Journal of Pharmaceutical Investigation (2019) 49:381–404
https://doi.org/10.1007/s40005-019-00446-y

Online ISSN 2093-6214
Print ISSN 2093-5552

REVIEW

Meeting the unmet: from traditional to cutting-edge techniques for poly lactide and poly lactide-co-glycolide microparticle manufacturing

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Received: 15 March 2019 / Accepted: 24 April 2019 / Published online: 29 April 2019

Abstract

Background Polylactides (PLA) and poly lactide-co-glycolides (PLGA) undoubtedly are among the major drivers in the pharmaceutical market. Their relevance in pharmaceutics and biomedicine is well established in light of their sustainability, safety, tunable biodegradability, and versatility. However, polymer degradability and plasticity can somehow restrain industrial developability of PLA and PLGA formulations, especially in the form of microparticles (MP).

Area covered This review wants to deal with the known manufacturing issues of PLA/PLGA MP, debating the potential contribution of modern and cutting-edge manufacturing technologies to the solution of unmet production needs. Technological and regulatory aspects will be considered outlining the potential role of advanced manufacturing techniques in the advancement of PLA/PLGA MP production processes.

Expert opinion The multifaceted complexity of PLA/PLGA MP manufacturing processes demands adequate standardization and updated guidelines covering the so far unmet industrialization requirements. Novel and evolving manufacturing technologies will surely support the future development of bench-to-production plant transfer for such products. Careful evaluation of production costs is demanded in order to ensure process sustainability and patient's outreach.

Keywords Microparticles · PLA · PLGA · Microparticle manufacturing · Advanced manufacturing technology

Introduction

A comprehensive history outline and a description of basic properties of polylactide (PLA) and polylactide-co-glycolide (PLGA) polymers and microparticle (MP) preparation are broadly available in literature (Lee et al. 2016; Swider et al. 2018) and therefore this review will not go back to the fundamentals on such materials and drug delivery systems but rather it will try to dig into the aspects impacting manufacturing of polyester-based MP and the new advanced technologies sought by industry. A particular emphasis will be given to those aspects enabling progress in the transfer to production scale of novel manufacturing techniques deemed to overcome the known limitations in the use of such polymers and the relative unmet issues.

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Strengths and weaknesses of PLA and PLGA polymers

PLA and PLGA polymers are shear thinning materials that, depending on their composition and molecular weight, can show different degree of plasticity and degradability. PLA polymers exist as D and L isomers according to lactic acid configuration, that leads to different polymer tacticity and therefore material properties (Baker et al. 2008; Shaver and Cameron 2010). As a result, while L-PLA is highly crystalline, D-PLA is completely amorphous. The isomerism of lactides influences also PLGA tacticity and physical state. Albeit mainly amorphous, L-PLGA and DL-PLGA polymers can show a certain degree of crystallinity depending on the lactide/glycolide ratio and stereoisomeric composition of the lactide monomers (Avgoustakis 2015). The knowledge of such properties is therefore important as crystallinity affects the rate of degradation and the mechanical properties of PLA and PLGA. As a consequence, the choice of proper polymers for manufacturing of PLA and PLGA MP should account for the insightful knowledge of these fundamental properties.

In fact, along with their recognized safety as FDA-approved parenteral materials, the undeniable attractiveness of such polymers in drug delivery is tightly bound to their tunable drug release behavior that grants sustained and extended drug delivery applications. The choice of copolymer composition and/or lactide isomer as well as polymer molecular weight consent to tailor MP degradation and drug release profile (Anderson and Shive 2012). However, this high versatility and workability is actually counterbalanced by polymer plasticity, which determines the PLA and PLGA attitude to undergo softening and unwanted degradation upon manufacturing and storage (Allison 2008). In fact, the tunable biodegradability of these polymers represents at the same time their strength and weakness as it makes them prone to acid- and base-catalyzed degradation. Such degradation has been found to occur even in MP formulations when basic or acidic drugs are being encapsulated (Selmin et al. 2012; D'Souza et al. 2014a, 2015). Naturally, these phenomena affect amorphous materials most. Since PLGA and PLA are generally low glassy polymers, interaction with other materials, such as excipients, solvents, drugs, and temperature can easily provoke plasticization and annealing of the solid matrix. Even though plasticization can be favorable to processing and the manufacturing of scaffolds and other devices, it can be detrimental to MP manufacturing and storage stability and today increased efforts are directed to identify effective stabilization strategies (Albertini et al. 2015; Benvenutti et al. 2018). Therefore, these features can represent a considerable bottleneck in the development of PLA and PLGA MP products. In fact, the susceptibility of these polymers to boundary conditions and the interaction with other materials, drugs included, makes PLA and PLGA MP manufacturing prone to high variability in the absence of a robust control over all process parameters that partially explains the lack of generic products in the market (Zhou et al. 2018). However, novel technologies with enhanced performances and stability, which will be herein discussed, may underpin remarkable advances in the manufacturing of these problematic products.

PLA and PLGA microparticles in the pharmaceutical market

To date, there are about 20 PLA/PLGA based products approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) mainly aimed to be administered by intramuscular or subcutaneous injection (Table 1) (Silverman et al. 2002; Wang et al. 2016; Tice 2017; Qi et al. 2018; CenterWatch 2019. Other products are to be inserted in the periodontal cavity (e.g., Arestin®) or by intra-articular injection (i.e., Zilretta®). The aim of using polyesters in these formulations are several and in particular PLA/PLGA consent to simplify the therapeutic schedule (i.e., reducing the administration frequency), to minimize drug concentration oscillation reducing side effects and to improve patient's adherence to the treatment. The low availability of PLA/PLGA based medicines can be mainly ascribed to the difficulties encountered during their development and industrial manufacturing. However, recently, two new formulations reached the USA market after FDA approval. Zilretta® are triamcinolone acetonide loaded MP for intra-articular injection in the treatment of knee pain in patients with osteoarthritis (Kaufman 2017, 2018a). Triptodur™, based on the use of triptorelin pamoate, was approved in 2017 for the treatment of central precocious puberty. This formulation is administered only twice yearly by intramuscular injection (2018b). In the European market, a triptorelin based formulation (Salvacyl® LP, Salvapar®, Moapar®) was approved in 12 countries from 2006 to 2014 for the treatment of severe sexual deviation (Debiopharm group; Briken et al. 2012). PLA/PLGA MP based technologies are being exploited for drug repurposing of commercial oral or extended release preparations as witnessed by the large number of completed clinical trials on risperidone based products and the ongoing efforts in several therapeutic areas (Table 2). These considerable research investments in such technologies somehow underpin the advantages of PLA/PLGA based long acting injectables (LAI) especially for the treatment of chronic pathological conditions. Unfortunately, these advantages are overweighed by the intrinsic complexity of such formulations as well as limited regulatory support. As a consequence, to date, no generic version of these products is available on the market even though patent protection of some of them has expired (e.g., Lupron® Depot). This can be explained by the difficulty in manufacturing PLA/PLGA MP obtaining perfectly reproducible characteristics such as drug loading and drug release profile. In fact, slight modifications of the manufacturing process can deeply affect MP properties and therefore treatment safety. There is also a lack of suitable tools to evaluate the impact of MP features on their performances (D'Souza et al. 2014b, c). That is why the FDA's Office of Generic Drug (OGD) supports research to develop in vitro-in vivo correlations and in vitro release testing methods (Schoubben et al. 2012; Leblanc 2018).

Conventional manufacturing technology

Lab-scale methods

Solvent evaporation and extraction

PLA and PLGA MP are often prepared by organic solvent evaporation/extraction from oil-in-water (o/w) or water-in-oil-in-water (w/o/w) emulsions (Schoubben

Table 1 FDA and EMA marketed microparticles based on PLA/PLGA (not intended to be fully exhaustive)

Brand name	API	Administration route	Indication(s)	Encapsulation technology	Encapsulation process	Approval/launched year
Arestin®	Minocycline HCl	Periodontal	Periodontal disease	NA	NA	2001
Bydureon®	Exenatide	Subcutaneous	Type 2 diabetes	Medisorb®	Solvent evaporation/extraction emulsion method	2012
Decapeptyl®, Decapeptyl® SR	Triptorelin acetate	Intramuscular	Prostatic cancer	Debio PLGA-2®	Oil-in-water emulsion method/phase separation	1986
Lupron® Depot, Enantone®, Prostap® SR	Leuprolide acetate	Intramuscular	Endometriosis Prostatic cancer	NA	Water-in-oil emulsion	1999 1989, 1996–1997
Lupron® Depot-PED, Enantone®, Prostap® SR	Leuprolide acetate	Intramuscular	Central precocious puberty	NA	Water-in-oil emulsion	2011
Pamorelin® LA, Trelstar® Depot, Trelstar® LA	Triptorelin pamoate/embonate	Intramuscular	Prostatic cancer	Debio PLGA-2®	Oil-in-water emulsion method/phase separation	2010, 2000, 2001
Parlodel® LAR	Bromocriptine	Intramuscular	Prolactin-secreting tumor	NA	Spray-drying	~ 1991
Risperdal® Consta™	Risperidone	Intramuscular	Schizophrenia, bipolar I disorder	Medisorb®	Solvent evaporation/extraction emulsion method	2003
Salvacyl® LP, Salvapar®, Moapar®	Triptorelin pamoate/embonate	Intramuscular	Severe sexual deviation in adult men	Debio PLGA-2®	Oil-in-water emulsion method/phase separation	2006–2014 (12 countries in Europe)
Sandostatin LAR	Octreotide	Subcutaneous	Acromegaly, severe diarrhea with metastatic carcinoma or with vasoactive intestinal peptide-secreting tumors	Medisorb®	Solvent evaporation/extraction emulsion method	1997
Signifor® LAR	Pasireotide pamoate	Intramuscular	Acromegaly, Cushing's disease	Novartis	NA	2014
Somatuline® Depot	Lanreotide	Intramuscular	Acromegaly	NA	NA	2007
Suprecur® MP	Buserelin acetate		Endometriosis	NA	Spray-drying	2002
Triptodur™	Triptorelin pamoate/embonate	Intramuscular	Central precocious puberty	Debio PLGA-2®	Oil-in-water emulsion method/phase separation	2017
Vivitrol®	Naltrexone	Intramuscular	Alcohol dependence Opioid dependence	Medisorb®	Solvent evaporation/extraction emulsion method	2006 2010
Zilretta®	Triamcinolone acetonide	Intra-articular	Osteoarthritis knee pain	NA	NA	2017

et al. 2009; Albertini et al. 2015; Casagrande et al. 2017). This technique has been developed at the end of the 1970s (Hu et al. 2017). Based on the nature of the active pharmaceutical ingredient (API), one can choose to use o/w or w/o/w emulsions (Jain 2000; Rosca et al. 2004; Lu and Park 2012; Kapoor et al. 2015; Lee et al. 2016; Swider et al. 2018). Commonly, o/w emulsion is used with hydrophobic API (Ricci et al. 2005; Giovagnoli et al. 2010), while w/o/w emulsion is preferred for hydrophilic API such as peptide and proteins to maximize drug

Table 2 PLA/PLGA MP based depot products under clinical investigation (not intended to be fully exhaustive)

Brand name	API	Route*	Indication(s)	Encapsulation technology	Description	Stage
Bydureon®	Exenatide	SC	Type 2 diabetes	Medisorb®	Effect of Bydureon on carotid atherosclerosis progression in T2DM	Phase 4
Copaxone® Depot	Glatiramer acetate	IM	Primary progressive multiple sclerosis	MAPI-pharma	A prospective, multicenter, single arm, open label, Phase IIa study to assess the safety and efficacy of once-a-month long-acting intramuscular injection of 40 mg glatiramer acetate (GA depot) in subjects with primary progressive multiple sclerosis (PPMS)	Phase 2
Copaxone® Depot	Glatiramer acetate	IM	Multiple sclerosis	MAPI-pharma	A prospective 1-year, open-label, two arms, multicenter, Phase IIa study to assess safety, tolerability and efficacy of once a month long-acting intramuscular injection of 80 or 40 mg glatiramer acetate (GA depot) in subjects with relapsing–remitting multiple sclerosis (RRMS)	Phase 1 Phase 2
Sandostatin® LAR	Octreotide	SC	Hereditary hemorrhagic telangiectasia Gastrointestinal hemorrhage Anemia	Medisorb®	An uncontrolled, pilot-study assessing the efficacy of octreotide long-acting release to decrease transfusion requirements and endoscopy frequency in patients with rendu-osler-weber and gastrointestinal bleeding	Phase 2
Sandostatin® LAR	Octreotide	SC	Angiodysplasia vascular Malformations Gastrointestinal hemorrhage anemia	Medisorb®	A multicenter, randomized, open-label clinical trial assessing the efficacy of octreotide in decreasing blood and iron requirements in patients with refractory anaemia due to angiodysplasias	Phase 2 Phase 3
Signifor® LAR	Pasireotide	IM	Neuroendocrine tumors Carcinoid Tumors	Novartis	Phase II study of Pasireotide LAR in patients with metastatic neuroendocrine carcinomas	Phase 2
Signifor® LAR	Pasireotide	IM	ACTH-producing pituitary tumour	Novartis	Pilot study of Pasireotide LAR treatment of silent corticotrophin pituitary tumors and effects on plasma levels of POMC	Phase 2
Vivitrol®	Naltrexone	IM	Opiate addiction	Medisorb®	Long-acting naltrexone for pre-release prisoners: a randomized trial of mobile treatment	Phase 3
Vivitrol®	Naltrexone	IM	Opioid use disorders	Medisorb®	Depot pharmacotherapies for opioid-dependent offenders: outcomes and costs	Phase 3

Table 2 (continued)

Brand name	API	Route*	Indication(s)	Encapsulation technology	Description	Stage
Vivitrol®	Naltrexone	IM	Opioid use disorders	Medisorb®	Long acting naltrexone for opioid addiction: the importance of mental, physical and societal factors for sustained abstinence and recovery	Phase 4
Vivitrol®	Naltrexone	IM	Opioid use disorders	Medisorb®	A feasibility study for testing the effects of extended-release naltrexone (Vivitrol) on recidivism and other participant outcomes in drug court settings	Phase 4
Vivitrol®	Naltrexone	IM	Opioid use disorders	Medisorb®	A strategy to improve success of treatment discontinuation in buprenorphine responders	Phase 3

**SC* subcutaneous, *IM* intramuscular

loading (Giovagnoli et al. 2004, 2005, 2010). In fact, it can be difficult to obtain high hydrophilic drug payload in PLA/PLGA MP. Briefly, polymer is solubilized in an organic solvent such as methylene chloride together with the hydrophobic API and emulsified under stirring or sonication in the aqueous phase containing the stabilizing agent (e.g., polyvinyl alcohol, PVA; hydroxypropylmethylcellulose, HPMC). Successively, MP hardening is achieved by evaporating the solvent under reduced pressure and increasing the temperature. In alternative, the organic solvent can be extracted by pouring the emulsion in a large volume of aqueous phase to favor the organic solvent diffusion in the continuous phase (Capan et al. 2003; D'Souza et al. 2013). Hydrophilic API are either solubilized in a minimum volume of water that is the inner aqueous phase of the w/o/w double emulsion (Giovagnoli et al. 2007) or directly suspended in the organic phase obtaining a solid-in-oil-in-water (s/o/w) emulsion (Giovagnoli et al. 2008). MP characteristics (i.e., dimensions, porosity, API content, release kinetics, degradation kinetics) depends on the polymer used and on preparation parameters such as the starting polymer concentration, o/w volume ratio, stabilizer nature and concentration, agitation conditions, and solvent evaporation rate (Lu and Park 2012). As evidenced in Table 1, the MP products existing in the market are essentially prepared using the emulsion technology. However, it is not clear how emulsion is obtained and therefore if this lab-scale method or the membrane emulsification technology described further on is employed.

Cryogenic solvent extraction

This technique has been developed to limit the exposure of sensitive peptides and/or proteins to the harsh conditions of the solvent evaporation/extraction method. In fact, protein exposure to the w/o interface and temperature used to evaporate the organic solvent can provoke denaturation (van de Weert et al. 2000; Bilati et al. 2005). Cryogenic solvent extraction consists in the nebulization of the suspension made of the protein in dichloromethane where PLA or PLGA has been solubilized above a beaker containing ethanol (Tracy 1998; Yeo et al. 2001). In particular, ethanol has been cooled using liquid nitrogen at a temperature lower that the freezing point of the suspension nebulized. The droplet will freeze coming in contact with the layer of liquid nitrogen present above the frozen ethanol and fall into ethanol bath. Successively, ethanol will be slightly warmed up thawing out dichloromethane that will diffuse in ethanol. As a result, MP will solidify encapsulating the protein. This strategy, namely ProLease® technology, has been applied in different marketed and non-marketed products (Johnson et al. 1997; Tracy 1998; Yaszemski et al. 2003).

Catalytic hydrolysis solvent removal

Besides dichloromethane, which is the solvent mainly used in the methods illustrated so far, ethyl acetate is an alternative. Its elimination from the o/w emulsion to achieve particle formation is obtained by catalytic hydrolysis in a HCl aqueous phase at about 30 °C.With respect to the

conventional extraction procedure, acidic hydrolysis of ethyl acetate granted a higher ketoprofen encapsulation efficiency (Lee et al. 2013). This process can have significative relevance with acidic API, since an acidic aqueous phase will limit their diffusion and loss in the continuous phase. Other papers used isopropyl formate (Im and Sah 2009) or methyl chloroacetate (Kim et al. 2007) as organic phase and their removal was carried out using ammonia solution that provoked solvent hydrolysis obtaining water-miscible formamide and isopropyl alcohol or chloroacetamide and methanol, respectively. As a result, the polymer precipitated encapsulating progesterone, used as a model API, with an encapsulation efficiency in the 64–97% range (Kim et al. 2007; Im and Sah 2009).

Coacervation

Coacervation is another technique used to produce PLA/PLGA MP. It is based on phase separation of the polymer (the coacervate) that coats the API particles. This process is commonly divided in three separate steps:

- Phase separation of the polymer that forms coacervate globules
- Adsorption of the coating polymer droplets on the API particle surface
- Solidification of the polymer around the API particles

In accordance with the triggering element that induces phase separation, different coacervation process can be individuated (i.e., non-solvent addition, temperature change, incompatible polymer addition, salting out, polymer–polymer interaction). However, in the case of PLA and PLGA, not all the different phase separation inducing events are applicable (Jain 2000; Yeo et al. 2001; Ye et al. 2010; Kapoor et al. 2015; Hu et al. 2017).

Non-solvent addition

Phase separation provoked by non-solvent addition is mainly employed to load water-soluble API but can also be used to encapsulate liposoluble API. Several parameters, such as polymer concentration and stirring rate, influence particle characteristics and non-solvent addition has to be slow to obtain a uniform polymer coating around the API particles (Jain 2000; Ding and Zhu 2018). The non-solvent must be selected to avoid API solubilization and it has to be miscible in the solvent used to solubilize the polymer. Examples of non-solvents that cause phase separation are silicone oil, vegetable oil, low molecular weight methacrylic polymers, which are called first non-solvents. Second non-solvents, used to solidify the polymer layer, can be hexane or petroleum ether (Thomasin et al. 1998; Yeo et al. 2001).

Salt addition

Salt addition is another strategy used to obtain phase separation of PLA/PLGA solubilized in a water miscible solvent, such as acetone or acetonitrile, together with the lipophilic API. This solution is then emulsified in water containing both the salting-out agent (e.g., calcium chloride, sucrose) and a stabilizer and is then diluted with an excess volume of water promoting acetone diffusion and particle solidification. This technique can be easily scale-up but its application is limited to lipophilic API and requires many washing cycles to remove the salting-out agent (Nagavarma et al. 2012; Lee et al. 2016; Swider et al. 2018). The optimization of the different conditions (e.g., salting out compound nature and concentration, solvent nature, polymer concentration) is essential to obtain MP and not nanoparticles (Wischke and Schwendeman 2008).

Current industrial methods

Spray-drying

The spray-drying (SD) technology has evolved over time to meet industry requirements in several production fields. In drug delivery, novel principles and methodologies in droplet formation and drying have enabled considerable expansion of SD applications, including biologicals and enteric formulations (Puccetti et al. 2018; Ziaee et al. 2019). This technique combines a relatively user-friendly setup with versatility and scalability, and ensures a completely closed environment, preventing the risk of room and personnel contamination. Granting fast one-step fabrication and simultaneous control on particle size and morphology, SD is particularly suitable to process susceptible materials and for the manufacturing of precisely tailored dry MP formulations, with the logical benefit of storage stability. According to the nozzle and drying chamber geometries, and recovery method, pulmonary powders, pellets as well as sustained release MP can be fabricated. Since SD can be run in a nearly continuous manner, it can produce large batch sizes with high reproducibility, granting low levels of residual solvent in a closed loop configuration. Nowadays, beside the classical equipment several configurations have been designed with different manufacturing purposes.

The unmatched appeal of SD as a one-step, scalable manufacturing technique has promoted a great deal of research in several fields and, it has been found particularly suitable for PLA and PLGA MP preparation (Sosnik and Seremeta 2015). Exploiting the well-known SD capabilities, a number of works have investigated PLA and PLGA inhalable MP for tuberculosis and other infectious diseases in the attempt to extend the action of pulmonary treatment (Schoubben et al. 2010; Ungaro et al. 2012; Palazzo et al. 2013; Giovagnoli

et al. 2014; Ibrahim et al. 2018; O'Connor et al. 2019). Additional applications have encompassed other antibiotics, antitumoral, antioxidants and antiinflammatory drugs (Wagenaar and Müller 1994; Mu and Feng 2001; Gavini et al. 2004; Rivera et al. 2004; Youan 2004; Sastre et al. 2007). Unfortunately, to date, none of them has reached the clinical stage.

For an in-depth analysis of the related issues and progresses in the field, interested readers can refer to Liang et al. (Liang et al. 2015), Miranda et al. (Miranda et al. 2018), Das et al. (Das et al. 2015), and Hickey et al. (Hickey et al. 2016).

Beyond its traditional role of controlled drying process and prominence in the inhalable powders area, current SD technologies may reshape manufacturing of injectable sustained release depots as well, as an alternative to emulsion-freeze-drying technologies (Mundargi et al. 2011; Guo et al. 2015; Wan and Yang 2016). In particular, SD is slowly emerging as a manufacturing process of controlled delivery systems for biomolecules and vaccines (Mueller et al. 2012; Allahyari and Mohit 2016; Kanojia et al. 2017). However, in order to climb over the ridge of compliance and controlled release requirements, traditional pitfalls have to be overcome. Among all, initial burst release and heat shock damage restrain most protein loaded spray-dried MP development (Yamaguchi et al. 2002; Mao et al. 2007). Such problems stem from the fast and turbulent drying process that results in poor control over molecular diffusion in the droplet. As a consequence, proteins are released fast from spray-dried MP due to the small particle size and the tendency to migrate at the liquid–air interface.

Nonetheless, novel atomization technologies, based on coaxial ultrasonic, electrospray, and three-fluid pneumatic actuation (Kondo et al. 2014; Wan et al. 2014), will likely prompt the progress towards the production of monodispersed particles with a core–shell structure providing higher drug payloads (Han et al. 2016) and more accurate control on the release behavior. Such innovations have boosted the research in the last years and, likely, in the near future SD is about to become one of the main technologies in the manufacturing of controlled delivery systems for biopharmaceuticals.

Albeit established in some areas of pharmaceutical manufacturing, scale up of SD methods is not straightforward as a result of the intimate liaison between process conditions and product powder properties. Direct scaling of key parameters seems not to be effective due to practical limitations and temporal differences in physical processes, e.g. at pilot and production scales the particle residence time is much higher than at lab scale and yield may vary due to a different adhesion extent to the equipment walls. Complete understanding of scale-dependent and scale-independent factors is therefore strategic along with the design and engineering of a pilot model accounting for critical geometrical and workout requirements (Al-Khattawi et al. 2018). This is one of the reasons for the as yet limited spray-dried depot products on the market.

Supercritical fluids

The properties of supercritical fluids (SCF) have been exploited in many different areas of pharmaceutics and biomedicine. Several organic solvents and almost all gases above their critical pressure and temperature assume peculiar properties that stem their capacity to act at the same time as a liquid and a gas. The consequence is that such SCF show the solubilization capacity of a solvent along with high diffusivity and low viscosity. The liquid-like properties enable application in extraction processes, solubilization of substances, and matrix plasticization, while gas-like features enhance mass transfer and reaction selectivity. Carbon dioxide is preferred over other SCF due to mild supercritical conditions, low cost and environmental impact.

SCF technologies are today well-established industrial processes that can be applied to manufacturing of fine powders and polymeric micro- and nanocarriers each with advantages and disadvantages (Table 3). In general, the process consists in the formation of solutions or dispersions by exploiting the SCF solvent or anti-solvent capacity and the subsequent coacervation induced by its fast removal through a rapid drop below supercritical conditions. This leads to solvent extraction with subsequent fast solidification of dissolved materials or drying of dispersed particles. SCF can be used as solvents or anti-solvents and solutes and over the years several different processes have been developed according to purposes (Table 3) for an in-depth description of which readers may refer to Kankala et al. (2017), Girotra et al. (2013), Tabernero et al. (2012), and Soh and Lee (2019).

The arsenal of techniques today available is the result of about three decades of continuous research efforts that have led to considerable advances in the methods for the fabrication of tailored drug delivery systems destined to virtually all administration routes. Among all, PLA and PLGA delivery systems have benefited from the increased versatility of RESS and SAS techniques either for MP or nanoparticle formulations. Refinement in the control over coacervation and hardening/drying processes has granted successful development of PLA and PLGA MP for oral, pulmonary and parenteral administration. Antiinflammatory drugs have been microencapsulated in homogeneous injectable PLGA and PLA MP using RESS, SEDS, SAILA, and SFEE processes (Kim et al. 1996; Ghaderi et al. 2000; Chattopadhyay et al. 2006; Kang et al. 2008a; Kluge et al. 2009b; Della Porta et al. 2010; Campardelli et al. 2016; Campardelli and Reverchon 2017). Other examples include morphine,

Table 3 Classification of SCF processes employed in microparticle and nanoparticle fabrication

SCF role	Process	
Solvent (RESS)	Rapid expansion of supercritical solutions	RESS
Solute	Particle from gas saturated solution	PGSS
Anti-solvent (SAS)	Solution enhanced dispersion by supercritical process	SEDS
	Supercritical fluid extraction of emulsion	SFEE
	Supercritical-assisted atomization	SAA
	Aerosol solvent extraction system	ASES
	Expanded liquid anti-solvent	ELS
	Precipitation with compressed anti-solvent	PCA
	Suspension-enhanced dispersion by supercritical fluids	SpEDS
	Supercritical anti-solvent with enhanced mass transfer	SAS-EM
	Gaseous anti-solvent	GAS
	Supercritical assisted injection in a liquid anti-solvent	SAILA
Mixed	Supercritical solvent impregnation	SSI
	Depressurization of an expanded liquid organic solution	DELOS
	CO_2-assisted nebulization with a bubble dryer	CAN-BD
	SCF-assisted spray-drying	SASD
	SCF-expansion depressurization	SFED
	SCF-processing	SCP

methotrexate, and paclitaxel (Kang et al. 2008b; Chen et al. 2012c, 2013b; Huang et al. 2015).

SAS methods have been developed to entrap water-soluble compounds in PLA and PLGA MP. One strategy was to increase solubility in organic solvents by hydrophobic ion pairing, as in the case of gentamycin, nalozoxone, naltrexone (Falk et al. 1997) or addition of co-solvents, as in the case of morphine, bupivacaine, and ketamine (Lee et al. 2006; Zhang et al. 2012; Han et al. 2018).

The possibility to finely control working temperatures and boundary conditions makes SCF-based methods suitable for processing labile materials (Adami et al. 2011). Therefore, microencapsulation of proteins and peptides, such as bovine serum albumin, lysozyme and lipase (Young et al. 1999; Mishima et al. 2000; Tu et al. 2002; Kluge et al. 2009a; Chen et al. 2012b; Tran et al. 2013), insulin (Elvassore et al. 2001; Della Porta et al. 2013), and monoclonal antibodies (Yandrapu et al. 2013), as well as vaccines (Baxendale et al. 2011; Tavares et al. 2017) has been achieved.

The SCF technology enables the rapid and effective assembling of complex composite systems. In this way, nanoparticles can be entrapped within PLGA or PLA MP (Chen et al. 2009b) or can be coated with PLA and PLGA polymers to form core–shell structures (Chen et al. 2009c). This technology can be exploited to produce functional systems, as in the case of magnetic or antibacterial MP (Chen et al. 2009a, 2012a; Campardelli et al. 2013; Cricchio et al. 2017), or composite PLGA/chitosan MP by PGSS (Casettari et al. 2011).

A continuous supercritical emulsion extraction (SEE-C) has been proposed for the production of PLGA MP for the encapsulation of proteins and polypeptides (Della Porta et al. 2011; Campardelli et al. 2012; Falco et al. 2012). SEE-C shows significant improvements compared to batch configuration, as it exploits countercurrent packed columns that enable rapid, continuous extraction of the organic solvents and reproducible formation of PLGA MP with controlled and narrow size distributions. This system demonstrates that SCF technology can be scaled to a high-throughput continuous mode to allow large production yields and batch control.

Naturally, as mentioned above, the highly efficient atomization technologies coupled to SCF can be exploited to produce inhalable powders. Lysozyme, celecoxib, deslorelin, and rifampicin loaded porous PLA and PLGA MP obtained by SAA represent a few examples (Koushik and Kompella 2004; Koushik et al. 2004; Patomchaiviwat et al. 2008; Chen et al. 2013a; Dhanda et al. 2013; Kang et al. 2013). The advantages of SFC in the manufacturing of pulmonary dry powders are a higher control upon the formation of feed dispersion and solutions and a higher efficiency in solvent removal at reduced temperatures. Consequently, the obtained powders show a lower residue of organic solvent, thus a less plasticized solid matrix, and improved particle size distribution and morphology. Moreover, the lower process temperatures enable processing of heat sensitive materials.

Membrane emulsification

Emulsion solvent extraction/evaporation-based methods still represent one of the major manufacturing processes for PLA and PLGA MP. As discussed above, such methods suffer from intrinsic low reproducibility and production

efficiency, and limited control on particle size that strongly bias industrial development. In the effort to meet industrial requirements, over the last two decades, membrane emulsification technology has taken the lead in particular in PLA and PLGA MP manufacturing (Liu et al. 2005a, b, 2006, 2011; Lloyd et al. 2014; Ramazani et al. 2016). The technique is based on a relatively simple concept. Emulsification is achieved by forcing a dispersed phase, usually an organic solution or a premixed coarse emulsion, into an aqueous continuous phase through a membrane of given porosity. The passage through the membrane produces homogeneous droplets, the size of which is determined by the membrane pore size and geometry, the droplet detachment regime from the membrane surface, and the flow shear resulting from the agitation method applied to the continuous phase (Hancocks et al. 2013). Additional attention should be taken in selecting the proper membrane wall material, depending on the polarity of the dispersed and continuous phases, as membrane wettability, charge and permeability influence droplet formation (Vladisavljević et al. 2012; Silva et al. 2017). Overall, ideal membranes should have a uniform pore size distribution over a wide range of sizes to grant tuneability of droplet size, low hydrodynamic resistance, high mechanical strength, thermal and chemical resistance, high tolerance to organic solvents, ease of surface modification and functionalization, constant wettability with respect to the dispersed and continuous phase, and low fabrication costs (Vladisavljević 2015). Shirasu Porous Glass (SPG) material meets the majority of the above requirements and for such a reason is widely employed for membrane production (Qi et al. 2014; Lu et al. 2017; Gu et al. 2018).

For a complete treatment of the method, readers may refer to Vladisavljević et al. (Vladisavljević et al. 2016) and Piacentini et al. (Piacentini et al. 2014, 2017).

Benefits of membrane emulsification include enhanced droplet size control, low shear stress and energy requirement, equipment setup flexibility. This technique is therefore suitable for high throughput production of precisely tuned and highly homogenous MP with sizes between < 1 and 100 µm (Gasparini et al. 2008). Two main membrane emulsification modalities exist: moving continuous phase or moving membrane (Fig. 1). In the first, the continuous phase is kept under movement by stirring or unidirectional or pulsed flow. In addition, vibrating elements generate a mixing effect that favors the emulsification process of the droplets protruding from the membrane. The second modality consists in a membrane cartridge containing the inner phase that is maintained under rotational or vibrational motion in the continuous phase (Fig. 1). The moving membrane emulsification method is considered superior as it prevents droplet damage due to the shear when circulating the continuous phase, shows a higher scale-up reproducibility, and can limit manufacturing costs as a result of a reduced energy demand as well.

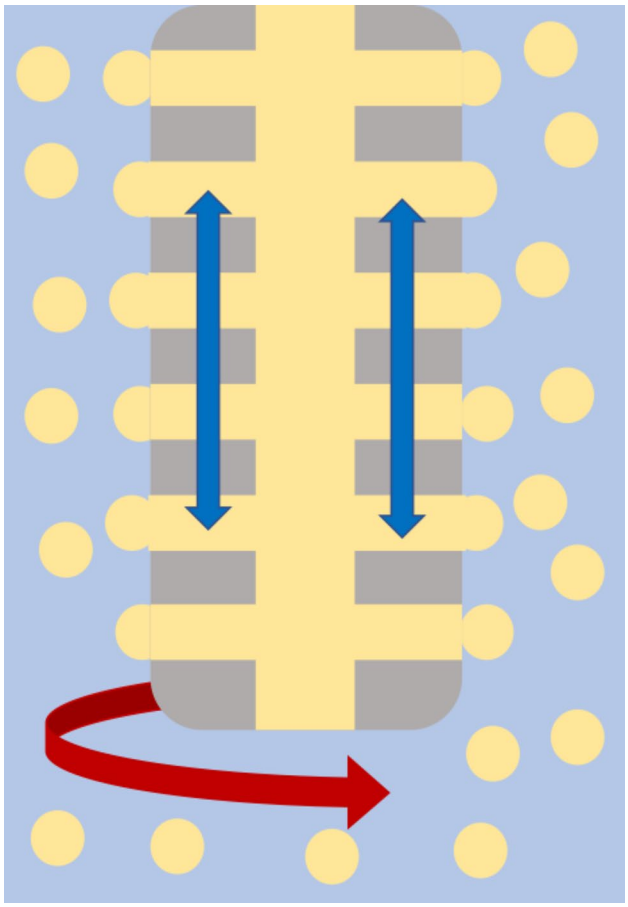

Fig. 1 Particle production using the membrane emulsification technology. The membrane is shown in grey, continuous phase in blue and dispersed phase in yellow. Two different process modalities exist: the moving continuous phase and the moving membrane. In the first, the external continuous phase is kept under mixing by a stirring bar or moved by a linear unidirectional or pulsed flow generated by a flow pump. In the second, it is the filter system to be maintained under rotational (red arrow) or vibrational (blue arrows) motion. In both the modalities, the movement generated is essential to allow the detachment of the droplets stemming from the membrane and their diffusion in the continuous phase. Adapted from Piacentini et al. (2014). (Color figure online)

The energy involved is usually very low compared to other homogenization techniques. Indeed, this important aspect underpins the industrial development of this manufacturing technique.

Progresses towards industrialization allowed the development of several PLA and PLGA technology platforms. Batch and continuous operation devices are currently available. The first is made up of a pressurized chamber, in which a membrane separates the dispersed phase and a constantly stirred continuous phase (Fig. 2a–c). The continuous

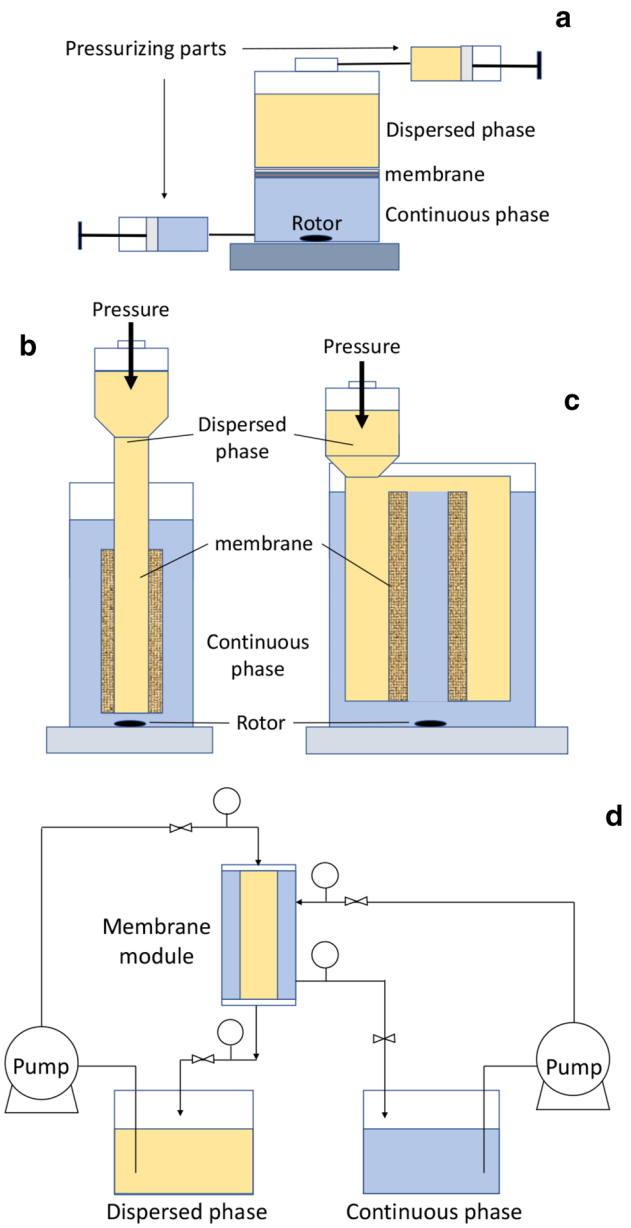

Fig. 2 Membrane emulsification devices. **a–c** Batch operation devices: the inner organic phase is pressurized through the membrane by a syringe or a controlled pumping system; the mixing effect is obtained by stirring the static continuous phase with a stirring bar; the organic solvent is evaporated and the dispersed particles recovered by filtration. **d** Continuous operation device: both the inner organic phase or the continuous phase flow through two separate loops that connect the respective reservoirs to the emulsifying chamber allowing continuous operation. Adapted from Piacentini et al. (2014)

operation device is instead a typical cross-flow apparatus in which the dispersed phase is continuously pumped through the membrane and recirculated (Fig. 2d) (Ho et al. 2013).

The undeniable attractiveness of the emulsion-based technologies is witnessed by the number of products in the market that exploit such platforms as also reported in Table 1.

The possibility to finely tune size and composition of PLA and PLGA MP by adopting proper multiple emulsification processes affords fabrication of complex composite particles. In this regard, a rotating membrane emulsification system was employed for the preparation of iron nanoparticle loaded PLGA MP for tumor arterial embolization and magnetic ablation (Liang et al. 2017).

W/o/w emulsions are generally employed for hydrophilic compounds, such as many proteins (Ma 2014) and insulin (Liu et al. 2006). Furthermore, a w/o/w emulsion followed by premix rotational membrane emulsification enabled the fabrication of bovine serum albumin loaded mPEG-PLGA MP possessing proper pulmonary delivery features (Zhao et al. 2018).

These evidences demonstrate that this technology shows great potential as it couples brilliant performances in the production of precisely tailored uniform MP with versatility and limited costs.

Spray freeze-drying

Potentially scalable technologies are today available which combine well known techniques into a one-step manufacturing process. One of the most promising for the preparation of PLGA and PLA MP is spray freeze-drying (SFD) of drug-polymer solutions/dispersions that enables a broad range of applications, particularly for proteins and biologics (Wanning et al. 2015). Spray freeze-drying is a well-established process since its first appearance in 1964 (Werly and Bauman 1964) in the food and pharmaceutical industry for processing and powder engineering (Ishwarya et al. 2015; Dutta et al. 2018).

The principle of combining spraying with lyophilization, rather than with common exsiccation processes, provides several advantages. Beyond the note improvement of drug solubilization and amorphization that minimizes potential phase separation phenomena (Vo et al. 2013), SFD shows its full potential in processing and encapsulation of unstable proteins and peptides for drug delivery and vaccination purposes (Cheow et al. 2011). Most important, SFD can provide additional control over MP morphology and size distribution. Compared to conventional freeze-drying, SFD is economically preferable in terms of time and energy consumption (Claussen et al. 2007). Moreover, the production of a flowable bulk powder, in place of filled vials, enables a considerable increase in production plant flexibility, allowing easy dosage adjustments.

In this regard, spray freeze-dried human growth hormone and recombinant human vascular endothelial growth factor loaded PLGA MP showed low burst release and the behavior

could be controlled by prior tuning of spray-freezing conditions (Cleland et al. 2001; Costantino et al. 2004).

A comparison of SFD with SD showed that the lipid-PLGA particles obtained by SFD exhibited improved characteristics in terms of size, yield, flowability, aqueous reconstitutibility, and aerosolization efficiency (Wang et al. 2012), supporting the usefulness of SFD even for the production of inhalable PLGA powders. Furthermore, SFD demonstrated superior performances compared to SD in encapsulating darbepoetin alfa, an erythropoiesis-stimulating protein, in PLGA MP in terms of yield and particle size control (Burke et al. 2004).

Beyond the highlighted virtues, a SFD caveat is the relative complexity of equipment setup at pilot/production scale, which demands particular care in the lab-to-plant transfer process, thing that can bear on manufacturing costs.

Other technologies

Hot-melt extrusion

A well-known method for the encapsulation of hydrophobic drugs in PLA and PLGA matrices is hot-melt extrusion (HME). The technique consists in a series of continuous processes in which micronized drugs are dispersed in a polymer melt, extruded, and then cooled down and ground or milled into fine particles (Wichert and Rohdewald 1990; Makadia and Siegel 2011). If spherical particles are desired, the obtained ground or milled particles can be dispersed in a hot polymer or surfactant solution (Crowley et al. 2007; Lang et al. 2014).

In fact, it is possible to produce injectable MP depots by coupling HME with micronization methods, such as wet milling or jet-milling in order to obtain spherical particles (Nykamp et al. 2002; Guo et al. 2017b). HME is a cost-effective method characterized by the absence of an organic solvent, continuous operation, and easy scale up. However, several limitations should be accounted many of which relate to drug exposure to thermal treatment and the often large number of steps required to produce smooth spherical MP (Wischke and Schwendeman 2008).

Potentially, the method could suit not only the encapsulation of hydrophobic but even of hydrophilic drugs that could be dispersed in the polymer matrix as a micronized solid. Nevertheless, the use of high temperatures discourages the application to biomolecules and biologics. Moreover, it should be minded that non-porous particles are usually obtained, feature that could slow down excessively the release of water-insoluble drugs.

Spray-congealing

Another potentially appealing technique that to date has been sparingly employed for the production of PLA and PLGA MP is spray congealing (SC). This method consists in a unit operation in which a liquid melt is atomized into a cooling chamber. The liquid is atomized into a congealing gas, droplets are promptly frozen, and particles solidify upon removal of the gas. Several configurations exist in which a liquid melt or a solution can be processed. The congealing media in the cooling chamber change accordingly and can be a gas or a frozen non-solvent, which is usually layered with liquid nitrogen to favor the successive cryogenic solvent removal, see also the section referred to cryogenic solvent extraction (Cordeiro et al. 2013). In many ways, SC shows hybrid features between SD and HME. As such, SC is a platform suitable for the microencapsulation of thermosensitive compounds, particularly proteins and peptides (Yeo et al. 2001).

As anticipated above, a modified SC technique has been developed in the Alkermes' ProLease® platform (Johnson et al. 1997). This technology has been employed for the manufacturing of Nutropin Depot®, a Genentech's somatotropin drug product discontinued in 2004. The Alkermes platform was also used in the Merck Serono's Prolease r-hFSH, a sustained release formulation of recombinant human follicle stimulating hormone for the treatment of infertility, and the Janssen's Procrit Prolease, a recombinant human erythropoietin to control red blood cells production, both discontinued at phase 1 clinical and pre-clinical stage, respectively.

In situ forming microparticles

Worth citing is a strategy that does not rely on any peculiar process or equipment, but consists in an injectable solution that precipitates in situ forming a sustained release MP depot (Royals et al. 1999; Jain et al. 2000; Luan and Bodmeier 2006).

Drug/polymer solutions are dissolved in water-miscible solvents, such as n-methyl pyrrolidone or dimethylsulfoxide (DMSO), that are then emulsified in an external oil phase. Upon injection, the solvent diffusion causes precipitation of the polymer resulting in MP entrapping the drug to be released. Naturally, safety issues limit types of solvents and oils that thus have to be carefully selected (Wischke and Schwendeman 2008).

This approach overcomes some drawbacks of conventional techniques, including manufacturing costs and complexities of manufacturing processes. Several FDA-approved long-acting depots exploiting this technology are available in the market (Table 4). An example is the leuprolide acetate depot which releases the drug over months.

Table 4 PLA//PLGA based in situ forming depot technologies and products marketed or under clinical development (not intended to be fully exhaustive)

Investigational or brand	API	Indication(s)	Encapsulation technology	Development stage
Atridox®	Doxycycline	Periodontitis	AtriGel®	Marketed
Atrisorb®	Doxycycline	Periodontitis	AtriGel®	Marketed
CAM2029	Ocreotide	Acromegaly and neuroendocrine tumors	FluidCrystal®	Phase I–II
CAM2032	Leuprolide acetate	Prostate cancer	FluidCrystal®	Phase I–II
CAM2038	Buprenorphine	Opioid dependence	FluidCrystal®	Approved
CAM4072	Setmelanotide	Genetic obesity	FluidCrystal®	Phase I–II
Eligard®	Leuprolide acetate	Prostate cancer	AtriGel®	Marketed
mdc-iRM	Not known	Schizophrenia	BEPO®	Phase III
mdc-CWM	Not known	Pain and inflammation	BEPO®	Phase II
Perseris™	Risperidone	Schizophrenia	AtriGel®	Approved
Sublocade®	Buprenorphine	Opioid dependence	AtriGel®	Marketed

Advanced manufacturing technologies

Microfluidics

Microfluidics is a technique that is quickly growing and that consents to prepare particles of the same dimensions and therefore characterized by a reproducible drug release pattern (Lee et al. 2016). To produce PLA/PLGA particles, a microfluidic device that may have different geometries is required. The device comprises of several microchannels, etched or molded in different materials such as glass, silicone or poly(dimethylsiloxane) (PDMS), that are connected together. These microchannels are filled in thanks to inlets and fluids flow rate is controlled by micropumps and microvalves until they are withdrawn through the device outlet (Swider et al. 2018). This relatively new strategy of PLA/PLGA MP production can be scaled up when PDMS devices are employed since their production is easy, cheap and grants the fabrication of channels with reproducible dimensions. This is on the contrary harder to obtain with glass devices. The limit of using PDMS microfluidics is their swelling behavior in contact with organic solvent such as methylene chloride. To avoid this problem, the microchannels inner surface can be coated with a PVA/glycerol solution (Duncanson et al. 2012; Li et al. 2015). Polymeric MP are produced exploiting single, double or multiple emulsions that can be formed in the device choosing the proper microchannel geometry. Particle dimensions can be easily tailored modifying the solvent nature, the polymer and stabilizer concentration, and the flow rate of the different solutions. Monodisperse droplets are obtained since the emulsion formation is strictly controlled passively or actively handling the flow rate, the volume ratio of the aqueous and organic phases, and the device geometry. The main difference between the active and passive technique is the use of additional accessories for the active technique such as microvalves, heaters that require energy to be actuated (Vladisavljević et al. 2013). Device microchannel geometry can be divided in T-junction, flow-focusing and co-flow

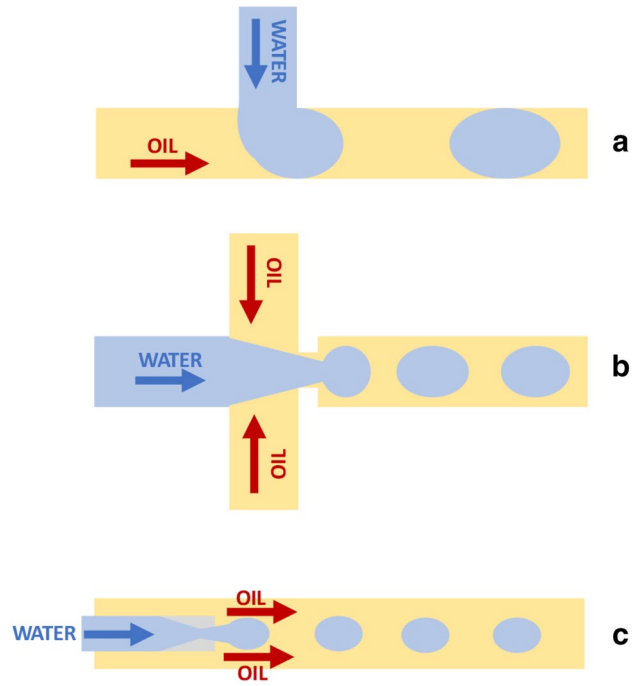

Fig. 3 Microfluidic channel geometries; **a** T-junction geometry: the aqueous phase flows orthogonally into the oil phase; **b** flow-focusing geometry: the oil phase enters orthogonally the channel while the aqueous phase flows coaxially into the oil phase flow; the oil phase flows through a bottleneck junction and the pressure drags the aqueous droplets into the oil stream; **c** co-flow geometry: the aqueous phase enters coaxially into the co-current oil phase flow; the oil phase pressure pushes the aqueous droplets into the parallel oil stream. Adapted from Swider et al. (2018)

geometries (Fig. 3). The T-junction microfluidic device possesses two inlets: the continuous phase flows through horizontally, while the organic phase containing the polymer is introduced from the second inlet and encounters the aqueous phase perpendicularly. In the flow focusing device, the continuous phase is introduced in the two side channels while the organic phase flows through the central channel. The organic phase is then forced to pass through a thin orifice by the symmetric shear forces of the aqueous phase meeting the organic solution from the two lateral channels (Martín-Banderas et al. 2005; Keohane et al. 2014; Perez et al. 2015; Li et al. 2015). The flow-focusing geometry device usually consents to obtain smaller droplets and therefore smaller particles than T-junction microfluidics due to the shearing forces applied (Xu et al. 2009; Vladisavljević et al. 2013). In the co-flow system (third geometry), both phases flow in the same direction but in two different coaxial microchannels. The organic phase flows in the inner channel, while the continuous phase flows in the outer microchannel. To obtain double or multiple emulsions, different geometries can be combined, such as the flow-focusing microchannels with the co-flow system (Duncanson et al. 2012).

Electrospray

The main difference between electrospinning and electrospray is the polymer solution concentration. To obtain particles, it is necessary to work with a low polymer concentration. The electric field applied to the syringe containing the polymer solution pushes the polymer outside the syringe needle to form monodispersed particles on the receiving grounded electrode (Oliveira and Mano 2011). Electrospray has the great advantage of being a one-step process. By tuning the voltage intensity applied, the solution flow rate, the drying time and rate, that depend on the distance between the needle tip and the collection plate and on the solvent vapor pressure, respectively, it is possible to produce particles with specific features in terms of dimensions and morphology (Berkland et al. 2004; Xie et al. 2010). The use of concentric coaxial nozzle conveying two different fluids (i.e., the inner one that is surrounded by the outer fluid) is an evolution of the electrospray process (Lee et al. 2010; Han et al. 2016). The encapsulation efficiency is commonly 100% and particles are characterized by a core of API surrounded by a PLA/PLGA outer layer. Electrospray apparatuses equipped with a coaxial nozzle are particularly indicated for the encapsulation of peptides and proteins, considering the high drug loading and the limited stress to which the drug is exposed (Xie and Wang 2007; Xie et al. 2008; Ye et al. 2010). Recently, ranibizumab has been encapsulated with 70% efficiency and a high activity preservation (Zhang et al. 2015).

Microfabrication methods

Soft lithography is a family of techniques, including micro-contact printing, micro-molding, nano-transfer printing, having in common the use of an elastomeric mold. Soft lithography is for instance the technique used to produce the microfluidic device mentioned above. The material used to produce the mold is commonly PDMS because of its low cost, biocompatibility, low toxicity, chemical inertness, and its mechanical flexibility and durability. PDMS mold can be fabricated with micro- or nanostructures to produce micro- or nanoparticles as reported in the paper by Guan et al. (Guan et al. 2006). Associating both micro-contact printing and micro-transfer molding, PLGA particles of different shape and size were produced evidencing the versatility of these techniques with respect to the lab-scale methods (Guan et al. 2006). To speed up and facilitate particle recovery from the mold, a template of gelatin was prepared exploiting the sol–gel phase transition of hydrogels. In this way, once the organic solvent containing PLGA evaporated, particles were recovered dissolving the gelatin mold in water at 40 °C and centrifugating the resultant suspension. This strategy is easily scalable, cheap and the conditions to which API are exposed are mild, making this technique advantageous to prepare MP for drug delivery (Acharya et al. 2010, 2011). These microfabrication methods are also reported in literature under the acronym PRINT that stands for Particle Replication In Nonwetting Templates (Fig. 4) (Enlow et al. 2011; Perry et al. 2011; Swider et al. 2018). This technology is mainly adopted for the production of nanoparticles but can also be applied to produce MP loaded with different API, both hydrophilic and lipophilic (e.g., doxorubicin) (Enlow et al. 2011). The main difference with respect to the processes described previously is the use of a different material to produce the mold. In particular, highly fluorinated perfluoropolyether (PFPE) elastomer is employed instead of PDMS. This new elastomer does not swell in the presence of organic solvents and is therefore advantageous in comparison to PDMS. It also possesses a low surface energy, a high gas permeability, a low toxicity, good mechanical and elastic properties and is chemically stable and resistant to solvents. The PRINT platform consents to produce particles of potentially any shape and size characterized by high loading efficiency with low polydispersity index. Monodisperse particles have the great advantage of showing a predictable drug release pattern and are therefore very suitable for drug delivery applications (Swider et al. 2018).

Inkjet technology

Inkjet printing is another technology that consents to control the shape and the dimensions of the particles produced (Ramazani et al. 2016; Gupta et al. 2017). The ink consists

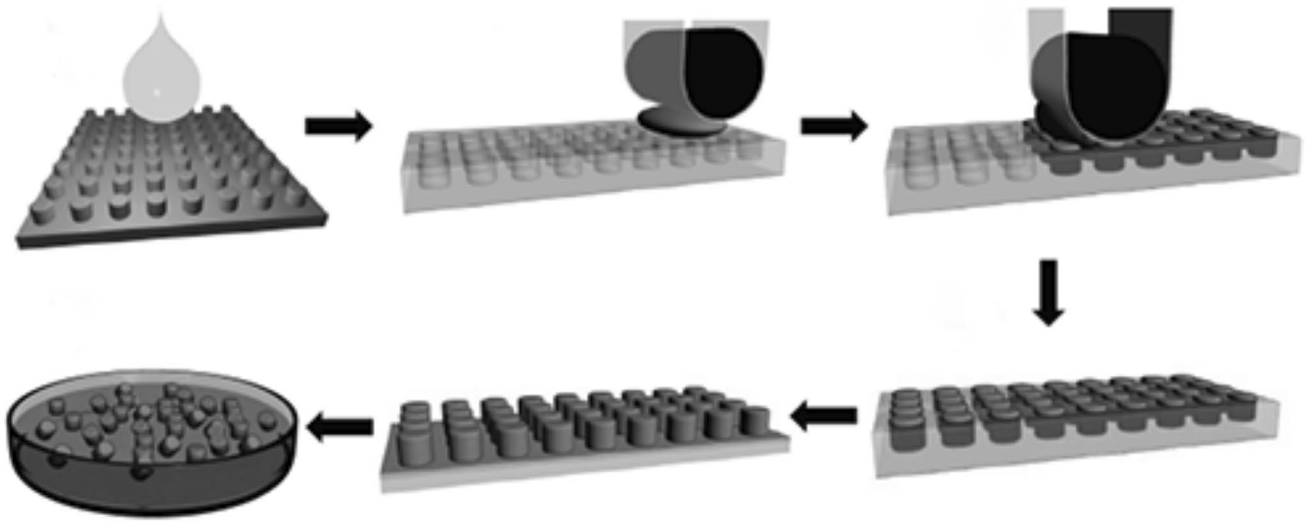

Fig. 4 Particle production using the PRINT method. The mold is initially prepared using PDMS, gelatin or PFPE by wetting the silicon wafer with micro- and nanosized patterns and is photocured to generate an elastomeric PRINT mold; then a solution of the polymer and the API is poured in the mold cavities using a film-split technique against a high-surface-energy polyethylene terephthalate counter sheet; particles of the desired shape and dimensions are obtained by solvent evaporation, photocuring or temperature quenching. The solid particles are removed by contact with an adhesive layer and freed by dissolving the adhesive layer. Reprinted by permission from Springer Nature: Springer eBook, Pharmaceutical Powder and Particles by Anthony J. Hickey and Stefano Giovagnoli, American Association of Pharmaceutical Scientists, 2018

in an organic solution or in a w/o emulsion containing the polymer that is PLA or PLGA and the API. The inkjet technology has first been proposed by Berkland et al. with the name of Precision Particle Fabrication® (PPF) technology (Berkland et al. 2001). Using this technique, PLGA MP with dimensions in the range 30–85 µm were obtained starting from an emulsion. In particular, an ultrasonic transducer was employed to break the liquid jet emitted from the nozzle into droplets. The nozzle was sunk in a water bath containing a stabilizer where the solvent was progressively evaporated to recover monodispersed particles (Berkland et al. 2007). Besides ultrasounds, a piezoelectric actuator can be used to break the inkjet in small droplets. In this case, several parameters of the ink such as volatility, viscosity and surface tension have to be optimized to be processable. With a single 30 µm nozzle, 24,000 drops per second corresponding to 86 million particles or 8 mL/h can be generated. Using this kind of nozzle submerged in an aqueous phase stabilized with polyvinyl alcohol, monodispersed particles with dimensions of about 15 µm were obtained (Böhmer et al. 2010). Palmer et al. also used a piezoelectric actuator to produce octreotide acetate and ciclosporin A loaded polyester particles. Here, the API and the polymer were solubilized in DMSO and inkjetted in a transverse anti-solvent flow that was water or tert-butanol/water solution (Fig. 5). The possibility to scale-up this technology was studied using an inkjet device featuring 256 nozzles working at 2–4 kHz frequency producing more than 1 million particles per second (Palmer et al. 2017). With the same scale-up purpose, Orbis Biosciences, Inc. (Orbis Biosciences 2019), founded by Berkland and Fishback, has developed an inkjet device able to produce kg/h and even kg/min particles with dimensions comprised in the range 10 µm to 1 mm. The other important advantages of this technique are the absence of material wastage, reduction of manufacturing cost and process steps (Lee et al. 2012; Qi et al. 2018). A variant of the process previously described has been reported by Lee et al. Droplets were produced using a continuous mode piezoelectric device and particles were recovered after 2 h drying of the ink that was printed on a glass slide. The particles showed distinctive paclitaxel release rate according to shape (Lee et al. 2012).

Combined technologies

PLA and PLGA MP were produced using different combined technologies. PLGA particles were prepared using a inkjet process followed by thermally induced phase separation (TIPS). Briefly, a PLGA solution in dimethyl carbonate was inkjetted using a piezoelectric actuator and droplets were collected in liquid nitrogen to freeze the solvent, obtaining phase separation. The solvent was finally removed by vacuum freeze-drying to recover porous particles (Go et al. 2014). Spray-drying is an industrial production method of PLA/PLGA particles that suffers of some drawbacks such as the large particle size distribution and morphology related to the atomization technology. To obtain more

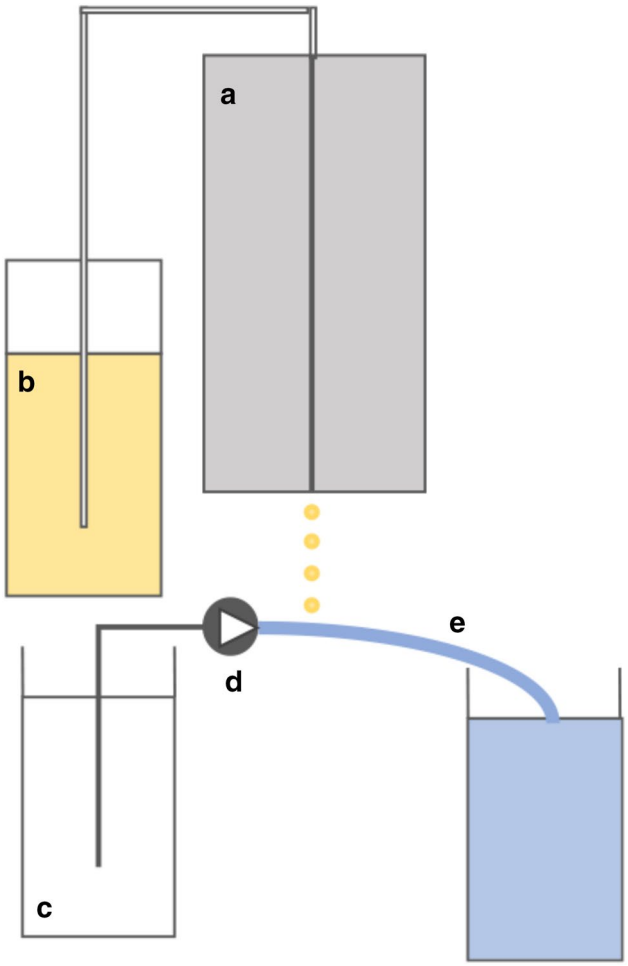

Fig. 5 Particle production using the inkjet technology. The piezoelectric actuator **a** nebulizes the polymer and the API solution, **b** in a transverse anti-solvent flow **e**, pumped with a pulseless micropump **d** from an anti-solvent reservoir (**c**). Adapted from Palmer et al. (2017)

homogeneous particle size and morphology, it is possible to combine SD with several droplet generation processes able to generate monodisperse droplets. To this aim, inkjet droplet generators or microfluidic jet were combined with SD obtaining uniform particles with tuneable characteristics for the encapsulation and controlled delivery of API (Liu et al. 2015). Another combined technology consists in the production of microdroplets with uniform dimensions using an ultra-fine particle processing system (UPPS) followed by solvent evaporation in a spray-dryer. The use of UPPS allows to evaporate the solvent at ambient temperature as a result of the long path the droplets have to travel. UPPS uses a nozzle that feeds the solution or suspension at the center of a rotating disk (1000–16,000 rpm) that drives the fluid towards its circumference obtaining a thin fluid layer that is nebulized in fine droplets. The droplets travel in the body cavity of the UPPS where endocentric airflow and tangent air vortex progressively dry the droplets (Zhu et al. 2015). These combined technologies were used to produce risperidone (Fu et al. 2012) and exenatide loaded PLGA MP (Zhu et al. 2015) with good encapsulation efficiency, homogeneous dimensions and prolonged in vitro release. This combined technology is particularly advantageous because heat sensitive macromolecules can be encapsulated under mild conditions (Zhu et al. 2015).

Technological and regulatory barriers

In recent years, the interest in depot drug delivery systems has experienced a noticeable growth in light of novel market opportunities. The extension of life expectancy, the general population aging, and striking risk factors, especially across industrialized areas, have led to a significant increase of chronic ailments. Chronic conditions place emphasis on the required high compliance of treatment in terms of dosing frequency and self-medication. Therefore, to achieve such a goal, prolonged and sustained action and low-invasive and easy administration modalities are compulsory. In this scenario, depot systems find a logical prominent position, which explains the estimated growth of this market area over the next few years (Greystone Research Associates 2018).

Biodegradable PLA and PLGA depots assume a natural leading role in this development pipeline for the aforementioned properties of such polymers and the vast possibility of formulation and modulation of their drug release behavior. Such a flexibility and versatility are witnessed by the several proprietary technologies that have been employed to produce a number of marketed PLGA and PLA sustained release depots (Table 1). The possibility of a long-term sustained release and safety of these formulations raise attractive perspectives for the treatment of chronic or semi-chronic conditions particularly when precise adherence to therapy is required, e.g., the case of antipsychotic therapies. On the other hand, compliance of administration modality can be met by existing and emerging smart needle-free injection technologies, which enable a dramatic reduction of invasiveness and sterility concerns as well as improved usability (Barolet and Benohanian 2018). These technologies exploit the transient permeation effect provoked by high speed jets of liquids or colliding particles. Skin permeabilization is the result of the shockwave produced by the liquid or gas/particles impinging the stratum corneum and causing a reversible disruption of the skin layers over a microseconds timeframe (Fig. 6). The propelling power is provided by mechanical forces such as spring actuated plungers, compressed gas, e.g. nitrogen and carbon dioxide, and electrical power (Kale and Momin 2014; Schoubben et al. 2015).

Modern injectors show considerable advantages compared to syringes or pen injectors (Guo et al. 2017a), such as a disposable nozzle, no sterility preservation issues, and

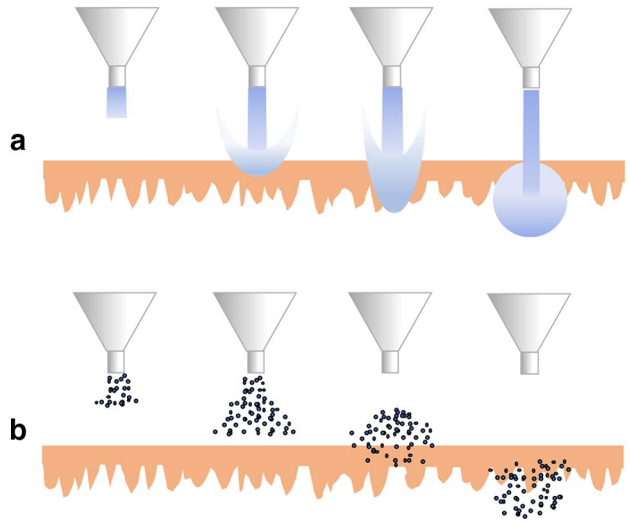

Fig. 6 Needle-free injection device injecting a high-speed jet of liquid (**a**) or of powder (**b**). In the first case, a piston pushes the liquid through a nozzle, which produces a jet at > 100 m/s (velocity); the jet starts the formation of a hole on the skin through surface erosion, fracture, or other skin disruptive processes; a few tens of microseconds of prolonged impingement of the jet provokes progressive increase of hole depth; the liquid accumulates in the skin hole slowing down the jet and further increase of the hole is stopped; the consequent stagnation favors diffusion of the liquid into the skin. In the case of powder injections, a chamber filled with the powder is pressurized with a gas and a jet is generated by rupture of a membrane set; the particles impinge the skin surface leading to formation of a hole into the skin depositing in a spherical pattern, penetrate across the stratum corneum, and distribute completely into the stratum corneum and the viable epidermis; to produce a proper powder jet, particle densities of about 1 g/cc and a mean diameter > 20 μm are desirable. Adapted from Kale and Momin (2014)

patient-friendly and high compliance features. Several FDA-approved injectors have been marketed and regulated by specific guidelines (FDA Guidance for Industry 2013).

Therefore, today technologies are available to move PLA/PLGA MP depots towards a new industrial era. Unfortunately, the technical and regulatory gap that separates injectable PLA/PLGA MP depots from well-established pharmaceutical products, e.g. oral, is still dramatically wide. Official validated methods for MP testing, in particular dissolution and stability assays, are lacking. Non-compendial drug release methods such as dialysis sac, reverse dialysis sac, and sample-and-separate have been proposed (Andhariya and Burgess 2016), but no standardization is warranted. A possible option may be the flow-through cell based USP apparatus 4 that has been found to grant good sink conditions, minimize microsphere aggregation, better mimic in vivo conditions, and it better suited long-term release studies (Rawat et al. 2011; Tomic et al. 2016). Recently, even the use of an orbital shaker based method has been positively evaluated, yet its application is far behind standardization (Garner et al. 2018).

Due to the long duration of action of PLA/PLGA depots, accelerated studies are desirable to shorten the testing period either for release or stability assessment. However, albeit some studies have demonstrated feasibility of accelerated release or stability assays, since such experiments are performed at increased temperatures, reliability and consistency of such approaches should be always checked and no standardization has been achieved so far. The reason is the effect of temperature on the low glassy polyester matrix, which tends to anneal if the testing temperature approaches the polymer glass transition temperature. Such critical features apply also to stability testing of MP. In this regard, directions are provided by the ICH Q1A guidelines that establish the proper conditions to assess product quality (ICH Q1A 2003).

This lack of compendial or biorelevant in vitro testing and related characterization standards as well as of adequate guidelines deeply hinder developability of PLA/PLGA depots. Indeed, bioequivalence assessment for these products is basically unmet. The reason is that PLGA/PLA heterogeneity and differences in manufacturing methods deeply influence the product physicochemical properties and thus release behavior and bioavailability. Even under high qualitative and quantitative sameness, bioequivalence may not be ensured (Zheng et al. 2017). Furthermore, adequate clinical settings along with sterilization requirement are another unmet challenge that are under intense evaluation.

All such reasons explain the to date absence of PLGA/PLA based generic drug products. The increased effort directed to overcome such considerable challenges has led to dedicated initiatives by regulatory agencies. The FDA's OGD has issued seven specific recommendations for MP products as guidance on bioequivalence study design (Wang et al. 2016) and it is working to develop recommendations for PLA/PLGA-based drug products.

Recognizing these challenges, a FDA's regulatory science research program was started in 2012 under the generic drug user fee amendments and is currently under implementation by OGD to provide new tools to support generic product development. Under this aegis, OGD has granted multiple research projects on PLA/PLGA based drug products involving MP, implants, and in situ gelling systems. These projects encompassed development of in vitro-in vivo correlations, in vitro release testing methods, characterization of PLA/PLGA polymers and formulations, and modeling and simulation of PLA/PLGA-based drug products. In spite of such efforts, none of the ongoing programs has completed its task so far, even though progresses in the field are continuous. Recently, an approach based on reverse engineering has been proposed to support generic development for 1-month Lupron® depot (Zhou et al. 2018). This could represent a valuable strategy to be expanded to other PLA/PLGA based depots.

Current scenario and future perspectives

The overall picture drawn so far looks rather twisted and the road to generic PLA/PLGA MP based products seems winding and full of barriers. These products may allow different routes of administration, such as pulmonary and parenteral, and a sustained effect that is highly beneficial to the treatment of chronic disease conditions. Availability of generic products, especially for LAI, would ease patient's access and adherence to therapy, considering the high production and market costs. This is particularly true if considering schizophrenic patients who have to be treated under rigorous medical control. A single long-term injection would improve compliance and nearly erase the non-adherence risk.

In particular, LAI products show a higher cost/effectiveness compared to oral antipsychotic treatment (Yang et al. 2009) with reduced hospital admissions, relapse rates and length of inpatient stay, especially for patients who may be at risk of non-adherence with oral antipsychotics (Peng et al. 2011; Nikolić et al. 2017).

Cost comparison of antipsychotic LAI versus other pharmaceutical forms clearly shows that LAI products may be more expensive compared to tablets or other injectables, however the difference is by far counterbalanced by the lower costs that burden on the health system for hospitalization, home visit and medical assistance (Ravasio et al. 2015; Patel et al. 2018; González et al. 2018). Similar considerations have been found to apply even in other therapeutic areas such as cancer and contraception (Ayyagari et al. 2017; Di Giorgio et al. 2018).

The clinical benefits of LAI are evident although their employment is still controversial as dosing flexibility and self-management skills might be undermined. Therefore, clinicians ought to be required to prescribe LAI treatments on a case by case basis by evaluating patient's risks and benefits (Mutsatsa 2017).

Naturally, this overall positive cost/effectiveness profile of LAI applies to PLA/PLGA MP based LAI as well. For this reason and the expired or expiring patent coverage for several products marketed in the 90s, the European Medicine Agency and the FDA are increasingly committed in the establishment of proper standards and guidelines useful to underpin the generic development of these peculiar products (EMA 2014).

As we have tried to point out in this review, the unmet aspects of PLA/PLGA MP based product development are reciprocally interconnected and influential on either the regulatory or manufacturing side. In fact, the progress of manufacturing techniques is hindered not only by the high complexity of such products but also, to a significant extent, by the absence of adequate standards and specific regulations, which impact the assessment of suitable clinical settings as well. Such a scenario is complicated further by the high costs associated with the technology employed to date for the manufacturing of PLA/PLGA MP based products. As highlighted above, victims of such miscalculations have been the discontinued Genentech's Nutropin Depot®, Merck Serono's Prolease r-hFSH, and Janssen's Procrit Prolease, all employing the Alchermes' Prolease® platform. Unsustainable management costs were at the origin of Nutropin discontinuation and, beyond undeclared issues, they also likely impaired the development of the other products that never reached the market.

This negative experience suggests that the choice of the manufacturing technology should be accurately weighed and it should evolve withholding an intrinsic simplicity and control. These aspects are crucial as they considerably impact the health technology assessment (HTA) process. In this regard, we have already underlined the importance of a proper evaluation of the manufacturing technology costs in HTA for advanced pharmaceutical forms that requires the contribution of an expert working side by side with clinicians (Panzitta et al. 2015). Unfortunately, still this aspect demands full implementation.

Seeing the glass half-full, the new opportunities driven by the novel emerging manufacturing technologies concisely described in this review will surely push forward the development of innovative and more reliable manufacturing methods for PLA/PLGA MP based depots. The contribution of the technology advancements recorded in the last years hold promises for the future assessment of robust and high-throughput manufacturing processes. Proper cost management favored even by new technological solutions may grant a bright future development for techniques such as SD and SCF that, albeit at present demanding, clearly hold considerable advantages compared with other techniques, especially considering the current tendency towards continuous manufacturing. In addition, microfluidics and membrane emulsification methods and combined techniques, such as TIPS and UPPS may help to meet the so far unmet demand for lean and efficient PLA/PLGA based products manufacturing system.

However, the future of this promising products is pending upon the fulfilment of updated and novel quality standards and guidelines for the consolidation of development processes.

Compliance with ethical standards

Conflict of interest All authors (S. Giovagnoli, A. Schoubben, and M. Ricci) declare that they have no conflicts 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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