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REVIEW

Poly(lactic acid)/poly(lactic-co-glycolic acid) particulate carriers for pulmonary drug delivery

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Abstract

Background Pulmonary route is an attractive target for both systemic and local drug delivery, with the advantages of a large surface area, rich blood supply, and absence of first-pass metabolism. Numerous polymeric micro/nanoparticles have been designed and studied for controlled and targeted drug delivery to the lung.

Area covered Among the natural and synthetic polymers for polymeric particles, poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) have been widely used for the delivery of anti-cancer agents, anti-inflammatory drugs, vaccines, peptides, and proteins because of their highly biocompatible and biodegradable properties. This review focuses on the characteristics of PLA/PLGA particles as carriers of drugs for efficient delivery to the lung. Furthermore, the manufacturing techniques of the polymeric particles, and their applications for inhalation therapy were discussed.

Expert opinion Compared to other carriers including liposomes, PLA/PLGA particles present a high structural integrity providing enhanced stability, higher drug loading, and prolonged drug release. Adequately designed and engineered polymeric particles can contribute to a desirable pulmonary drug delivery characterized by a sustained drug release, prolonged drug action, reduction in the therapeutic dose, and improved patient compliance.

Keywords Poly(lactic acid) · Poly(lactic-co-glycolic acid) · Microparticles · Nanoparticles · Pulmonary drug delivery

Introduction

Pulmonary drug delivery provides non-invasive method of drug administration with several advantages over the other administration routes. These advantages include large surface area (100 m^2), thin (0.1–0.2 mm) physical barriers for absorption, rich vascularization to provide rapid absorption into blood circulation, absence of extreme pH, avoidance of first-pass metabolism with higher bioavailability, fast systemic delivery from the alveolar region to lung, and less metabolic activity compared to that in the other areas of the body (Ali 2010; Lee et al. 2018; Yu et al. 2016). The local delivery of drugs using inhalers has been a proper choice for most pulmonary diseases (Pison et al. 2006), including asthma (Basheti et al. 2017; Lavorini et al. 2008), cystic fibrosis (Adi et al. 2010; Bilton et al. 2011), chronic obstructive pulmonary disease (COPD) (Schulte et al. 2008; Sulaiman et al. 2017), lung infections (Cipolla and Chan 2013; Golshahi et al. 2011; Oliveira et al. 2017), lung cancer (Zhu et al. 2017), and pulmonary hypertension (Gupta et al. 2011; Kanwar et al. 2016). In addition to the local delivery of drugs, inhalation can also be a good platform for the systemic circulation of drugs (Moroz et al. 2016; Rytting et al. 2008; Thwala et al. 2017). The pulmonary route provides a rapid onset of action even with doses lower than that for oral administration, resulting in less side-effects because of the increased surface area and rich blood vascularization (Ali 2010).

After administration, drug distribution in the lung and retention in the appropriate site of the lung is important to achieve effective treatment (Labiris and Dolovich 2003a). A drug formulation designed for systemic delivery needs to be deposited in the lower parts of the lung to provide optimal bioavailability (Poursina et al. 2016). However, for the local delivery of antibiotics for the treatment of pulmonary

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infection, prolonged drug retention in the lungs is required to achieve proper efficacy. For the efficacy of aerosol medications, several factors including inhaler formulation, breathing operation (inspiratory flow, inspired volume, and end-inspiratory breath hold time), and physicochemical stability of the drugs (dry powder, aqueous solution, or suspension with or without propellants), along with particle characteristics, should be considered (Labiris and Dolovich 2003a, b).

Microparticles (MPs) and nanoparticles (NPs), including micelles (Mahajan and Mahajan 2016), liposomes (Bhardwaj et al. 2016), solid lipid NPs (Ji et al. 2016), inorganic particles (Seydoux et al. 2016), and polymeric particles (Oliveira et al. 2017) have been prepared and applied for sustained and/or targeted drug delivery to the lung. Although MPs and NPs were prepared by various natural or synthetic polymers, poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) particles have been preferably employed owing to their biocompatibility and biodegradability (Kumari et al. 2010; Mohamed and van der Walle 2008; Na et al. 2007). Polymeric particles retained in the lungs can provide high drug concentration and prolonged drug residence time in the lung with minimum drug exposure to the blood circulation (Harush-Frenkel et al. 2010). This review focuses on the characteristics of PLA/PLGA particles as carriers for pulmonary drug delivery, their manufacturing techniques, and their current applications for inhalation therapy.

Polymeric particles for pulmonary delivery

The preparation and engineering of polymeric carriers for local (Tables 1 and 2) or systemic delivery (Table 3) of drugs to the lung is an attractive subject. In order to provide the proper therapeutic efficiency, drug deposition in the lung as well as drug release are required, which are influenced by the design of the carriers and the degradation rate of the polymers (Ali 2010). Different varieties of natural polymers including cyclodextrin, albumin, chitosan, gelatin, alginate, and collagen or synthetic polymers including PLA, PLGA, polyacrylates, and polyanhydrides are extensively used for pulmonary applications (Abdelaziz et al. 2018). Natural polymers often show a relatively short duration of drug release, whereas synthetic polymers are more effective in releasing the drug in a sustained profile from days to several weeks (Rytting et al. 2008). Synthetic hydrophobic polymers are commonly applied in the manufacture of MPs and NPs for the sustained release of inhalable drugs (Abdelaziz et al. 2018; Ungaro et al. 2012).

PLA/PLGA polymeric particles

PLA and PLGA are the most commonly used synthetic polymers for pharmaceutical applications (Campardelli et al. 2016; Panyam and Labhasetwar 2003). They are approved materials for biomedical applications by the Food and Drug Administration (FDA) and the European Medicine Agency (Campardelli et al. 2016; Ernst et al. 2018). Their unique biocompatibility and versatility make them an excellent carrier of drugs in targeting different diseases (Ernst et al. 2018). The number of commercial products using PLGA or PLA matrices for drug delivery system (DDS) is increasing, and this trend is expected to continue for protein, peptide, and oligonucleotide drugs (Mohamed and van der Walle 2008). In an in vivo environment, the polyester backbone structures of PLA and PLGA go through hydrolysis and produce biocompatible ingredients (glycolic acid and lactic acid) that are eliminated from the human body through the citric acid cycle. The degradation products do not affect normal physiological function. Drug release from the PLGA or PLA particles is controlled by diffusion of the drug through the polymeric matrix and by the erosion of particles due to polymer degradation (Anderson and Shive 1997). PLA/PLGA particles often show a three-phase drug release profile with an initial burst release, which is adjusted by passive diffusion, followed by a lag phase, and finally a secondary burst release pattern (Amatya et al. 2013; Rytting et al. 2008). The degradation rate of PLA and PLGA is modulated by pH, polymer composition (glycolic/lactic acid ratio), hydrophilicity in the backbone, and average molecular weight; hence, the release pattern of the drug could fluctuate from weeks to months (Alexis 2005; Campardelli et al. 2016). Encapsulation of drugs into PLA/PLGA particles afford a sustained drug release for a long time ranging from 1 week to over a year, and furthermore, the particles protect the labile drugs from degradation before and after administration (Hang et al. 2015). In PLGA MPs for the co-delivery of isoniazid and rifampicin, free drugs were detectable in vivo up to 1 day, whereas MPs showed a sustained drug release of up to 3–6 days (Dutt and Khuller 2001). By hardening the PLGA MPs, a sustained release carrier system of up to 7 weeks in vitro and in vivo could be achieved. This study suggested that PLGA MPs showed a better therapeutic efficiency in tuberculosis infection than that by the free drug.

Large porous microparticles

Inhalable PLA/PLGA MPs have been widely studied with the aim to find strategies for the prolonged release of drugs in the lung. The inhalable particles need to be small for appropriate lung deposition, but this may result in low drug encapsulation into MPs. The low drug content may require frequent administrations to achieve maximal drug concentration in the lung, which may cause the accumulation of incompletely degraded polymers in the lung and subsequent adverse effects (Abdelaziz et al. 2018). Therefore,

Table 1 Inhalable poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) microparticles (MPs) for local delivery of drugs to the lung

Particles	Drug	Indication	Preparation Technique	Excipients	Particle properties and outcome	References
Large porous PLA/PLGA MPs	Montelukast	Asthma	Double emulsion-evaporation (w/o/w)	PEI-1	MMAD: 1.59–2.51 µm EE:75.7–89.3%	Patel et al. (2017a)
PLA MPs	Rifampicin	Pulmonary infection	Electrospray	PEC	MMAD: 4–5 µm Sustained release	Priemel et al. (2018)
Large porous PLGA MPs	Montelukast and heparin	Asthma	Double emulsion-evaporation	PEI	EE: 66.8% for montelukast Heparin adsorption efficiency: 91.7% Sustained drug release	Patel et al. (2017b)
Homogenous PLGA MPs	Rifampicin	Tuberculosis	Single emulsion-evaporation (o/w) with glass beads	PVA, PEI	Particle size: 2–3 µm Sustained release at 7 days	Liu et al. (2016)
Porous PLGA MPs	Doxorubicin and miR-519c	Lung cancer	Double emulsion-evaporation (w/o/w)	Ammonium bicarbonate	MMAD < 10 µm Sustained release and good anti-tumor efficacy	Wu et al. (2016)
PLA/PLGA MPs	5-fluorouracil	Lung cancer	Spray drying	–	Particle size: 1.2–1.5 µm	Hitzman et al. (2006)
Large porous PLGA MPs	Doxorubicin	Metastatic lung cancer	Double emulsion-evaporation (w/o/w)	PEMA, Ammonium bicarbonate	Particle size: 14.1 µm MMAD: 3.6 µm Good phagocytosis escapement Retention for 14 days in mice lung	Kim et al. (2012)
Large porous PLGA MPs	Doxorubicin and TRAIL	Metastatic lung cancer	Double emulsion-evaporation (w/o/w)	PEMA, Ammonium bicarbonate	Particle size: 11.5 µm EE: 86.5% (doxorubicin), 91.8% (TRAIL) Sustained release in 7 days and retention for 7 days in mice lung Proper anti-tumor effect	Kim et al. (2013)
Large porous PLGA MPs	Budesonide	Asthma	Double emulsion-evaporation (w/o/w)	PVA, Ammonium bicarbonate	Particle size: 6.4–9.2 µm MMAD: 2.5–6.4 µm Density: 0.7–0.98 g/cm^3 Pore size: 0.7–1.5 µm EE: 56–76%	Oh et al. (2011)
PLGA MPs	PGE1	Pulmonary arterial hypertension	Double emulsion-evaporation	PVA, PEI	Particle size: 7–22 µm MMAD: 2.5–3.5 µm PDI: 1.5–5.2 Density: 0.1–0.45 g/cm^3 FPF: 50.9–63.2% EE: 61.2–99% Bioavailability: 82-96%	Gupta and Ahsan (2011)
PLA MPs	Isoniazid and Rifabutin	Tuberculosis	Spray drying	–	Particle size: 5 µm MMAD: 3.6 µm FPF: 78.9% Yield > 60%	Muttil et al. (2007)
PLGA MPs	Capreomycin	Tuberculosis	Solid in o/w solvent diffusion-evaporation and Spray drying	Sodium oleate	Particle size: 11.4–17 µm MMAD: 6.7–9.1 µm EE: 89–90%	Schoubben et al. (2010)

Table 1 (continued)

Particles	Drug	Indication	Preparation Technique	Excipients	Particle properties and outcome	References
Large porous PLGA MPs	Doxorubicin and p53 gene	Lung cancer	Double emulsion-solvent evaporation (w/o/w)	Ammonium bicarbonate	Particle size: 21.1–26.6 µm EE: 88.2% (doxorubicin), 36.5% (plasmid) Enhanced in vitro anti-tumor and apoptosis	Shi et al. (2014)
PLGA MPs	PGE1	Pulmonary arterial hypertension	Double emulsion-evaporation (w/o/w)	HPβCD, PVA	Particle size: 8.5–14.5 µm MMAD: 0.7–5.5 µm Tapped density: 0.1–0.4 g/cm^3 PDI: 0.1–1.7 FPF: 35–92% Bioavailability: 67–91%	Gupta et al. (2011)
PLGA MPs	Rifapentine	Tuberculosis	Single emulsion-evaporation (o/w) and spray drying	PVA	MMAD: 2.4–3.0 µm Span ~ 2 FPF: 52–57% ED: 81–86%	Parumasivam et al. (2016)
Large porous PLGA MPs	Cinaciguat	Pulmonary hypertension	Single emulsion-evaporation (o/w)	PVA, PVP, Pluronic F127	MMAD: 4.8-6.2 µm FPF: 19.8–36% Retention > 36 h Sustained drug release	Ni et al. (2017)
PLGA MPs	Levofloxacin	Cystic fibrosis	Double emulsion-evaporation (w/o/w) with a membrane homogenization	Lauric acid, PVA	ED: 85.0% FPF: 30.2% MMAD: 7.1 µm Sustained-release: 75% in 72 h	Gaspar et al. (2019)
Large porous PLGA MPs	Curcumin	Cystic fibrosis	Double emulsion-evaporation (w/o/w)	PVA	Particle size > 10 µm MMAD: 3.12 µm FPF: 13.41% 71% release in 9 h	Hu et al. (2018)

MMAD mass median aerodynamic diameter, *ED* emitted dose %, *FPF* fine particle fraction %, *EE* encapsulation efficiency %, *PDI* polydispersity Index, *PVP* polyvinyl pyrrolidone, *PVA* polyvinyl alcohol, *HPβCD* hydroxypropyl-β-cyclodextrin, *PEMA* poly(ethylene-alt-maleic anhydride), *TRAIL* tumor necrosis factor-related apoptosis inducing ligand; PGE1, prostaglandin E1, *PEI* polyethyleneimine; *PEC* polyethylene carbonate, *PEG* polyethylene glycol

good porosity of the MPs is a desired feature for inhalation (Ungaro et al. 2006).

Large porous MPs (LPMs) demonstrate a sophisticated formulation to improve deep lung localization and avoid macrophage clearance (Fig. 1). They are light particles with ideal characteristics for pulmonary delivery, including large geometric diameter (5–30 µm), low density (< 0.4 g/cm^3), and acceptable aerodynamic diameter (1–3 µm) (Edwards et al. 1998). The numerous pores in LPMs make them light enough to ensure their deep lung deposition through inhalation. However, MPs with geometric diameters < 5 µm are susceptible to aggregation through van der Waals force. This causes some of the drugs to be retained in the device, resulting in a lower yield of drug delivery to the lungs. In addition, 1–3 µm particles are phagocytosed by macrophage clearance in the lung, thus, decreasing their activity (Patton and Byron 2007; Ungaro et al. 2012). Alveolar macrophages cannot capture large MPs with geometric diameters ≥ 20 µm; hence, there is a prolonged residence time in the lung. This implies that light particles as well as large ones (5–30 µm) are highly desirable for drug delivery into deep lungs. Different types of porogens have potentials for the preparation of LPMs including extractable porogens (pluronics), effervescent porogens (ammonium bicarbonate), osmogens (cyclodextrins), and gas bubbles (hydrogen peroxide/catalase) (Abdelaziz et al. 2018). Extractable porogens and osmogens manifest the drawback of drug leakage through pores because of aqueous channels formed within polymeric microspheres. Effervescent porogens are preferred to minimize drug loss and improve the encapsulation efficiency. Kim et al. prepared doxorubicin-encapsulated large porous PLGA MPs (DOX-LPM) by a water-in-oil-in-water (w/o/w) double emulsion-evaporation technique using ammonium bicarbonate as a gas-foaming porogen (Kim et al. 2012).

Table 2 Inhalable poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) nanoparticles (NPs) for local delivery of the drugs to the lung

Particles	Drug	Indication	Preparation technique	Excipients	Particle properties and outcome	References
PEG-PLGA NPs	Ibuprofen	Cystic fibrosis	Emulsion- evaporation	PEG, Polyaspartamide	Particle size: 126.3–186.8 nm PDI: 0.187–0.218 EE: 55.7–82.2%	Craparo et al. (2016)
Mannosylated PEG-PLA/PLGA NPs	Surfactant protein A	Pulmonary infectious	Nanoprecipitation	PEG, mannose	Particle size: 140 nm PDI: 0.114 Increases in vitro & in vivo macrophage uptake	Ruge et al. (2016)
PLGA nanocomposite	Rifampicin	Tuberculosis	Spray drying	Mannitol	Particle size: 213 nm (NPs), 2.1–3.2 µm (MPs) In vivo uptake by alveolar macrophages in the lungs	Ohashi et al. (2009)
PLGA NPs	Tobramycin	Cystic fibrosis	Spray drying	–	Spherical hollow porous particles	Geller et al. (2007)
PLGA Nanocomposite	Colistin	Cystic fibrosis	Emulsion-solvent diffusion	PVA, chitosan, lactose, mannitol	Particle size: 267 nm PDI: 0.15–0.18 EE: 63% Prolonged efficacy	d'Angelo et al. (2015)
Magnetic-PEG-PLGA NPs	SiRNA	Lung cancer	Double emulsion- solvent diffusion	PEG	Lower gene expression of telomerase	Fekri Aval et al. (2016)
PLGA Nanocomposite	Rifampicin	Tuberculosis and lung cancer	Emulsion-evaporation	PVA, arginine, leucine	Particle size: 190–207 nm (NPs), 8.2–11.5 µm (nanocomposite) MMAD: 0.65–11 µm FPF: 13.4–32.63% Yield: 33–68% EE: 43–65%	Takeuchi et al. (2017)
PLGA NPs	Levofloxacin	Pulmonary *P. aeruginosa* biofilm infections	Single and double emulsion-evaporation	PVA, PEG, Lecithin, Tyloxapol, Chitosan	Single emulsion: 200–240 nm, EE 15–23% Double emulsion: 110–360 nm, EE 6–22% Multi-phase double emulsion: 170–720 nm, EE 4–11% Good antibacterial activity	Cheow and Hadinoto (2010)
PLGA NPs/MPs	Tobramycin	Cystic fibrosis	Double emulsion- solvent diffusion	PEG, 7-amino-4-methyl-3-coumariny lacetic acid	EE: 2.4–3.6% Particle size: 896–902 nm, 228–233 nm	Ernst et al. (2018)

Table 2 (continued)

Particles	Drug	Indication	Preparation technique	Excipients	Particle properties and outcome	References
PLGA NPs	Ciprofloxacin	Cystic fibrosis	Nanoprecipitation	Pluronic F68	Particle size: 190.4 nm PDI: 0.089 EE: 79%	Türeli et al. (2017)
PLGA NPs	Ciprofloxacin	Cystic fibrosis	Nanoprecipitation	Pluronic SDS	Particle size: 145.2–979.8 nm PDI: 0.05–1.0 EE > 65%	Türeli et al. (2016)
PLGA NPs	Ethionamide	Tuberculosis	Solvent evaporation	PVA, mannitol	Particle size: 225.7 nm PDI: 0.216 MMAD:1.8 µm FPF: 94.38% ED: 97.22% 95% release in 24 h	Debnath et al. (2017)
DOTAP-modified PLGA NPs	siRNA	Severe lung diseases	Spray drying	PVA, Mannitol, Lactose, Trehalose	Smooth/raisin particles MMAD: 2.2–5.6 µm Low water content: 0.78% w/w Yield: 19.3–56.4%	Jensen et al. (2010)
PEG-PLGA nanocomposite	pDNA	Cystic fibrosis	Double emulsion-solvent evaporation (w/o/w)	PEI, Lactose	Particle size: 166–246 nm PDI: 0.216–0.092 MMAD: 3.8–6.6 µm FPF: 17.4–34.2% Enhanced luciferase expression	Kolte et al. (2017)
PLGA NPs	Ethionamide	Tuberculosis	Emulsion- evaporation	PVA	Particle size: 225.7 nm PDI: 0.216 MMAD: 1.79 µm FPF: 4.38% ED: 97.22% 90% release in 24 h	Debnath et al. (2017)
PEG-PLA NPs	–	Lung diseases	Solvent displacement	PEG, Stearylamine, Tween 80	Particle size: Anionic NPs: 129.3 nm Cationic NPs: 141.3 nm	Harush-Frenkel et al. (2010)

MMAD mass median aerodynamic diameter, *ED* emitted dose %, *FPF* fine particle fraction %, *EE* encapsulation efficiency %, *PDI* polydispersity Index, *PVP* polyvinyl pyrrolidone, *PVA* polyvinyl alcohol, *PEI* polyethyleneimine, *PEG* polyethylene glycol, *DOTAP* dioleoyltrimethylammoniumpropane; *SDS* sodium dodecyl sulfate

Table 3 Inhalable poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) particles for peptides, proteins, genes, or other systemic drug delivery systems

Particles	Drug	Indication	Preparation technique	Excipients	Particle properties and outcome	References
PLGA MPs	Rosiglitazone	Diabetes and pulmonary arterial hypertension	Double emulsion-evaporation (w/o/w)	PVA, PEI	MMAD: 6.92 µm Release: 87.9% in 24 h	Rashid et al. (2018)
Large porous PLGA MPs	Insulin	Diabetes	Double emulsion-evaporation	HPβCD, phenolphthalein, Tween 80, PVA	Particle size: 25.1–31.4 µm MMAD: 10–19 µm EE: Insulin → 52–100% EE: HPβCD → 24–60%	Ungaro et al. (2006)
Albumin-coated porous hollow PLGA MPs	Palmitylacylated exendin-4	Diabetes	Double emulsion-evaporation (w/o/w)	PEMA, HPβCD, NaCl	Particle size: 17.2 µm MMAD: 3.2 µm	Kim et al. (2011)
PLGA MPs	BSA	Vaccine delivery	Supercritical CO_2-spray drying	L-leucine	Particle size: 9.6–10.6 µm MMAD: 1.7–3.5 µm FPF: 25.4–43.4% ED: 95.3–99.6%	Tavares et al. (2017)
PEG-PLGA NPs	DNA, Protein EPO	–	Emulsion-solvent evaporation	PVA, PEG	Particle size: 160–191 nm PDI:0.07–0.14 Bi-phasic drug release	Menon et al. (2014)
Hallow PLGA MPs	DNA	–	Double emulsion-evaporation (w/o/w)	Pluronic L92	Particle size: 7.85 µm Span: 1.5 MMAD: 3.8 µm Density: 0.24 g/cm^3 EE: 15–28%	Mohamed and van der Walle (2006)
PLGA-chitosan MPs/NPs	Calcitonin	Osteoporosis	Emulsion-solvent diffusion	Span 80, PVA, Chitosan	Particle size: 660 nm (NPs), 7.07 µm (MPs)	Yamamoto et al. (2005)

MMAD mass median aerodynamic diameter, *ED* emitted dose %; fine particle fraction %, *EE* encapsulation efficiency %, *PDI* polydispersity Index, *PVP* polyvinyl pyrrolidone, *PVA* polyvinyl alcohol, *HPβCD* hydroxypropyl-β-cyclodextrin, *PEI* polyethyleneimine, *PEG* polyethylene glycol, *SDS* sodium dodecyl sulfate, *PEMA* poly(ethylene-alt-maleic anhydride), *BSA* bovine serum albumin, *EPO* erythropoietin

The DOX-LPM with a geometric diameter of 14 µm and aerodynamic diameter of 3.6 µm showed successful aerodynamic behavior—they were deposited in the lungs and remained for up to 2 weeks. In a mouse model of B16F10 melanoma metastasis, there was a significant anti-tumor effect in the DOX-LPM-treated group when compared with the untreated group.

Nishimura et al. constructed porous and non-porous PLGA MPs for inhalation by using a single-step emulsion-evaporation method (Nishimura et al. 2017). They prepared porous particles having a geometric diameter of 5–10 µm with very low tapped density (0.04 g/cm^3). The particles with a geometric diameter of 5 µm showed lower emitted dose and higher fine particle fraction (FPF) than those with a geometric diameter of 10 µm. PLGA MPs that were prepared in the presence of Tween 85 were non-porous, and they had the highest emitted dose with the lowest FPF, indicating a weak aerosol performance. From this observation, it was suggested that an electrostatic attraction force between the porous particles and the capsules decreased the emitting efficiency of the MPs from the capsules. Their study showed that the aerodynamic diameter of the porous PLGA particles was approximately 5 µm with an approximate FPF value of 40–65%; however, the aerodynamic diameter of the non-porous particles was approximately 14 µm with a lower FPF (< 20%). These results indicate that the porous particles had unique internal structures and proper aerodynamic properties attributable to the spontaneous emulsion preparation. Therefore, porous PLGA MPs can provide a suitable aerodynamic diameter for inhalation and deposition in the lungs

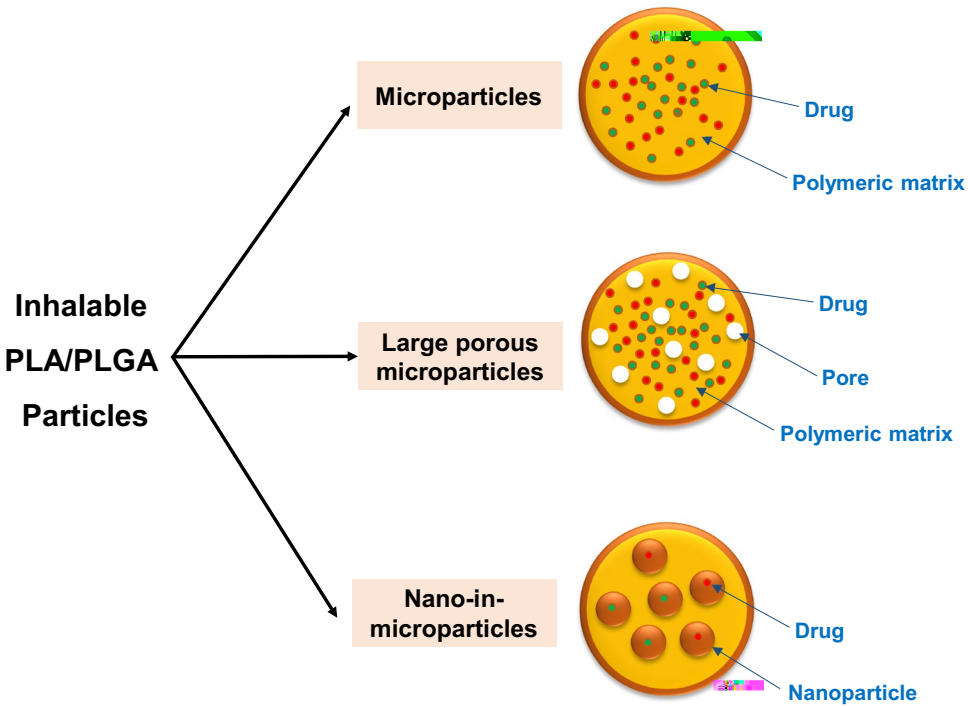

Fig. 1 Different types of polymeric poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) particles as carriers for pulmonary drug delivery

to achieve high and efficient delivery of therapeutic agents to the lung.

Nano-in-microparticles (Nanocomposites)

NPs as polymeric carriers for respiratory delivery have the ability to enter the intracellular compartments and evade the alveolar macrophages and mucociliary clearance mechanisms, resulting in enhanced bioavailability and prolonged drug residence time (Rogueda and Traini 2007). Moreover, NPs can be modified for drug targeting to a specific lung tissue and cell populations (Hillaireau and Couvreur 2009). The interaction of NPs with lung tissue often depends on the size and surface charge of the particles. Hence, adequate engineering of particles at the nanosize level to produce NPs with different features (size, morphology, and zeta-potential) is an important aspect with excipient selection and formulation design (Lai et al. 2009).

However, the pulmonary delivery of NPs has two major drawbacks: NPs, with the exception of particles < 50 nm, are generally exhaled upon inhalation, and they are prone to aggregation owing to their high surface energy (Rogueda and Traini 2007; Yang et al. 2008). To overcome these drawbacks, the most widely employed inhalation approach is the nebulization of aqueous dispersions of NPs. However, this approach can generate problems with instability of the nanosuspensions, such as aggregation and/or drug leakage (Dailey et al. 2003). These problems can be overcome by applying NPs as dry powder. Direct drying of NPs suspensions has been shown to have some success in generating dry powders composed of agglomerated PLGA NPs, but with this approach, it may be difficult to preserve the integrity of NPs, including in terms of inappropriate overflow and aerosolization properties (Ungaro et al. 2012). As an alternative approach, particles obtained by the embedding of drug-loaded PLGA NPs within sugar MPs have been suggested to improve the formulation stability and aerodynamic properties of the entrapped NPs (Al-Qadi et al. 2012; Sham et al. 2004). The NPs-incorporated MPs, also termed nano-in-microparticles, are designed to release primary NPs from inert microcarriers into lung lining fluid after reaching the alveolar surface (Abdelaziz et al. 2018; Ungaro et al. 2012).

Preparation of inhalable PLA/PLGA particles

Several studies have investigated the various preparation methods for polymeric MPs/NPs and their applications for pulmonary DDS (Bailey and Berkland 2009; Menon et al. 2014; Mundargi et al. 2008). The conventional methods used in the production of NPs and MPs involve single/double emulsion-solvent evaporation, spray freeze drying, spray drying, supercritical fluid drying, and coacervation (Fig. 2). Each process has its advantages as well as limitations (Campardelli et al. 2016; Emami et al. 2018a).

Single/double emulsion-solvent evaporation technique

Emulsion-solvent evaporation method has been extensively applied to prepare biodegradable polymeric carriers for

respiratory drug delivery (Patil and Sarasija 2012). This technique involves the preparation of oil/water emulsion and subsequent removal of the organic phase through evaporation procedure. The oil phase diffuses out of the polymer matrix into the water phase and finally is evaporated, producing drug-encapsulated polymeric MPs/NPs (Patil and Sarasija 2012). One of the easiest procedures used in the preparation of MPs and NPs is the single emulsion-solvent evaporation method. Hydrophobic drugs are dissolved with polymer in an organic phase, which are then emulsified in an aqueous phase. Different types of emulsions, such as oil in water (o/w), oil in oil (o/o), or water in oil (w/o), were prepared by exposure to a high shearing energy, including homogenizing, ultrasonication, or milling. The organic phase is evaporated under vacuum or low pressure by the extraction method. The tailored particle is then lyophilized for long-term storage (Lee et al. 2016).

For hydrophilic drugs, the double w/o/w emulsion–solvent evaporation process has been widely employed. However, this technique often results in low drug loading owing to the difficulty in controlling the migration of hydrophilic drugs from the inner to the outer aqueous phase. Some formulation approaches have been applied to enhance the incorporation efficiency of hydrophilic drugs including the adjustment of aqueous phase pH, ion-pairing using counter ions to drug molecule, and addition of fatty acid to organic phase (Govender et al. 1999; Holmkvist et al. 2016). For the preparation of PLGA MPs of a water-soluble drug—levofloxacin, Gaspar et al. added fatty acid (lauric acid) to the oil phase or the saturated aqueous phase with levofloxacin to avoid the escape of the drug from the organic phase in the w/o/w emulsion, resulting in a higher drug encapsulation when compared with the conventional double emulsion method (Gaspar et al. 2019). Although the addition of lauric acid resulted in a larger particle size and no sustained release, the saturation of the aqueous phase with levofloxacin resulted in an appropriate particle size for inhalation (~5 μm) and a controlled drug release.

Spray drying

Spray drying (SD) is the commonly used particle engineering method for the preparation of particles with appropriate size and morphology for pulmonary delivery (Muttil et al. 2007; Nandiyanto and Okuyama 2011). The SD method includes three phases comprising of atomization,

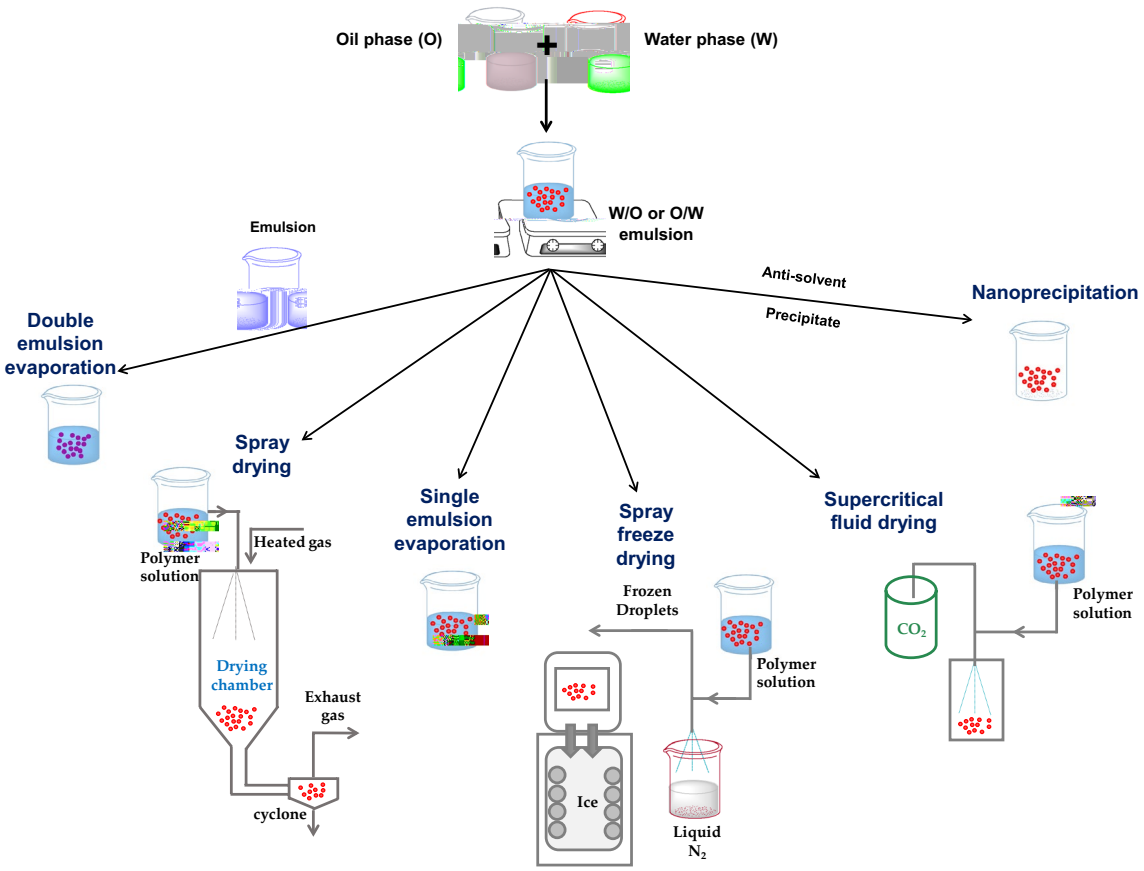

Fig. 2 Preparation techniques of poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) particles for pulmonary drug delivery

drying in the hot chamber, and separation of particles. The feeding solution is atomized through nozzles into a drying chamber. The generation of polymeric droplet and subsequent dehydration are performed in a chamber with hot air flow. The dried powders are transferred into a cyclone (Faghihi et al. 2014; Nandiyanto and Okuyama 2011; Ramezani et al. 2013). Yamamoto et al. prepared insulin-loaded PLGA nanocomposite particles for inhalation by the spray-fluidized bed granulation method (Yamamoto et al. 2007). At first, PLGA NPs were prepared, insulin was encapsulated, and finally nanocomposites were prepared. Briefly, PLGA and 6-coumarin were dissolved in an organic solvent mixture, and the resulting solution was injected into polyvinylalcohol solution. The evaporation of the organic solvent resulted in NPs with an average size of 250 nm. Next, lyophilized powder and mannitol were suspended in the aqueous phase and spray-dried in a fluidized bed granulation system. In this method, the feeding solution was sprayed into the hot chamber, and the spray-dried particles are dispersed into the granulation zone by a rinsing pulsed air jet. Finally, NPs were granulated by the coalescence of wet particle collision, which resulted in the formation of nanocomposites. The average aerodynamic diameter of the tailored particles was reported to be 1–10 μm, as measured by cascade impaction. The nanocomposites exhibited greater aerodynamic performance than that by freeze-dried NPs. The nanocomposite granules demonstrated preferable physicochemical characteristics for inhalation and lung dispersion in both in vitro and in vivo studies.

Spray freeze drying

Spray freeze drying (SFD) method combines the advantages of both SD and freeze-drying techniques (Abdelaziz et al. 2018). Furthermore, this method can overcome the limitations of SD method for heat sensitive molecules. In SFD process, a feeding solution is atomized through a nozzle into a vapor above liquid nitrogen, frozen in liquid nitrogen, and subsequently lyophilized in a freeze dryer (Emami et al. 2018a, b). Ali and Lamprecht studied the SFD procedures used for the synthesis of inhalable nanocomposite microcarriers suitable for pulmonary deposition (Ali and Lamprecht 2014). In this study, spray freeze-dried MPs with an aerodynamic diameter of 3.0 ± 0.5 μm were prepared, and they had larger specific surface areas (67–77 m^2/g) and lower densities (0.02 g/cm^3) than those of the MPs similarly prepared by SD method. The SFD showed better performance than SD in terms of maintaining the particle size of NPs following reconstitution. Furthermore, SFD provided highly porous MPs with proper aerodynamic diameters for inhalation.

Supercritical fluid drying

A particle generation process using supercritical fluids (SCF) has been proposed for the preparation of polymeric particles by dehydration in the absence of extreme temperature (Campardelli et al. 2012; Tavares et al. 2017). SCF drying (SCFD) uses materials such as carbon dioxide or methanol above its critical pressure and temperature. The critical temperature of a liquid is the temperature at which its vapor cannot be liquefied. The pressure that is required to condense a gas at its critical temperature defines its critical pressure. SCF above its critical point exhibits the appropriate characteristics of gas and liquid, including the flow characteristics of a gas (low viscosity) and the solubility of a solute. SCF has the potential to penetrate within materials because they do not exhibit any surface tension, and the solvent power is proportional to their density. SCFD is a tunable procedure that can control the density of SCF and the solubility of a solute by altering the pressure or temperature used during the process (Emami et al. 2018b). Carbon dioxide is the most frequently used SCF because it is nontoxic, inexpensive, and nonflammable. It also has a low critical point (31.1 °C and 73.8 bar), which makes it suitable for thermo-sensitive drugs at minimal procedure cost (Tavares et al. 2017).

Tavares et al. constructed dry powder PLGA MPs by supercritical carbon dioxide-assisted SD (SCF-SD) for vaccine delivery to the lung (Tavares et al. 2017). Vaccine formulations were prepared using bovine serum albumin (BSA) as a model vaccine in the presence of L-leucine. The aerodynamic performance of dry powder inhaler was characterized using the Andersen cascade impactor. Tailored BSA-PLGA particles showed fine particle fraction of 43.4% with an aerodynamic diameter of 1.7–3.5 μm, which represents the proper characteristics for inhalation. The authors concluded that the addition of L-leucine in BSA formulation as a dispersibility enhancer could overcome the stress in SCF-SD method. In addition, they demonstrated that the SCF-SD process is appropriate for the preparation of PLGA dry powder inhaler.

Nanoprecipitation

Nanoprecipitation involves crystallization and precipitation using anti-solvent jets. Crystalline drug particles with proper size distribution are produced by controlled crystallization. Inhalable NPs can be prepared by rapid precipitation using anti-solvents. In addition, ultrasonic radiation has been applied to control precipitation. Various drugs against asthma were prepared using the sonocrystallization technique (Patil and Sarasija 2012). Recently, Türeli et al. constructed ciprofloxacin-loaded PLGA NPs against *Pseudomonas aeruginosa* infections in cystic fibrosis (Türeli et al. 2017). PLGA NPs were prepared by an optimized

nanoprecipitation method using Microjet Reactor. The tailored particles had a particle size of 190.4 ±

more efficiently present antigen to macrophages by 100- to 1000-fold and offer superior immunization in comparison with the soluble antigen (Lu et al. 2007).

Protein and peptide delivery

The therapeutic use of biomolecules has been substantially increased by the development of biotechnology techniques, and various peptides and proteins have been shown to have therapeutic potential against various diseases. However, these biomolecules have therapeutic limitations owing to chemical and physical instability, high susceptibility to proteolytic degradation, and short circulation half-life requiring multiple injections (Mundargi et al. 2008; Song et al. 2017).

by FDA in 1990 for the treatment of acute respiratory distress syndrome and Arikace® (drug: amikacin) approved by FDA in 2018 for the treatment of *Mycobacterium avium* complex lung disease (Paranjpe and Muller-Goymann 2014; Shirley 2019). However, liposomes are prone to instability problem with the possibility of drug leakage during storage. Compared with liposome, polymeric MPs and NPs present higher structural integrity providing enhanced stability, higher drug loading, and prolonged drug release (Abdelaziz et al. 2018). Therefore, biodegradable PLA/PLGA-based MPs and NPs are highly beneficial carrier option for both local and systemic inhalation therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

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