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Application of Electrosprayed Nanoparticles as Targeted Drug Delivery Systems: A Mini Review

[1]Sanaz Khademolqorani, [2]Seyedeh Nooshin Banitaba*

[1]Textile engineering department, Isfahan University of Technology – Iran

[2]Textile engineering department, Amirkabir University of Technology – Iran

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Corresponding Author:
Seyedeh Nooshin Banitaba
nooshin_bt@yahoo.com

Abstract

Nanoparticles (NPs) are referred to as tiny materials in size ranging from 1 to 100 nm. Unique characteristics of the NPs, including small sizes and high surface area, appropriate reactivity, proper stability, great strength, and many more, have resulted in their wide use in numerous fields. Among different techniques reported for synthesizing the nanoparticles, electro-hydrodynamic atomization or electrospray has been identified as a well-practiced and high efficient technique for the formation of fine and homogenous NPs from a liquid under the influence of electrical forces. This process allows feasible encapsulation of different drugs, vitamins, and proteins applicable in the targeted drug delivery systems. Since the release rate of the loaded pharmaceutical materials could be easily tuned via varying the properties of core and shell components. Herein, we summarized the importance of the electrospray technique for the production of drug-loaded nanoparticles applicable in controlled drug delivery systems.

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1. Introduction

Nanotechnology has recently been regarded as one of the most unrivalled processes due to its increasing implementation in various applications ranging from food and drug release to biology and sensor fields. Feynman pioneered nanotechnology in the last century, allowing for the creation of several materials at the nanoscale level. Nanomaterials are classified based on their morphology, including size, shape, composition, and origin [1]. Nanoparticles (NPs) are a broad class of materials that comprise particulate compounds with dimensions ranging from 10 to 1000 nm [2, 3]. Depending on the overall shapes, these materials can be 0D, 1D, 2D, or 3D [4]. NPs are not simple molecules in and of themselves and are thus consist of three layers: (a) the surface layer, which can be functionalized with a variety of small molecules, metal ions, surfactants, and polymers; (b) the shell layer, which is a chemically distinct material from the core in all respects; and (c) the core component, which is the center section of the NP [5]. Nanoparticles have distinct physical, chemical, and biological properties compared to bulk materials. This is due to a greater surface area to volume ratio, improved chemical reactivity or stability, increased mechanical strength, and other unique factors. These features have led to their usage in a variety of applications; drug delivery [6, 7], chemical and biological sensing [8], gas sensing [9-11], CO_2 capture [12], and many more [13]. Controlled drug carrier science has aimed to fabricate targeted devices with the potential to

release pharmacological agents, vitamins, proteins, etc., in specific sites and an optimal dosage, which is claimed to be ascertained via the usage of NPs. Depending on their inherent characteristics, NPs are classified into spherical, cylindrical, tubular, conical, hollow core, spiral, flat, and so on. In addition, some nanoparticles are either crystalline or amorphous, with single or multi-crystal solids that can agglomerate. Carbon, metal, ceramics, semiconductor, polymeric, and liquid-based NPs are some of the most well-known types of NPs based on physical and chemical characteristics. Bottom-up and top-down methods are two main classes of synthesis routes toward NP formation [14]. Bottom-up manufacturing involves assembling atoms or molecular components, as opposed to top-down production, which entails etching smaller and smaller shapes from bulk material. These approaches are further subdivided depending on the operation, response condition, and procedures. Optical lithography, E-beam lithography, scanning probe lithography, atomic layer deposition, sol-gel nanofabrication, molecular self-assembly, vapor-phase deposition, mechanical attrition, and specifically electro-hydrodynamic atomization or electrospray are some of the methods used to synthesize nanoparticles [15]. According to the statistical analysis in Figure 1, the number of publications involving 'electrospray nanoparticles applied in drug delivery systems has rapidly increased, which indicates that the research on electrospray nanoparticles is in full swing during the past decade. In addition, the application of electrospray nanospheres in drug loading systems has increased from 11 to 25 cases up to 2020, showing growing interest for researchers in using these structures as targeted devices. In the following section, the fabrication of NPs through the electrospray technique and their applications in the targeted drug delivery systems are explained.

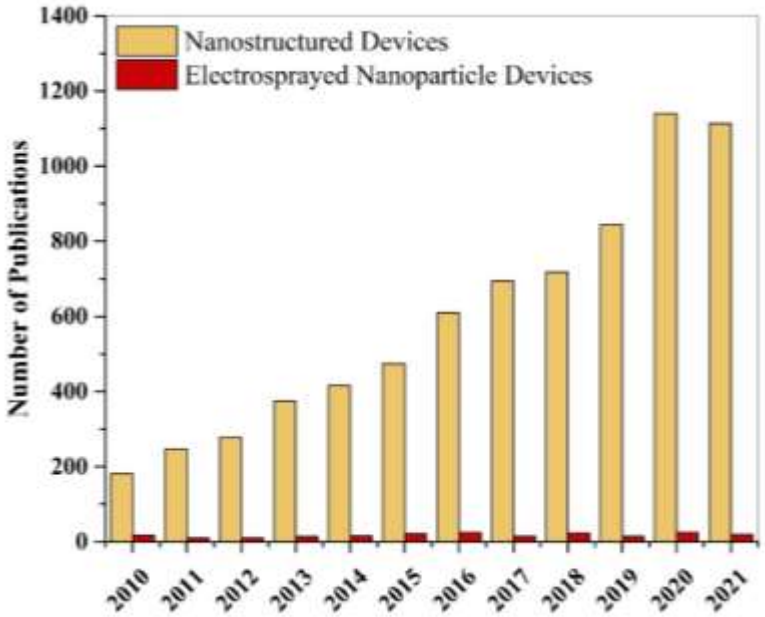

Figure 1: The number of publications per year from Web of Science on nanostructures and electrospray nanoparticles applied in drug delivery systems. Data accessed on 20 November 2021.

2. Electrosprayed Core-shell Nanoparticles as Controlled Drug Delivery Systems

Electrospray technology is extensively applied in food industries, medication delivery and carrier systems, coating and coloring applications, biology and tissue engineering, and sensor or catalyst modifications. Monoaxial electrohydrodynamic atomization is a process by which a high voltage, generally in the kilovolt range, causes very small liquid droplets from bulk liquid [16]. During electrospray, the electrical forces overcome the surface tension of the liquid under the influence of an external electric field. This phenomenon has been effectively used to fabricate a diverse range of polymeric and composite particles with controlled size, shape, and morphology from a dilute solution of polymer composites in organic solvents [17]. As an electrospray setup, a high voltage power source, a syringe pump, a syringe capped by a metallic needle with a specified diameter, and a collector are assembled [16]. Overall, the electric forces result in the naturally spherical meniscus deforming into a conical shape known as the Taylor cone, formed by surface tension equilibrium and electrical and gravitational forces.

When the accumulated charge at the apex of this cone generates an electric field strong enough to overcome the liquid's surface tension, a thin liquid jet erupts from the tip, removing the excess charge. Accordingly, the electrically charged jet disrupts into droplets due to the electrical repulsion of charges placed on its surface. The droplet formation process can be pulsing or continuous, depending on the physical properties of the liquid, the flow velocity, and the magnitude and polarity of the nozzle's high potential. A constant flow rate is required to sustain the liquid flow from this meniscus. The sizes of particles and their distribution are influenced by the applied voltage, solution concentration, flow rate, and syringe needle diameter, along with material characteristics [15]. Besides numerous reported applications for the monoaxial electrosprayed NPs, the fabrication of core-shell NPs has received wide attention for targeted drug delivery systems. Core-shell structures allow encapsulation of different vitamins, drugs, etc., in a polymeric shell component. In this procedure, a coaxial syringe needle is commonly applied to generate both core and shell phases. The components are fed into the syringe needle by using two feeding pumps. Typically, the shell part contains a spinnable material, while the core component comprises the non-spinnable one [18]. A coaxial electrospray setup is illustrated in Figure 2.

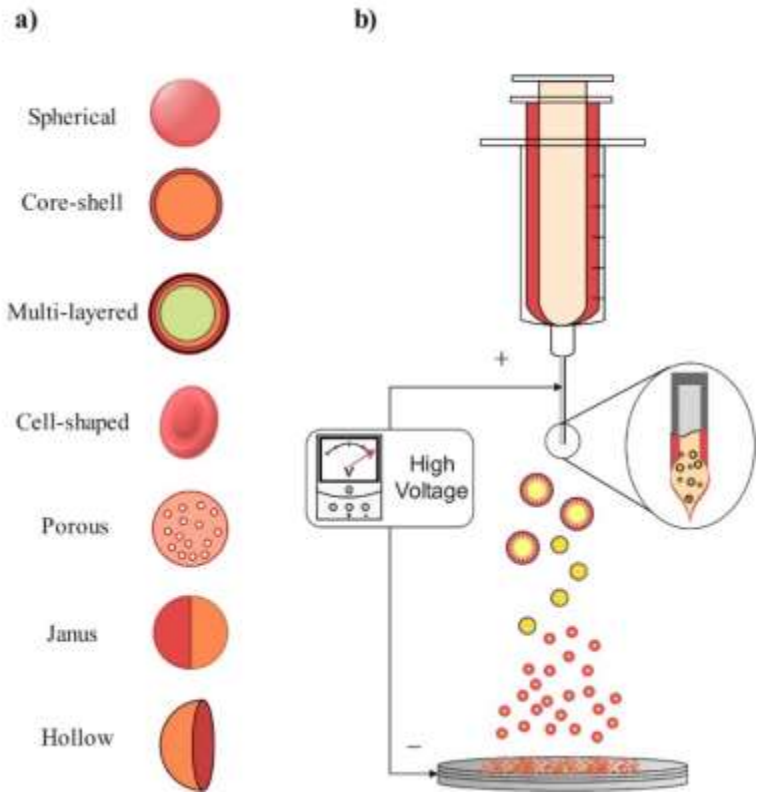

Figure 2: Schematic illustration of (a) various nanosphere structures produced by electrospray technique and (b) electrospray set up for fabrication of core-shell particles.

Since the invention of medicine, a broad scope of drugs has been applied against various diseases. Solutions, mixtures, powders, and pills are conventional drug delivery systems. In these cases, the drug level rises to its maximum after each dose and gradually falls below the effective level. This necessitates the administration of multiple dosages of the drug to maintain an adequate average level. Meanwhile, delivering precise concentrations of essential agents at the right location has remained a significant challenge. In recent decades, targeted drug delivery systems have been extensively reported to address this critical issue by controlling the therapeutic agent release. Such devices can reduce toxicity, enhance the therapeutic effects on the body, inhibit unpleasant usage of drugs, and increase patient convenience. Encapsulation of drugs in polymers and applying their mixtures have been numerously reported to approach targeted drug release. In these polymer-based systems, the physical properties of inner and outer components influence the release rate. Nano-sized polymeric materials are a great candidate for encapsulation or conjunction with different drugs. This capability has resulted from high surface area to volume, tiny pores, and appropriate porous structure. Unique features of the nano-sized polymers provide a

large capacity for drug loading and surface functionalization [19, 20]. In 2002, Kenawy [21] introduced electrospun tetracycline hydrochloride fibers as a highly potential targeted drug delivery system. Since then, numerous loaded electrospun fibers by vitamins, antibiotics, therapeutics, etc., have been introduced. Whereas nanoparticles, nanospheres with small sizes, can easily move in the body than the bigger materials [21, 22]. Three main strategies have been reported to fabricate electrosprayed nanoparticles for targeted drug release. In the first method, a homogenous matrix is fabricated through uniform dispersion of loading components throughout the electrosprayed nanoparticles. This procedure reveals a high encapsulation capacity and a prolonged drug release [19, 20]. In the next process, loading materials cover the nanoparticles and form the shell part leading to a fast drug release [19, 20]. Meanwhile, the third procedure is linked with the loading material in the core section covered by the polymeric shell component. Drug release in this strategy is governed by Fick's law and depends on the core component's physicochemical properties and the thickness and density of the shell part. In addition, Fick's law provides the possibility to describe the solute transport from a polymeric matrix [20, 22]. As for the polymer content, both synthetic and natural-based polymers and their mixtures have been utilized. Extracted polymers from natural resources, such as chitosan, alginate, albumin, and gelatin could offer a quick release rate Meanwhile, biocompatible synthetic polymers, including polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA), etc., have revealed less release rate than the natural-based ones [19, 20, 22]. Among the various reported fabrication methods for drug-loaded electrosprayed nanoparticles, core-shell ones containing drugs in the core components have been identified as the most beneficial targeted drug release structures. As an example, Kawakami et al. [23] used a coaxial electrospray apparatus to encapsulate a poorly soluble Fenofiberate (FEN) drug in a poly (methacrylic acid-co-methyl methacrylate) shell. They applied poly (vinyl pyrrolidone) to disperse FEN particles in the core component. This method synthesized a uniform distribution of FEN particles in the core part. In addition, the bioavailability of the FEN drug was enhanced via encapsulation. In another attempt, Curcumin (diferuloylmethane, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) was loaded in the core component of PLGA electrosprayed nanoparticles with particle diameters ranging from 1.87 to 2.25 µm. The particle size was claimed to be a tunable parameter by varying the applied electric voltage and feeding rate. However, Curcumin is an unstable material in light and has poor in vivo bioavailability conditions. Meanwhile, these two issues were addressed via encapsulating this material in core-shell structures fabricated through a coaxial electrospray system [24]. Yao et al. [25] utilized a three coaxial needle to produce multilayer microspheres and evaluated the effect of the intermediate layer on the resulting particles. Based on the obtained results, using the PCL/HAc and ethyl cellulose/HAc could lead to the fabrication of homogenous microspheres due to the formation of a stable jet during the electrospray procedure. Some similar attempts regarding encapsulation of drugs in the electrosprayed nanoparticles are summarized in Table 1.

Table 1: Electrosprayed core-shell structures loaded by various materials applicable as targeted drug release systems.

Core	Shell	Particle Size (nm)	Therapeutic Area	Electrospray Condition	Ref.
Gem in chitosan	Folic Acid in chitosan	200-300	Blood Circulation	Shell Flow Rate: 0.4 mL/h, Core Flow Rate: 0.1 mL/h, Distance: 15 cm, and Voltage: 10 kV	Xu et al. [26]
Rhodamine B or Naproxen on PCL/PLGA and PVP/PLGA	PLGA	394±35 606±39	-	Shell Flow Rate: 0.8 mL/h, Core Flow Rate: 0.2 mL/h, Distance: 9 cm, and Voltage: 16 kV	Cao et al. [27]
Doxorubicine/PVA	Silk	984	Cancer	Shell Flow Rate: 0.2 mL/h, Core Flow Rate: 0.8 mL/h, Distance: 9 cm, Voltage: 16 kV	Cao et al. [18]

Cont'd Table1.

Tamoxifen citrate (TC) and polyvinylpyrrolidone (PVP)	Shellac	740±70	Breast Cancer	Shell Flow Rate: 0.2 mL/h, Core Flow Rate: 0.8 mL/h, Distance: 15 cm, Voltage: 21 kV	Wang et al. [28]
PCL	PEG	less than 100 nm	-	Shell Flow Rate: 1.0 mL/h, Core Flow Rate: 0.3 mL/h, Distance: 20 cm, and Voltage: 20 kV	Chen et al. [29]
Acetyl Curcumin	PLGA	350±50	Human Cervical Cancer Cell Line	Flow Rate: 0.6 mL/h, Distance: 10 µm, and Voltage: 15 kV	Reddy et al. [30]
Berberine	PLA	-	Anticancer Drug	-	Ghaffarzadegan et al. [31]
Cellulose Nanocrystalline	alginate	200-500	Orchestrating Wound Healing	Flow Rate: 25 mL/h, Distance: 10 µm, and Voltage: 9 kV	Chen et al. [32]
Natamycin/ Clotrimazole on chitosan	PLGA	406±8	Fungal Keratitis	Shell Flow Rate: 0.5 mL/min, Core Flow Rate: 0.25 mL/min, Distance: 10 cm, and Voltage: 9.45 kV	Cui et al. [33]
Imatinib/PLGA	Paclitaxel/ Sodium hyaluronate	14.65×10^3	Cervical Cancer	Shell Flow Rate: 2 mL/min, Core Flow Rate: 1 mL/min, Distance: 15 cm, and Voltage: 17 kV	Liu et al. [34]

3. Conclusions

This paper explains the application of electrosprayed nanoparticles in targeted drug delivery systems. Electrospray is a well-known procedure for the preparation of drug-loaded nanospheres with mono/multi-layered structures. Single-step fabrication of nano and micro-sized particles, control of particle morphology, and efficient substance loading are beneficial characteristics of the electrospray method. NP structures incorporated with pharmacological substances could sustain drug release at localized sites, reduce the unwanted release, decrease the side chemical reactions, decline the essential dosage of the drug, and increase the drug performance such as bioavailability and solubility. Meanwhile, particle fabrication with a narrow size distribution, particle agglomeration, and low production rate are still the main challenges facing the electrospray procedure, which should be addressed in the future

Conflict of Interest

The authors declare that they have no conflict of interest.

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