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Review

Pharmaceutical Applications of Electrospraying

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ABSTRACT

The electrohydrodynamic atomization technique, or simply called electrospraying, has been extensively studied for biomedical as well as for pharmaceutical applications over the past years. The simplicity, flexibility, and efficiency of producing particles at the microscale or nanoscale, with tailored size, shape, morphology, and microstructure, make electrospraying to become one of the most promising and well-practiced approaches to be applied in many biomedical and pharmaceutical fields, from improving the bioavailability of poorly aqueous soluble drugs, preparing targeted drug delivery systems, and controllable drug release systems to delivering sensitive therapeutic agents such as protein-based drugs or even living cells. Nevertheless, some issues still remain with respect to low throughput as well as the complex interplay between a great number of processing and formulation factors. A comprehensive understanding of these fundamental aspects is essential for the successful application of electrospraying for the production of particulate formulations with desired properties.

Introduction

Ever since the first observation of a phenomenon in the early 17th century, later referred to as electrohydrodynamic atomization (EHDA) or electrospraying,[1] there have been significant efforts to elucidate the underlying physics of this process and to apply this technology in various fields ranging from food, ceramics, paints, to polymers and recently in drug delivery. The reason for the recent focus on electrospraying in the pharmaceutical field is that nanotechnology is acknowledged as an emerging tool for preparing mediated drug delivery systems (nanoemulsions, polymeric nanoparticles, liposomes, nanofibers and so forth) with proven efficiency in various treatments.[2-4] Searching for new and more effective techniques which can interfere with materials and molecules on the nanoscale is therefore of utmost interest. Electrospraying with its ability to produce many small droplets at the microscale or nanoscale from the breakup of a flowing conductive liquid by means of an electrical field has opened new routes to nanotechnology. However, compared to its counterpart, electrospinning, electrospraying seems to be lagging behind in terms of application, even though they share the same working principle. In fact, on account of the ease of fabrication and functionalization as well as versatility, electrospinning is already used extensively in a wide range of industries.[5] A large number of advanced applications for polymers, environmental protection, sensors, energy storage, tissue engineering, and drug delivery based on electrospinning can be found in literature.[6-9] Nevertheless, also electrospraying has begun to gain more attention as evidenced by its rapidly growing literature. Reasons for the recent focus on electrospraying, arguably one of the most promising, efficient, and well-practiced techniques to generate particulate materials for pharmaceutical and biomedical applications, is that it has several key advantages over other techniques to produce particles, which can be summarized as follows:

- Production of smaller particles (even <1 μm) with narrow particle size distribution and much less or no agglomeration and coagulation due to self-dispersing properties (compared to other conventional mechanical atomizers).
- Wide range of materials that can be processed by electrospraying, even sensitive and susceptible products such as proteins or cells.
- The experimental setup requires low investment and can be assembled and installed easily with common on hand means in a regular laboratory.
- Flexibility and versatility with various and simple setup configurations for diverse purposes (e.g., using single, coaxial dual

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or tricapillary nozzle) to prepare micro- and nanoparticles with controllable compositions, customized microstructures, and tailored properties of size, morphology, and shape for a variety of biomedical applications.
- The EHDA principle can also be simply incorporated into the configuration of different techniques (fluid bed granulation,[10] spray drying,[11] or inhalers)

In the framework of this review, we will discuss some fundamental aspects of electrospraying as well as critical formulation and process parameters determining the quality attributes of the final particles. Moreover, the article will cover diverse aspects of electrosprayed formulations and the feasibility of the development of these electrospraying-based products with particular focus on pharmaceutical applications.

The Basic Principles of Electrospraying

There are many excellent reviews that have been published in recent years regarding the fundamentals of electrospraying.[12-15] In this section, a brief summary will only cover the basic principles of electrospraying as well as the most important process and formulation parameters which will determine the electrospraying mode and the properties of the resulting particles.

The standard electrospraying configuration consists of 4 major components: a pumping system (often a syringe pump), a metal nozzle wired with a high voltage power supply, and a grounded substrate as collector (Fig. 1). This electrospraying setup can operate under ambient condition but can also be isolated in a closed or shuttle chamber with modifiable temperature and relative humidity for a better control of the drying process as well as preventing unwanted external contamination. During electrospraying, a conductive liquid jet breaks up into very fine droplets under the influence of an electrical field (thus, also called EHDA). More precisely, the conductive liquid is injected slowly by the pump through the nozzle to which the electrical potential is applied. For a sufficiently high applied voltage, the free charges at the surface of the liquid exiting the nozzle cause an electrical stress that leads to the formation of what is commonly called the Taylor cone-jet mode (the meniscus at the tip of the nozzle forms a conical shape). At the apex of the cone where the free charges are highly concentrated, the liquid accelerates away from the nozzle and a jet with high charge density is obtained. There will be 2 possibilities for the fate of the jet determined by the competition between the electrostatic repulsion, the surface tension stress on the liquid-gas interface, and the kinetic energy of the liquid affected from the Taylor cone. In the first case, for a sufficiently high axial tension in the jet, the charged liquid jet does not break up into droplets but is elongated and experiences a whipping instability stage during its flight to the collector. The tension in the jet is usually induced via the dissolution of higher molecular weight polymers. As a result, uniform, ultrafine polymeric fibers ranging from a few nanometers to several micrometers in diameter are obtained, and this process is usually referred to as electrospinning. In the second case, the charged liquid jet, at some point, will break up into droplets. These primary droplets then usually experience a phenomenon which is called Rayleigh disintegration or Coulomb fission. During their flight to the collector, the solvent evaporation makes the primary droplets to shrink which leads to the increase in charge concentration so the primary droplets finally will break up into smaller offspring

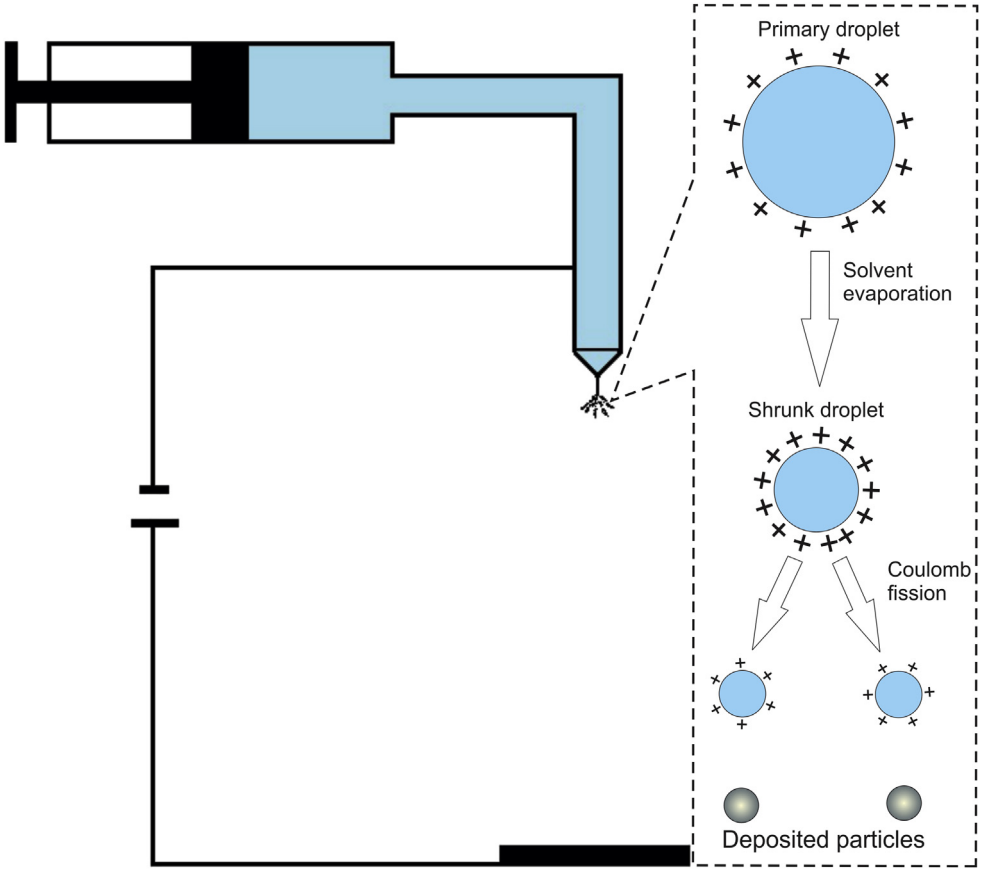

Figure 1. Schematic illustration of a standard electrospraying setup.