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Coaxial electrohydrodynamic atomization: Microparticles for drug delivery applications

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ABSTRACT

As cancer takes its toll on human health and well-being, standard treatment techniques such as chemotherapy and radiotherapy often fall short of ideal solutions. In particular, adverse side effects due to excess dosage and collateral damage to healthy cells as well as poor patient compliance due to multiple administrations continue to pose challenges in cancer treatment. Thus, the development of appropriately engineered drug delivery systems (DDS) for effective, controlled and sustained delivery of drugs is of interest for patient treatment. Moreover, the physiopathological characteristics of tumors play an essential role in the success of cancer treatment. Here, we present an overview of the application of double-walled microparticles for local drug delivery with particular focus on the electrohydrodynamic atomization (EHDA) technique and its fabrication challenges. The review highlights the importance of a combination of experimental data and computational simulations for the design of an optimal delivery system.

1. Introduction

Over the last few decades, fabrication of polymeric microparticles with different geometries has gained numerous interesting applications in many industrial as well as biomedical areas. In the biomedical domain, the polymeric microparticulate structures can find applications in drug delivery as depots encapsulating anti-cancer agents or in tissue engineering as scaffolds used for the growth of cells with spatial configurations. In addition, these polymeric matrices can be loaded with multiple agents which may stimulate specific signaling pathways and instruct cellular responses in a biological micro-environment [1,2].

The rising demand for polymeric microparticles with superior functionalities and complicated release profiles has led to the development of many processes for the fabrication of composite microparticles with well-defined configurations and morphologies [3]. Generally, the composite microparticles consist of a heterogeneous distribution of different polymers together with encapsulated agents integrated inside a polymeric shell layer. Based on the ultimate application, different hydrophobic and hydrophilic polymers can be utilized during the fabrication process. However, the number of polymers which can be employed is confined by the nature of the fabrication techniques and the compatibility between the inherent properties of the encapsulated agent and polymer matrix.

With increasing understanding about cancer cells and their proliferation pathways, the number of anti-cancer drugs that have appeared in the market has significantly increased. However, many of available and new drugs (i.e., biopharmaceutics classification system (BCS) class II components) often fail to show significant therapeutic efficacy due to their poor solubility in aqueous solutions. Therefore, one of the main objectives of utilizing drug delivery systems is to find solutions to (i) improve the solubility of these drugs, (ii) enhance their bioavailability, (iii) increase cell targeting functionalities, and (iv) reduce the number of downstream processes (e.g., handling and storage). However, the capability of conventional methods such as emulsion/solvent evaporation, spray drying and supercritical anti-solvent to synthesize microparticles with controlled morphology and complex micro-/nano-structures remains fairly uncertain. In fact, traditional particle preparation techniques face challenges in producing uniform-sized microparticles for drug delivery purposes. Moreover, long contact with organic solvents and a high level of shear stress on the solution dissolving the agents during fabrication process could accelerate denaturation of biomolecules (e.g., protein and DNA). For instance, in spray drying, the production of fine particles in large quantities and narrow size range distribution remains a challenging problem to be resolved.

Electrohydrodynamic atomization (EHDA), also called electrospraying, has been widely employed for encapsulating therapeutic agents in biodegradable polymeric particles and microbubbles for controlled and sustained drug release applications [4–7]. EHDA produces

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very fine droplets from a capillary liquid stream by using an electric field [8]. Depending on the properties of the liquid, the liquid flow rate and the applied electric potential, different modes of EHDA (i.e., dripping, cone-jet or multi-jets) can occur. The cone-jet mode is the most popular EHDA condition for the production of uniform-sized particles. For drug-loaded particles, narrowly dispersed particles are able to provide a precise controlled drug release with minimum batch-to-batch variations [9,10]. Henceforth, EHDA could be a potential improvement over the aforementioned techniques for generating particles in the micro-/nano-meter range with a narrow size distribution by posing less destructive effects on pharmaceutical agents [11–13].

This review aims to summarize the recent progress of the EHDA technique for the fabrication of composite microparticles via coaxial electrospraying, which has been employed for the encapsulation of therapeutic agents in biodegradable polymeric particles for controlled and sustained release. The important parameters affecting EHDA process for the reproducible tailoring of particle morphology, size distribution, encapsulation efficiency and in vitro drug release characteristics will be discussed. Finally, the major constraints and the proposed solutions for fabrication of reduced size and functionalized multi-layered microparticles will be presented.

2. Coaxial electrospraying for core-shell microparticle production

2.1. Coaxial electrospraying: basic concept

The concepts of monoaxial and coaxial electrospraying processes are similar, regardless of differences in the experimental setup. For monoaxial electrospraying, a polymer solution is injected into a capillary nozzle and subjected to a strong external electric field, created between the nozzle and a grounded collector by a high electric potential generator. Given that the liquid is electrically conductive, it will result in the formation of a fine polymer jet. The jet eventually breaks up into charged droplets that fly towards the grounded collector. Some setups make use of a closed chamber with continuous air or nitrogen flow that reduces the evaporation rate of solvent and allows the formation of particles with smooth surface morphology [14,15]. If the liquid is highly viscous or solidifies at the onset of jetting, fibers can be formed.

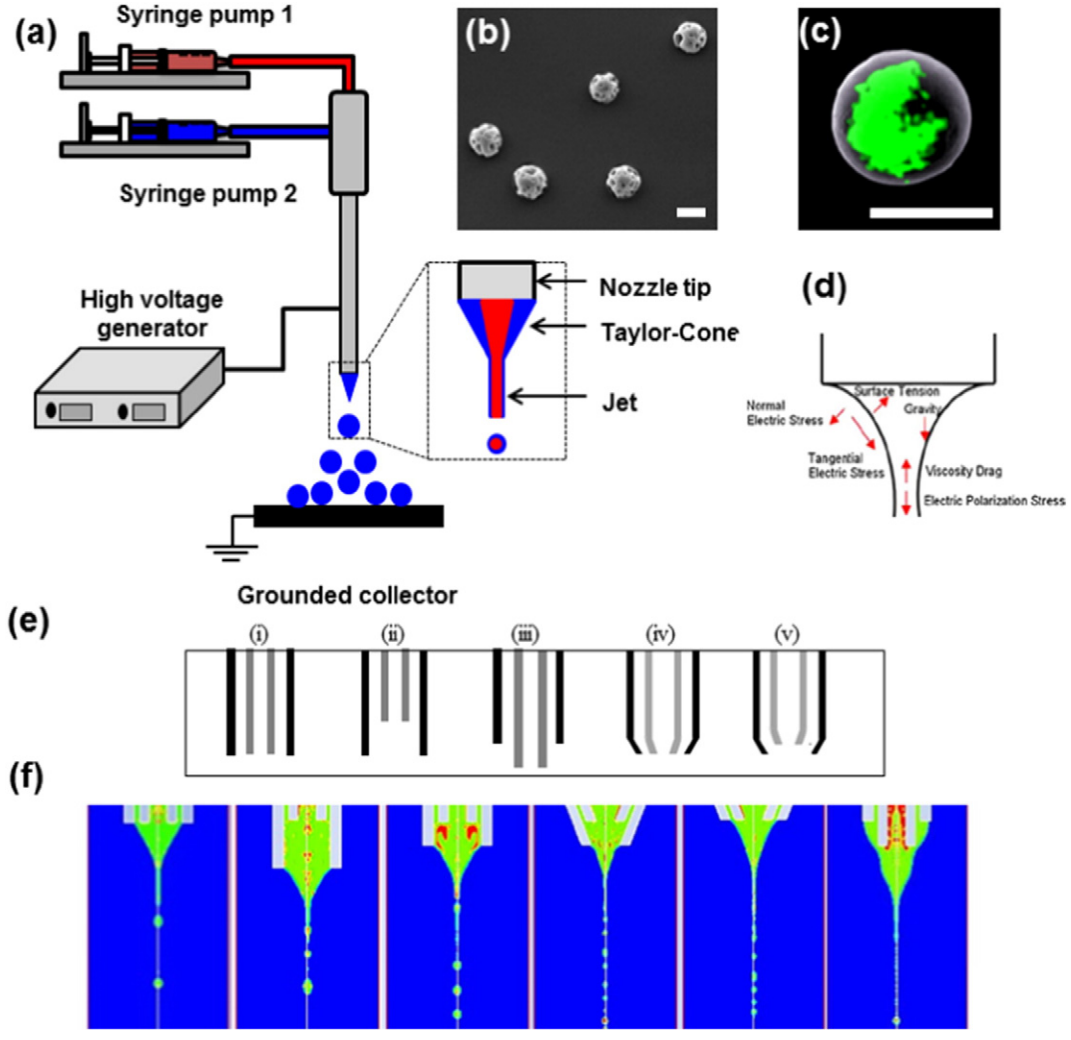

Fig. 1. (a) Experimental setup for coaxial electrospraying technique for the production of core-shell structured microparticles. The process involves the use of two syringe pumps to dispense two different polymer solutions through a coaxial nozzle. A high voltage is applied to the nozzle tip via a power generator to form a stable Taylor cone-jet, and the electrosprayed particles are accelerated towards the grounded collector. (b) Scanning electron micrograph depicting the morphology and monodispersity of electrosprayed particles obtained from coaxial electrospraying (scale bar = 10 μm). (c) Confocal micrograph depicting the intraparticle drug distribution. The drug is localized in the core phase of the composite particle (scale bar = 10 μm). (d) Schematic representation of the cone-jet mode in electrohydrodynamic process indicating the controlling forces [18] (reproduced with permission from Elsevier). (e) Different nozzle configurations: (i) uniform lengths of inner and outer needles, (ii) outer needle longer than inner needle, (iii) inner needle longer than outer needle, (iv) cone-shaped tip with uniform lengths of inner and outer needle, and (v) cone-shaped tip with outer needle longer than inner needle. (f) Flow behavior and droplet formation predicted by CFD simulation for different nozzle configurations. The red, green and blue colors represent core fluid, shell fluid and air, respectively.