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A comparative assessment of continuous production techniques to generate sub-micron size PLGA particles

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ABSTRACT

The clinical and commercial development of polymeric sub-micron size formulations based on poly(lactic-co-glycolic acid) (PLGA) particles is hampered by the challenges related to their good manufacturing practice (GMP)-compliant, scale-up production without affecting the formulation specifications. Continuous process technologies enable large-scale production without changing the process or formulation parameters by increasing the operation time. Here, we explore three well-established process technologies regarding continuity for the large-scale production of sub-micron size PLGA particles developed at the lab scale using a batch method. We demonstrate optimization of critical process and formulation parameters for high-shear mixing, high-pressure homogenization and microfluidics technologies to obtain PLGA particles with a mean diameter of 150–250 nm and a small polydispersity index (PDI, ≤0.2). The most influential parameters on the particle size distribution are discussed for each technique with a critical evaluation of their suitability for GMP production. Although each technique can provide particles in the desired size range, high-shear mixing is found to be particularly promising due to the availability of GMP-ready equipment and large throughput of production. Overall, our results will be of great guidance for establishing continuous process technologies for the GMP-compliant, large-scale production of sub-micron size PLGA particles, facilitating their commercial and clinical development.

1. Introduction

Nanoparticle-based drug delivery systems have emerged as a major field of research in nanomedicine with direct benefit to human health (Bala et al., 2004; Murday et al., 2009; Paliwal et al., 2014; Ragelle et al., 2017). Particularly, polymeric nanocarriers encapsulating active pharmaceutical ingredients (APIs) such as small drug molecules, biomacromolecules, and vaccines, offer unique advantages for improved stability, targeted delivery and controlled release of APIs *in vivo,* (Chan et al., 2010; El-Say and El-Sawy, 2017; Hines and Kaplan, 2013; Kumari et al., 2010) which can reduce drug burden while enhancing efficacy (Singh and Lillard, 2009). In this context, polymeric carriers based on poly(lactic-co-glycolic acid) (PLGA) have been one of the most commonly studied materials for API delivery due to excellent biocompatibility, tuneable degradation characteristics and long clinical history of PLGA (Danhier et al., 2012; Makadia and Siegel, 2011). Several applications of PLGA particles for the delivery of various APIs such as small drugs, (Derakhshandeh et al., 2007; Fonseca et al., 2002; Jose et al., 2016; Khan et al., 2016; Sun et al., 2015) proteins, (Feczkó et al., 2011; Mohammadi-Samani and Taghipour, 2015; Pirooznia et al., 2012; Rescignano et al., 2013; Santander-Ortega et al., 2010) nucleic acids, (Colombo et al., 2015; Cun et al., 2011; Harguindey et al., 2017; Lü et al., 2016; Patil et al., 2010) and vaccines (Allahyari and Mohit, 2016; Clawson et al., 2010; Dölen et al., 2016; Ma et al., 2014; Prasad et al., 2011) have been reported within the past decades.

Despite the tremendous efforts and much research emphasis put on the development of API-loaded PLGA particles, only a limited number of micron size formulations are currently available (Wang et al., 2016). Unlike the micron size spheres that are usually designed to act as implants or drug reservoirs, sub-micron size particles offer better suitability for intravenous use and enable significantly higher cellular uptake (Cruz et al., 2010; Danhier et al., 2012). Furthermore, sub-micron

Abbreviations: PLGA, poly(lactic-co-glycolic acid); API, active pharmaceutical ingredient; GMP, good manufacturing practice; DCM, dichloromethane; EtOAc, ethyl acetate; ACN, acetonitrile; PVA, polyvinyl alcohol; FRR, flow rate ratio; TFR, total flow rate

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formulations can provide additional therapeutic potential as they tend to accumulate at the inflammation sites or within tumours due to enhanced permeability and retention (EPR) effect (Maeda et al., 2000). Rapid angiogenesis at the tumor site results in an incomplete endothelial lining, which causes tumor vasculature to form large pores (0.1–3 μm) (Danquah et al., 2011; Maeda et al., 2013). Sub-micron size particles can escape through this leaky vasculature and accumulate in the tumor microenvironment, which eliminates the need for surface functionalization of the particles to target the tumor site. In addition, sub-micron size particles are efficiently taken up by immune cells (Oyewumi et al., 2010) and elicit strong immune responses (Dölen et al., 2016). Therefore, PLGA based immunotherapies for disease management (including cancer immunotherapy) can greatly benefit from the clinical translation of sub-micron size PLGA formulations.

One of the major challenges in clinical and commercial development of sub-micron polymeric particle formulations is scaling up their production without affecting the formulation specifications obtained at the lab scale (Desai, 2012; Paliwal et al., 2014; Ranjan et al., 2012; Ye and Squillante, 2013). Several methods that have been established for lab scale development of sub-micron size PLGA particles usually involve emulsion-based batch techniques. Emulsification via direct sonication using a transducer probe is among the most common approaches for the formation of PLGA particles due to inexpensive instrumentation and ease of operation. However, this method is also known to introduce modification of particle properties, including drug release profiles, upon scaling up the production to commercial batch sizes (Porta et al., 2011; Taurozzi et al., 2011; Valencia et al., 2012). As subtle variations in the manufacturing process can significantly alter the product characteristics that ultimately determine the therapeutic outcome, alternative production techniques with 'seamless' scalability should be explored. In this respect, continuous processes offer the advantage of preferential termination of the production at the desired target scale without changing the process parameters.

Continuous production of emulsion formulations in pharmaceutical, food, chemical and cosmetic industries commonly involves the use of high-energy emulsification devices such as high-shear mixer and high-pressure homogenizer (Sani et al., 2009). The high-shear mixing process is based on application of intense shear forces that can considerably shorten the mixing cycles in processes that require immiscible fluids to be formulated into emulsions. Although high-shear mixing is widely utilized for the production of micron size particles, several studies highlight the opportunity to reach sub-micron size scale using this method (Tukulula et al., 2018; Tukulula et al., 2015). High-pressure homogenization is a highly versatile technique, which is achieved by continuous flow of liquids through micro-fabricated channels where the pressure can reach up to 275 MPa/40 000 psi. Several studies have already demonstrated the applicability of high-pressure homogenization for the production of sub-micron size formulations with encapsulated active ingredients (Dillen et al., 2006; Sani et al., 2009).

In addition to aforementioned high-energy homogenization methods established well in industrial practice, microfluidics technology has recently become a highly promising approach for the production of sub-micron size formulations (Karnik et al., 2008). Rapid advances in nanofabrication techniques have enabled the development of mixing geometries capable of generating highly monodisperse particles due to precise control over flow and mixing parameters (Wang et al., 2014). In addition to emulsion-based approaches, production of sub-micron PLGA particles using microfluidics devices can be achieved by nanoprecipitation method as well (Xie and Smith, 2010). In this case, PLGA solution is prepared using an organic solvent that is miscible with the aqueous phase. An extremely fast mixing of both phases in sub-millimeter channels enables controlled precipitation of polymer with subsequent formation of particles (Ding et al., 2016). Despite the advantages that microfluidics technology can offer as a continuous process, studies exploring its suitability for the production of sub-micron particles at large-scale are limited (Jeong et al., 2016).

In this study, we present a detailed assessment of three process technologies for continuous production of sub-micron size PLGA particles developed at the lab scale based on a probe sonication batch method. We demonstrate the optimization of critical process and formulation parameters for high-shear mixing, high-pressure homogenization and microfluidics technologies in order to obtain PLGA particles with a mean diameter in the range of 150 nm–250 nm and a small polydispersity index (PDI, ≤ 0.2). We critically evaluate each method in terms of particle size distribution, throughput and applicability to good manufacturing practice (GMP)-compliant production.

2. Experimental

2.1. Materials

Poly(D,L-lactic-co-glycolic acid), PLGA RESOMER® RG 503H with a 50:50 ratio of lactic acid:glycolic acid was obtained from Evonik Nutrition & Care GmbH (Germany). Mowiol® 4–88 (31 000 M_w) and polyvinyl alcohol (PVA, 9000–10 000 M_w, 80%, hydrolyzed) were purchased from Sigma-Aldrich (USA). Ethyl acetate (EtOAc) was obtained from Avantor Materials (USA). Acetonitrile (ACN) and dichloromethane (DCM) were from VWR (the Netherlands).

2.2. Production of sub-micron size PLGA particles

Sub-micron size PLGA particles were formulated and developed at the lab scale using a batch method based on probe sonication. Three different techniques were explored for their suitability for continuous production of particles. Each method with the corresponding equipment used are summarized in Table 1.

2.2.1. Probe sonication

For batch production of particles, 1%, 5% and 10% of PLGA solution in DCM or EtOAc were added to a 1% Mowiol® 4–88 or PVA solution and emulsified for 2 min using a probe sonicator equipped with a 6.3 mm microtip (Branson Ultrasonics, St. Louis, USA) at 20% amplitude with 60 s ON/10 s OFF cycle. The emulsion was stirred overnight at room temperature to evaporate the organic solvent and particles were collected for further characterization.

2.2.2. High-shear mixing:

An EtOAc solution of PLGA (1%, 5% and 10%) was pumped into the inner chamber of a Silverson® in-line mixer at 2 mL/min rate and emulsified with the continuous aqueous phase containing 1% Mowiol® 4–88. Different ratios of organic and aqueous flow rates (2:10, 2:20, and 2:40) and different rotation mixing speeds (8 000 rpm, 10 000 rpm and 12 000 rpm) were tested in order to gather the best process parameters. The collected emulsion was stirred overnight at room temperature to evaporate the organic solvent, and particles were collected for further characterization.

Table 1
Routes for the production of sub-micron size PLGA particles and the corresponding equipment used in each method.

Technology	Device	Provider	Method
Probe sonication	Branson Ultrasonics Sonifier™	Branson Ultrasonics (St. Louis, USA)	Batch
High-shear mixing	Silverson® L4RT-A	Silverson Machines, Inc. (East Longmeadow, USA)	Continuous
High-pressure homogenization	Microfluidizer® M110-P	Microfluidics™ (Westwood, USA)	Continuous
Microfluidics	NanoAssemblr™	Precision NanoSystems Inc. (Vancouver, Canada)	Continuous

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