 2 (continued)

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
MPs	PLGA 50:50 (Mw 20KDa)	Basic fibroblast growth factor (bFGF)	Instability in acidic environments and at high temperatures and short half-life (3–5 min)		5.22 µm		Articular cartilage injury	In vitro (change in Mw-mass loss)	bFGF–PLGA MPs were proven to be stable with no obvious deformation or structure damage under joint mimicking condition Significantly higher degradation and drug release during static pressure loading experiment	Xiong et al. (2016)
Surface modified (Lf-TMC PLGA) NPs	PLGA 5050 2A 50:50 (Mw 18,000 Da)	Huperzine A	Lack of brain selectivity and serious systemic side effects (gastrointestinal and peripheral cholinergic systems)	Lactoferrin (Lf) "targeting ligand"-conjugated N-trimethylated chitosan (TMC) "mucoadhesive polymer"	153.2 nm	Nasal	Alzheimer's disease (brain targeting)	In vitro (cytotoxicity)/In vivo (mice)	Superior cytocompatibility with 16HBE cell line as compared to drug solution The surface modification resulted in markedly higher promoted uptake of anti-Alzheimer drug into the brain with longer residence time than that of non-targeted analogs	Meng et al. (2018)

Table 2 (continued)

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
NPs	PLA–PEG–PLA (Mw 84.7 kDa)	Nisin	Limited intracellular targeting, enzymatic degradation, in stability at physiological pH and rapid removal through kidney filtration		~ 200 nm		Cancer chemotherapy	In vitro (cytotoxicity)	Safety and cytocompatibility of NPs in terms of negligible hemolysis capacity and marked cell viability (normal Vero cell line) Cytotoxic effect on cancer cell lines (AGS, KYSE-30, HepG2, and K562 cancer cell lines) and induced apoptosis were signs of an efficient anti-tumor activity	Goudarzi et al. (2018)

Table 2 (continued)

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
NPs	PLA (Mw 16,000–35,000)	Curcumin	Insolubility in water, low bioavailability, rapid metabolism and excretion and lack of specific targeting	Hyaluronic acid (targeting ligand)	60–70 nm	IP	Liver fibrosis	In vitro (cytotoxicity)/in vivo (liver histopathological analysis)	Bioinert plain NPs on normal hepatic cells Potentiated cytotoxicity of coated NPs bearing curcumin on activated hepatic stellate cells (aHSCs) (30 fold) as compared to free curcumin Promising ameliorative potential and prominent recovery from Thioacetamide (TAA)-Induced Hepatic Fibrosis following histopathological analysis	Chen et al. (2017)

Table 2 (continued)

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
NPs	PLGA (PURASORB_PDLG 5002A,)	Bosentan	Low bioavailability (50%), short duration of action, adverse effects (hepatotoxicity and systemic hypotension) and lack of pulmonary vascular selectivity	–	< 500 nm (optimized)	Pulmonary	Pulmonary hypertension	In vitro/in vivo (histological examination)	Nebulization of respirable droplets of NPs ensured deep lung deposition Improved bioavailability and prolonged vasodilation effect Lack of tissue damage following histological assessment	Hanna et al. (2017)

Table 2 (continued)

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
NPs	PLGA 50:50 & 75:25 (Mw 30,000–60,000)	Paclitaxel	Rapid removal by cancer cells via P-glycoprotein and serious life-threatening side effects (hypersensitivity, super infections and myelosuppression)	Hyaluronic acid (coating polymer)	200–400 nm		Breast cancer	In vitro (biodegradation and hemolysis study)	Achievement of small-sized NPs using PLGA 50/50 as compared to PLGA 75/25 and polycaprolactone The positive impact of drug and hyaluronic acid on polymer degradation owing to increased porosity and acidity respectively Proven non-hemolysis of coated PLGA and cell viability of plain NPs Cytotoxic potential and endocytosis using human triple negative breast cancer cells (MDA-MB-231)	Cerqueira et al. (2017)

Table 2 (continued)

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
MPs	PLGA/PEG–PLGA (Resomer® RG 503H (MW 34 kDa) and PLGA:PEG (50:50) Resomer® RGP d 50105 (10% PEG with MW 5 kDa)	The growth factor neuregulin (NRG)	Low bioavailability, short half life, lack of cardiac targeting and long term instability		10.16 µm (PLGA NPs)–12.28 µm (PEG–PLGA)		Myocardial infarction (cardiac regeneration)	In vitro (biodegradation)	More Noticeable long term degradation (4 weeks) of PEG–PLGA as compared to PLGA as manifested by low mass loss and conserved morphology	Pascual-Gil et al. (2015)
MPs	PLGA 50:50 (free-acid terminated "Mw 37 kDa" and ester end-capped (Mw 50 kDa")	Leuprolide acetate	High aqueous solubility and rapid release	–	~ 80 µm	–		In vitro (Mw decline and mass loss, determination of acid release)	Augmented hydrolysis of Acid-end PLGA (owing to autocatalysis) as compared to ester end-capped PLGA Evidence of strong dependency of peptide release on water uptake, mass loss and carboxylic acid release in PLGA	Hirota et al. (2016)

Table 2 (continued)

Type of carrier	Polyester type	Drug/protein	Limitations of free drug/protein	Excipients/coating moieties	Particle size	Route	Target disease/Possible application	Status of investigation	Observations/outcome	References
MPs (large porous particles)	PLGA 50:50 (Resomer® RG 502,502H, 503 and 503H)	Cinaciguat	Lack of pulmonary targeting	Polyvinylpyrrolidone (PVP) (porogen)	>10 µm	Pulmonary	Pulmonary hypertension	In vitro/in vivo (histological assessment)	Deep prolonged lung deposition and improved therapeutic effect with a significant reduction in phagocytosis by macrophages (aerodynamic diameter < 5 µm) The absence of any pathological findings following histological study ensured the safety of large porous particles	Ni et al. (2017)
MPs	PLGA 50:50 (Mw 6622 Da)	Progesterone	Variability of drug concentration in blood and rapid release		9.3–131.3 µm		Hormone replacement therapy	In vitro (degradation modeling)	Negligible impact of degradation on release from small microparticles when compared to larger MPs release owing to autocatalysis	Busatto et al. (2018)

Table 3 Application of PLA and PLGA based MPs and NPs systems for gene delivery

Type of carrier	Polyester type	Nucleic acid	Limitations of nucleic acid	Cationic polymer/surface modification	Particle size	Status of investigation	Transfected cells	Outcomes of transfection, cytotoxicity and gene delivery	References
NPs	PLGA 50:50 (Mw 20,000 kDa)	pDNA (encoding for firefly luciferase)	Instability and retention of structure and low transfection	DC-Chol cetrimide-chitosan-protamine-DODAB	~ 200 nm	In vitro (cytotoxicity)	Human lung adenocarcinoma cells (A549)	Higher cytocompatibility of the cationic surface modified NPs Enhanced cellular uptake of the cationic NPs, specially chitosan coated Promising sustained gene expression Unexpected Lack of gene expression of NPs coated with both chitosan and protamine	Baoum et al. (2010)
NPs	PLGA (50:50; Resomer RG 503H)	mRNA (mRNA–mCherry)	Instability under physiological conditions and low transfection	Lipid (DOTMA)-chitosan (CS)	< 250 nm	In vitro (cytotoxicity)	Bone-marrow-derived murine dendritic cell line (DC2.4) Human lung adenocarcinoma cells (A549)	Greater cell viability of chitosan-PLGA NPs in comparison to lipid-PLGA NPs Superior transfection efficiency of lipid-PLGA NPs over chitosan-PLGA NPs in DC2.4 cells and A549 cells Promising prospects for cellular internalization of NPs and translation of the mCherry protein.	Yasar et al. (2018)

Table 3 (continued)

Type of carrier	Polyester type	Nucleic acid	Limitations of nucleic acid	Cationic polymer/surface modification	Particle size	Status of investigation	Transfected cells	Outcomes of transfection, cytotoxicity and gene delivery	References
NPs	PLGA	siRNA	Poor access of siRNA into the cytosol, lack of specific targeting and rapid degradation by nucleases	PEI	~ 150 nm	In vitro (cytotoxicity)/in vivo	Murine epithelial cell line (MODE-K)	No detectable toxicity of siRNA-loaded PLGA NPs and excellent in vitro cellular internalization, target gene silencing capacity and in vivo targeted uptake accompanied with knockdown of target genes at the site of inflammation	Frede et al. (2016)
NPs	PLGA 50:50 (Mw 17 kDa)	pDNA	Instability, low cellular uptake and transfection	PEI–DSPE–PEG (coating)	< 200 nm	In vitro (cytotoxicity)/in vivo (Bronchoalveolar lavage (BAL) studies and lung histology)	Cellosaurus cell line (CFBE41o–)	High cytotoxic effects of PEI-modified NPs, greatly reduced by surface modification with PEGylation of PEI-modified NPs greatly promoted transfection efficiency Favorable in vivo safety profile of PEGylated NPs, in terms of the absence of tissue injury and histopathological changes	Kolte et al. (2017)

Table 3 (continued)

Type of carrier	Polyester type	Nucleic acid	Limitations of nucleic acid	Cationic polymer/surface modification	Particle size	Status of investigation	Transfected cells	Outcomes of transfection, cytotoxicity and gene delivery	References
NPs	PLGA 75:25 (Mw 5000)	pDNA	Instability, low cellular uptake and transfection	Chitosan	> 250 nm	In vitro (cytotoxicity)	Human lung adenocarcinoma cells (A549)	Excellent enhanced tolerability Desirable more prolonged in vitro gene transfection capacity	Tahara et al. (2011)
NMs (Nano micelles)	mPEG–PLA-b-Polyarginine	siRNA	Rapid degradation by nucleases, fast elimination, poor cellular uptake and lack of targeting	Polyarginine	54.3 nm	In vitro (cytotoxicity, hemolysis and erythrocytes aggregation)/in vivo (toxicity and immunogenicity)	Human breast cancer cells (MCF-7)	Greater cytocompatibility and hemocompatibility of triblock copolymers over polyethyleneimine (PEI) Proven systemic non-toxicity and non-immunogenicity Evidenced in vitro gene silencing and in vivo suppression of tumor growth	Zhao et al. (2012)

Table 3 (continued)

Type of carrier	Polyester type	Nucleic acid	Limitations of nucleic acid	Cationic polymer/surface modification	Particle size	Status of investigation	Transfected cells	Outcomes of transfection, cytotoxicity and gene delivery	References
NMs	Star-branched PLA-co-PDMAEMA	microRNA (miR-21i)-Doxorubicin	Lack of intracellular targeting and poor tumor chemosensitivity of anti-cancer drug	PDMAEMA	< 100 nm	In vitro (cytotoxicity)/in vivo	Cellosaurus cell line (GES-1 cells)-Human glioma cell lines (LN229)	Higher cytocompatibility of the star-branched copolymers as compared to PEI (GES-1 cells) Promising maximal synergy of microRNA and chemotherapeutic agent, expressed by effective gene transfection, intracellular uptake of DOX, both in vitro "toxic effect on LN229 cells" and in vivo "anti-glioblastoma effect"	Qian et al. (2014)
NPs	PLGA	siRNA	Rapid degradation by nucleases, poor cellular uptake, short circulation half life and poor tumor accumulation	DOTAP–DOTMA–PEG	≤ 100 nm	In vitro (cytotoxicity)/in vivo (Hematologic examination and histology on mice)	Luciferase-expressing HeLa cells (Luc-HeLa) and murine macrophage cells (RAW264.7)	Non-toxicity of NPs, both in vitro on cells and in vivo (no organ toxicity-normal range of hematological parameters Promising features of long-circulating systemic siRNA delivery in terms of tumor accumulation and in vivo anti-tumor efficacy	Zhu et al. (2015)

Table 3 (continued)

Type of carrier	Polyester type	Nucleic acid	Limitations of nucleic acid	Cationic polymer/surface modification	Particle size	Status of investigation	Transfected cells	Outcomes of transfection, cytotoxicity and gene delivery	References
NPs	PLGA (Mw 66,000 Da)	pDNA-vascular endothelial growth factor (VEGF)	Instability, low cellular uptake and transfection-poor therapeutic effect (angiogenesis) of VEGF	Dimethylaminoethane carbamoyl cholesterol (DC-Chol)	> 400 nm	In vitro (cytotoxicity)/in vivo (apoptosis)	Mouse neural stem cells (mNSCs)	Confirmed significantly negligible cytotoxicity in vitro and apoptotic activity in vivo for PLGA/DC-Chol NPs as compared to PEI Promising biological responses in terms of high levels of uptake and gene expression in mouse neural stem cells and enhanced in vivo gene transfection in the rat spinal cord	Gwak et al. (2016)
NPs-in MPs (composite)	PLA-PEG (Mw 33,000 KDa)	pDNA	Instability, low cellular uptake and transfection	Cationic cell-penetrating peptide (RALA)-transferrin	< 200 nm	In vitro (cytotoxicity)	Breast cancer cells (ZR-75-1)	Superiority of cellular uptake of unencapsulated RALANPs over encapsulated RALA NPs within PLA–PEG NPs and transferrin conjugated NPs in translocation of the DNA into the cells Efficient prolonged and safe gene delivery	Jain et al. (2015)

Table 3 (continued)

Type of carrier	Polyester type	Nucleic acid	Limitations of nucleic acid	Cationic polymer/surface modification	Particle size	Status of investigation	Transfected cells	Outcomes of transfection, cytotoxicity and gene delivery	References
NPs	PLGA 50:50 (Mw 10–12 KDa)	siRNA (immunosuppressive)-ovalbumin (tumor antigen)	Instability and very low in vivo targeting efficiency (immunotherapeutic effect)		< 200 nm	In vitro (cytotoxicity)/in vivo	Bone-marrow-derived dendritic cells (BMDCs)	Undetectable toxic effects of PLGA NPs on BMDCs viability Potent cancer immunotherapy strategy of antigen and siRNA combined delivery	Heo et al. (2014)
NPs	PLGA (Mw 10 &20KDa)	siRNA	Rapid degradation by nucleases, fast elimination, poor cellular uptake and lack of targeting	Lipidoids (triethylenetetramine core and N-dodecylacrylamide-derived tails)	< 250 nm	In vitro (cytotoxicity)	Human non-small lung carcinoma cell line (H1299) transfected with EGFP (EGFPH1299)	Favorable biological performance of lipid hybrid NPs at the cellular level (in vitro gene silencing effect and cell viability), highly correlated with lipidoid content and siRNA:lipidoid ratio	Thanki et al. (2017)

Table 3 (continued)

Type of carrier	Polyester type	Nucleic acid	Limitations of nucleic acid	Cationic polymer/surface modification	Particle size	Status of investigation	Transfected cells	Outcomes of transfection, cytotoxicity and gene delivery	References
NPs	PLGA	pDNA "RUNX2/SP7-ATF4 "(sequential gene transfection)	Transfection of hMSCs with ATF4 alone, RUNX2 plus SP7 (DFs), and all three genes at the same-time (TFs) induced their osteogenic diferentiation. However, this was insuf-ficient for the gene ration of osteoblasts	–	< 200 nm	In vitro (cyto-toxicity)	Human mesen-chymalstem cells (hMSCs)	No notice-able cytotoxic effects of pDNAs coated NPs, whatever the type of the delivered genes Proven RUNX2/SP7transfection followed by the promotion of osteogenic differentiation of hMSCs by ATF4	Kim et al. (2018)

PLA and PLGA based NPs loaded with nucleic acids can be delivered to various animal models through different routes of administration such as IM, ID, SC and oral (Bala et al. 2004). Outstanding features of non-immunogenicity and non-toxicity of PLA and PLGA have been keyed the researchers to design PLA and PLGA particles loaded with nucleic acids cargo, such as oligonucleotides, plasmid DNA, and small interfering RNA (siRNA), as an alternative to immunogenic and toxic viral vectors (Xu and Zhang 2009). In addition to previously mentioned PLA and PLGA merits, such biomaterials could give favorable outcomes of potentiating poor intrinsic transfection efficiency of nucleic acids (Heo et al. 2014; Kolte et al. 2017; Xu and Zhang 2009), providing long term gene expression or gene silencing (Jain et al. 2015; Zhu et al. 2015), enhancing translocation inside the cell (Jain et al. 2015), maximizing protection from enzymatic degradation and enhancing gene delivery system cytocompatibility and tolerability (Baoum et al. 2010; Qian et al. 2014; Zhao et al. 2012).

In the future, nanotechnology and gene therapy will be inseparable because, the successful development of efficient non-toxic, non-immunogenic, and biodegradable NPs will improve the efficiency of gene therapy, resulting in breakthroughs for the cure of specific diseases (Wong et al. 2017). Indeed, the successful development and optimization of therapeutic nuclei acids and subsequent clinical gene therapy trials seem to pave the way for recent expansion of market authorization (Lächelt and Wagner 2015).

Special focuses on some research papers, covering the application of PLA and PLGA based MPs and NPs systems that are combined with different cationic polymers for gene delivery as well as addressing safety issue, are summarized in Table 3.

Conclusion

Development of new DDS with excellent safety profile, avoiding unwanted tissue responses and tunable degradation is highly warranted. Biocompatibility and biodegradability of PLA and PLGA polymers pose them as a promising choice in many local and systemic therapeutic applications. Their degradation rate can be traced and modeled using different techniques and was revealed to affect drug release kinetics from PLA and PLGA-based DDS. Insights into the described mechanisms of sustained drug release, PLA and PLGA MPs and NPs have been utilized for vaccine development as well as encapsulating various conventional drugs, proteins and nucleic acids for gene delivery. Based on the abovementioned data and therapeutic outcomes, the idea of the technology transfer of a number of new DDS could gain grounds in the near future. New therapies might be seen in

clinics, specifically in the fields of vaccination and cancer immunotherapy.

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Compliance with ethical standards

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