Process Biochemistry xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Process Biochemistry

journal homepage: www.elsevier.com/locate/procbio

Review

# Micro- and nanocarriers by electrofludodynamic technologies for cell and molecular therapies

Rosaria Altobelli, Vincenzo Guarino*, Luigi Ambrosio

*Institute for Polymers, Composites and Biomaterials, Department of Chemical Sciences & Materials Technology, National Research Council of Italy, V.le Kennedy 54, 80125, Naples, Italy*

ARTICLE INFO

*Article history:*
Received 1 April 2016
Received in revised form 30 August 2016
Accepted 5 September 2016
Available online xxx

*Keywords:*
Electrospraying
Electrodynamic atomization
Microscaffolds
Diagnostics
Drug delivery

ABSTRACT

Electrofluidodynamic technologies (EFDTs) are receiving attention in the biomedical field as high-throughput technologies to encapsulate different types of molecules for cell and drug delivery. In this study, we propose an overview of the most cutting-edge approaches based on EFDTs to create, process and assemble biomaterials in the form of micro-/nanoparticles with unique and intriguing properties for different biomedical applications. After a brief description of the basic mechanisms involved in the formation of microparticles – by electrodynamic atomization (EDA) or nanoparticles – by electrodynamic spraying (EDS), we propose a critical review of the main applications of EFDTs in different biomedical fields (*e.g.*, drug delivery, regenerative medicine and diagnostic/theranostic applications) so as to highlight the role of materials and process conditions. In this way, we discuss the potential of EFDTs to design a large set of smart microscale devices (*i.e.*, nanoparticles, capsules, multicompartment systems, microgels, and microscaffolds) suitable to successfully face new challenges of nanomedicine (*i.e.*, cancer targeting) and tissue regeneration (*i.e.*, cell or molecular printing).



**Contents**



## 1. Introduction

The opportunity to manipulate materials at micro and sub-micrometric scales has been explored in various interdisciplinary research areas designing engineered nanomaterials with improved performance and significant commercial impact for automotive, metallurgical, optoelectronic and medical devices. In the last decade, many technological solutions have been provided for tissue engineering, regenerative medicine and nanomedicine, based on "bottom-up" or "top-down" manufacturing strategies with relevant benefits and different drawbacks [1]. Traditional tissue engineering strategies use a "*top-down*" approach, in which cells are seeded on a biodegradable polymeric scaffold with tailored morphological (*i.e.*, porosity) and chemical cues [2–4]. In this case, cells have to populate the scaffold, rapidly creating the appropriate extracellular matrix (ECM) and microarchitecture by the support of fluidodynamic (*i.e.*, perfusion), chemical (*i.e.*, growth factors) and/or mechanical stimulation [5].

* Corresponding author.
*E-mail addresses:* vguarino@unina.it, vincenzo.guarino@cnr.it (V. Guarino).

http://dx.doi.org/10.1016/j.procbio.2016.09.002
1359-5113/

On the contrary, Electrofluidodynamic Technologies (EFDTs) may be classified as a series of "bottom-up" technologies including electrospinning, spraying, or atomization suitable to synthesize micro- and nanostructures in the form of particles or fibers, through the use of high-voltage electric forces on viscoelastic polymer solution. They are mainly popular for their process simplicity and the ability to be easily implemented to fabricate smart devices with controlled size from micro- to submicrometric scale and with high scalability for industrial processes [6]. The high versatility of EFDT processes is due to the full control of experimental setup, process conditions and solution properties, which allows for a fine manipulation of morphological features in terms of characteristic size and distribution, shape, crystallinity, surface roughness and porosity [7]. The most part of experimental results proves that EFDTs can be successfully used for the production of electrospun scaffolds based on the capability of the assembled bioactive nanofibers to regulate and favor cellular interactions in the place of the native ECM [8–10]. More recently, electrospun fibers have been explored as carrier for the delivery of pharmaceutical species to design molecular loaded platforms suitable to trigger late cell events during the regeneration process. However, several problems in terms of adequate dose forms and stabilization, often occur because of the structural complexity of electrospun systems, which limits the chance to design efficient vehicular fibrous matrices for molecular release.

In this context, the increased acquisition of knowledge about interaction mechanisms between short and long polymer chains and electrical forces consolidates the idea of exploring EFDTs as attractive tools to assembly a wide range of devices (*i.e.*, nanoparticles, capsules and microscaffolds) for different applications (*i.e.*, pharmaceutics, food industry, and health care) [11]. By properly identifying materials and process conditions, EFDTs let the generation of monodispersed droplets – hundreds of micrometers down to tens of nanometers in size – controlling applied voltage, working distance, fluid flow rate, nozzle diameter, and the physical/chemical properties of the precursors [12]. In this case, size and surface-to-volume ratio of particles – not only material properties – drastically affect encapsulation/delivery mechanisms as a function of the specific processing routes. Among them, the electrospray (ES) techniques – namely electrodynamic atomization (EDA) and electrodynamic spraying (EDS) – have been recently explored as efficient methods to design cell and molecular carriers. In particular, EDS has been proposed as an alternative technological solution to traditional emulsion techniques for the incorporation of bioactive molecules into dense polymer structures, not exposing them to fast and uncontrolled denaturation, but preserving the carrier functionalities [13,14]. Alternatively, it is also suggested that the integration of electrosprayed nanoparticles into electrospun fiber network (*i.e.*, additive electrospraying – AES) [15] controls "separately" release and functional properties of the scaffolds during tissue formation. Electrodynamic atomization (EDA) has been more recently applied to non-Newtonian polymer solutions to produce microcarriers in order to investigate cell and molecular activities in health or pathological niche [16].

After a circumstantial description of the basic mechanisms involved in the formation of microscale devices by different EFDTs, the goal of this study is to provide an overview of the current and future applications in different biomedical fields (*i.e.*, drug delivery, regenerative medicine, and cancer therapy).

## 2. EDA vs. EDS

EFDTs include all the spraying processes in which an electrical gradient is applied to overcome the liquid surface tension producing a relatively monodisperse size distribution of droplets. Unlike induction and contact charging for electrostatic spraying, where conductive liquids are used, electrodynamic spraying (EDS) is only suitable for liquids that are capable of sustaining strong electrical gradients by virtue of their intrinsic high electrical resistivity. The basic working principle is simple: a liquid is expelled from an orifice connected to high-voltage polarity. Optionally, a collector that is grounded or connected to opposite polarity can be positioned downstream of the liquid exit, to establish the electrical gradient required for the atomization. The formed droplet size is controlled by several parameters, including excitation voltage, liquid surface tension, flow rate and orifice diameter through a process that is robust, stable and not noisy. Major advantages mainly concern the use of low electrical power for jet breaking, no mechanical force and low-pressure liquid pumping, despite some limitations such as the combined use of not electrically resistive liquids and low flow rates [17].

In general, EFDTs to produce particles may be schematically classified into two categories, as shown in Fig. 1. The first one, EDA, refers to all the processes characterized by non-continuous jetting. Liquid is emitted in the form of relatively large drops – dripping mode and microdripping mode – or elongated spindles or multispindles. The second category refers to all the processes in which the liquid – in the form of long and stable continuous jet – is disrupted into a fine droplet distribution. In this case, the process is classified as EDS [18–21] (Fig. 1).

In the case of EDA, different phenomena may occur: in dripping mode, solution drops with spherical shape are ejected tearing off from the capillary as the drop weight coupled with electric forces overcome capillary forces. Once voltage increases, fluid meniscus tends to stretch and the drop becomes smaller. On the contrary, in microdripping mode, a droplet is ejected without further disruption at the end of a fluid meniscus, because of the higher surface stability, and droplets become smaller as the capillary diameter decreases. In this case, low applied flow rates and less viscous liquids generally concur to more easily disintegrate the jet into smaller droplets under the applied electrostatic and inertial forces. Despite the fact that dripping and microdripping modes can be generated only in limited range of voltage and flow rates, the size of the droplets can range from a few micrometers up to a few hundreds of micrometers in diameters (Fig. 2) and their size distribution is usually monodisperse. Alternative modes (i.e, spindle and multispindle) generally occur in the presence of more viscous solutions because of the use of higher concentration or polymer molecular weights and require a more fine control of process parameters to prevent the formation of spindle-like jets usually generating elongated irregular fragments [22].

Analogously, the EDS process includes different processing modes: in the case of a stable cone jet formation, the liquid tends to form a regular, axisymmetric cone with a thin jet at its apex. In this case, the jet may flow along the capillary axis or slightly deviate from it, thus promoting instability, forming a fine dispersion of solid submicrometric particles once the complete solvent evaporation occurs (Fig. 2). In the oscillating jet mode, the continuous jet ejected from the cone tip may oscillate along all the planes generated by the capillary axis. Despite the high stability of the oscillation plane, it may change spontaneously to another orientation, thus limiting the control of particle deposition area. In both cases, the formation of multijets may be observed, mainly for low-surface tension liquids, which can be reduced by properly reducing electric field strength.

It is noteworthy that a good control of liquid properties and process parameters (*i.e.*, voltage, flow rate, and distance) is extremely important to switch among different spraying processing modes. For instance, a slight increase of voltage for liquid flow rate constant generally provokes an acceleration of the free dripping process with the formation of smaller droplets. However, further increase in voltage induces stronger stretching of polymer solution at the tip

Please cite this article in press as: R. Altobelli, et al., Micro- and nanocarriers by electrofludodynamic technologies for cell and molecular therapies, Process Biochem (2016), http://dx.doi.org/10.1016/j.procbio.2016.09.002