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Electrohydrodynamic methods for the development of pulmonary drug delivery systems

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ABSTRACT

Electrospinning and electrospraying are two highly versatile and scalable electrohydrodynamic methods, which have attracted considerable attention during the last years towards the fabrication of polymer-based drug delivery systems. The latter may be obtained in the form of nano- or microfibers (*via* electrospinning) or as drug-loaded nano- and microparticles (*via* electrospraying). This review article begins with an introduction on the basic principles and the important influencing parameters governing the electrospinning/electrospraying processes, followed by an overview on their use for the development of nano/microfibers and nano/microparticles destined for use in pharmaceutical applications. Focus is given on research efforts targeting in the formulation of drug delivery systems and devices designed for pulmonary drug delivery applications thus emphasizing on the potential use of electrospinning and electrospraying in the area of inhaled medicines.

1. Electrospinning and electrospraying – general overview

Electrospinning and electrospraying are the two dominant electrohydrodynamic methods employed for the fabrication of nano/microfibers and nano/microparticles, respectively with particular focus in the biomedical field (Chakraborty et al., 2009; Enayati et al., 2011a; Prabaharn et al., 2012; Bock et al., 2012; Ramakrishna et al., 2013). Their simplicity, scalability and high versatility in surface tailoring and multifunctionality enables the production of novel, functional materials having at least one dimension at the nano/micrometer scale. This generates new prospects in materials science and nanotechnology allowing for their exploitation not only in biomedicine but also in many other fields including sensing, catalysis, electronics, environmental and energy (Scampicchio et al., 2012; Ding et al., 2010; Zhang et al., 2017; Li et al., 2015; Lu et al., 2009; Dai et al., 2011; Luzio et al., 2014; Thavasi et al., 2008; Kumar et al., 2014; Chen et al., 2013; Pampal et al., 2015; Theonmozhi et al., 2017).

Electrospinning is the electrohydrodynamic method employed for the fabrication of continuous nano/microfibers deriving from natural and synthetic polymers, ceramics and composites (Chronakis, 2005). A typical electrospinning set-up consisting of a high-voltage power supply, a syringe where the polymer solution is placed connected to a needle (spinneret), a syringe pump with precise flow control and a grounded conductive collector, on which the produced polymer fibers are deposited, is schematically presented in Fig. 1a.

Upon connecting the positive electrode of the high-voltage power supply to the metallic needle of the spinneret and the negative electrode on a grounded conductive collector, a powerful electrical potential is applied onto the polymer liquid (typically between 5 and 40 kV). This induces the generation of positive charges onto the surface of the polymer solution droplet formed at the tip of the needle. Consequently, at a certain critical voltage the development of strong electrostatic repulsive forces exerted on the droplet overcome the surface tension of the solution, resulting in the ejection of a charged liquid jet from the tip of the needle that is directed towards the grounded metallic collector. Upon ejection, the jet undergoes stretching and whipping processes and the solvent evaporates rapidly resulting in the solidification and collection of polymer nano/microfibers onto the collector (Reneker et al., 2007).

The electrospraying technique also known as electrohydrodynamic atomization (Xie et al., 2015), is used for the fabrication of nano/microparticles. As in the case of electrospinning, upon applying a high voltage onto the polymer solution and when the critical voltage is reached, a charged liquid jet is ejected from the tip of needle in the form of droplets and it is directed towards the collector. The rapid evaporation of the solvent, results in the generation of nano- or microparticles (Fig. 1b).

As seen in Fig. 1, the same experimental setup can be used in both, electrospinning and electrospraying. Consequently, both techniques depend on the same influencing factors. The latter include (i) *processing parameters* such as the solution flow rate, the polymer solution concentration and the type of solvent used (solvents of higher conductivity

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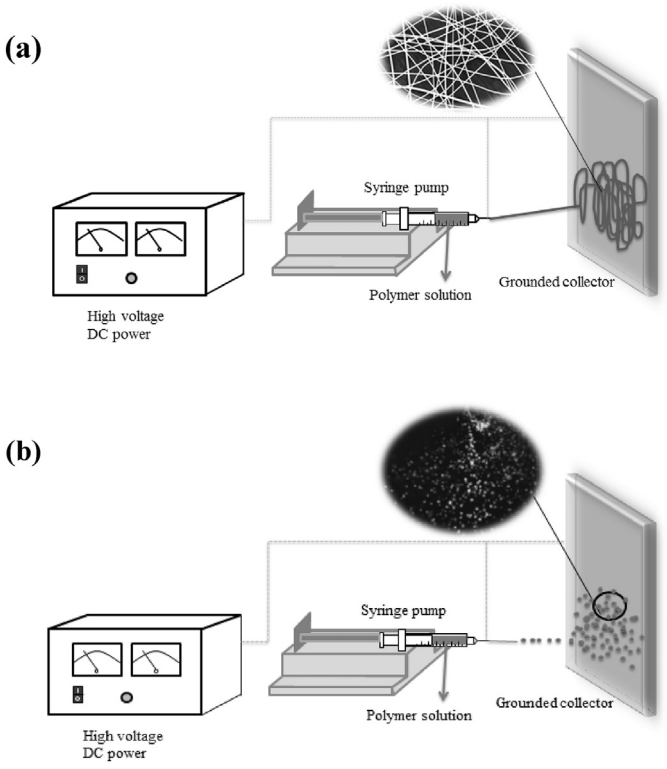

Fig. 1. Schematic of the basic electrospinning (a) and electrospraying (b) set-up employed for the generation of nano/microfibers and nano/microparticles respectively.

promote the generation of bead-free fibers even at lower polymer solution concentration regimes, (Uyar and Besenbacher, 2008; Jarusuwannapoom et al., 2005; Wannatong et al., 2004) whereas highly conductive fluids cannot be electrosprayed (Chan and Kwok, 2011), the applied voltage, the needle-to-collector distance and the needle diameter and (ii) *ambient parameters* including temperature and humidity. Therefore by modifying the aforementioned it is possible to tune the morphological characteristics and dimensions of the resulting nano/microstructures.

Fig. 2 illustrates schematically the effect of polymer solution concentration on the morphology of the obtained structures. At low solution concentration regimes, collapsed particles are usually obtained, whereas by increasing the solution concentration spherical particles are generated. Near a critical solution concentration, bead-on-string morphologies are typically observed, *i.e.* electrospun fibers co-exist with particulates, whereas above the critical solution concentration uniform fibers are produced.

Important influencing parameters also include the solution flow rate and the applied voltage. More precisely, an increase in the solution flow rate results in an increased diameter in both the particles (obtained by electrospraying) and the electrospun fibers whereas upon increasing the applied voltage, the particle and fiber diameters decrease. The

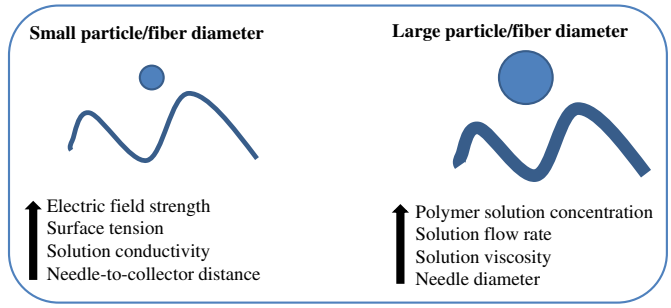

Fig. 3. Schematic illustration of the main influencing experimental parameters governing the diameters of electrospun fibers and electrosprayed particles.

diameters and morphologies of the obtained structures are also influenced by the distance between the spinneret and the collector. At smaller distances the solvent does not have sufficient time to completely evaporate, resulting in defects in both types of morphologies (particles or fibers).

Furthermore, in the case of electrospinning, at shorter distances the presence of bead-on-string morphologies may be observed, whereas upon increasing the distance continuous, bead-free fibers are generated and the fiber diameters decrease. Fig. 3 provides a schematic illustration of the effect of various experimental parameters on the diameters of fibers and particles produced by electrospinning and electrospraying.

2. Electrohydrodynamic methods in drug delivery

Drug delivery technologies target at improving efficacy and safety of the pharmaceutical compounds accumulated in the body by controlling the rate, the time, and the place of release (Jain, 2008). Drug refers to any type of molecule exhibiting a therapeutic effect (*e.g.* peptides and proteins, anti-cancer agents, antibiotics, *etc.*). Nowadays, polymeric nano/microstructures attract high attention in the biomedical field for the development of novel drug delivery systems. Among others, the increased surface areas of such materials lead to a higher drug loading efficiency and enhance the drug-dissolution rate (Elsabahy and Wooley, 2012; Kim and Lee, 2017). There are two different mechanisms of drug release from nano/micro structures: Passive diffusion and release *via* polymer degradation. Initially, the profile of the drug over time usually exhibits a very rapid (burst) release, owed to the presence of drug molecules on the surface of the nano/micro structures. This is followed by a more sustained release of the drug that is encapsulated within these structures.

During the last few years, many researchers have been focusing on the production of polymer-based drug delivery systems in the form of nano/microparticles and nano/microfibers by means of electrospraying and electrospinning respectively (Chakraborty et al., 2009; Enayati et al., 2011a; Prabaharn et al., 2012; Bock et al., 2012; Ramakrishna et al., 2013; Radhakrishnan et al., 2015). In the following, a brief overview is provided on the use of these two electrohydrodynamic methods for the development of such materials designed for use in the

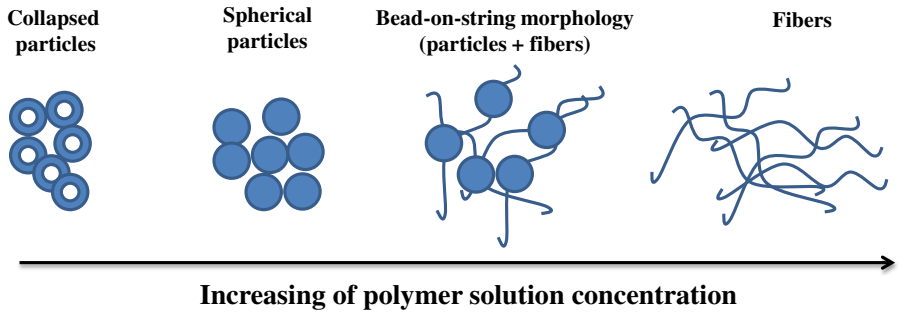

Fig. 2. Schematic presentation showing the effect of polymer solution concentration on the morphological characteristics of the nano/microstructures obtained *via* electrohydrodynamic processes.