Electrohydrodynamics in Fabricating Drug Delivery Systems

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Background

Modern therapies clearly demonstrate the need for pharmacokinetic and pharmacodynamic principle-driven administration of drugs. The term 'drug' has been broadened over the years to include bioactive proteins, growth factors, and nucleic acids. This evolution of new therapeutic agents demands for development of novel drug delivery systems (DDS) to realize the actual therapeutic potential of these delicate bioactive agents. One exciting development in this area is the application of electrohydrodynamics (EHD) to fabricate drug-loaded nanofibers and nanoparticles. The former is mostly used in creating an optimal microenvironment for regenerative medicine, and the latter being developed to meet the demand of targeted and intracellular delivery of therapeutics. Especially the electrohydrodynamic atomization technique, commonly known as electrospraying, offers several main advantages over the other techniques such as improvement of dissolution rate of poorly water-soluble drugs, batch-scalability, reproducibility, effective encapsulation in a single step microparticle fabrication. In this process drug release characteristics are tuned by using suitable biodegradable polymer carriers, leading to a sustained release of encapsulated drugs. Moreover, the novel concepts like multi-pharmacy or polypharmacy can be made possible by loading different drugs into multi-layered particles using the electrospray technique.

Electrohydrodynamics (EHD)

EHD also known as electro-fluid-dynamics or electrokinetics, is the study of the dynamics of electrically charged fluids. EHD is actually at the interface of electrodynamics and fluid dynamics. In EHD, when a liquid is infused into a nozzle (needle) and a free-spherical-droplet is formed at the tip of the nozzle. However, when a strong electric field is applied, a charge is induced on the surface of the droplet. When the force generated by the electric field is strong enough to overcome the surface tension of the liquid, the droplet deforms into a Taylor cone, and a charged jet of the liquid is propelled to the collector, which is of opposite charge to the droplet or grounded (Figure 1). If a polymer solution is being fed to the nozzle, the solvent evaporates forming solid products at or before the collector. EHD technique has two subcategories: Electrospraying and electrospinning, they differ only in their final products. Both of these processes transform liquid droplets emerging from a nozzle, under a strong applied electric field, into micro and nano products. In electrospraying, typically a low-viscous conductive liquid is dispersed into fine droplets. These charged droplets stay stable till they reach the Rayleigh limit and then undergo coulombic fission resulting in even smaller droplets. Electrospinning is a process in which a high-viscous solution or a melt can be spun into fibers with smaller diameters. The electrospinning process could generate fibers of various diameters and lengths from almost any soluble polymer.

Electrospun fibers

Electrospun fibers have attracted much attention in the field of tissue engineering because of its ease of fabrication and its resemblance to nanotopographical elements in the extracellular matrix of tissues. There is also an increased interest to incorporate drugs into the fibers to get an enhanced functionality of these scaffolding materials. Drugs can easily be embedded in the fiber through dissolution or dispersion in the polymer solutions. Controlled release of the drug integrated into a tissue engineering scaffold offers temporal spatial gradient to mimic the complex tissue microenvironment for tissue development or regeneration. Many biochemical factors needed for tissue development are protein or nucleic acid in nature, and most importantly, they do not dissolve in common organic solvents. In addition, they may lose their bioactivity if dispersed in the polymer solutions. Co-axial electrospinning would be an ideal alternative for this issue, here the drug is dissolved in an aqueous core solution and the polymer in an organic shell solution.

Electrospray

Electrospraying on the other hand has generated immense interest as a facile single-step method to generate nano/micro particles. Several other techniques have been established to make nano/micro particles encapsulating therapeutic agents such as spray drying, emulsification-evaporation/extraction, salting-out/emulsification, nanoprecipitation, and ionic gelation. Emulsion-based methods are the most extensively studied in terms of DDS fabrication.

It would be highly beneficial to synthesize nano/micro particle based DDS with the following features: 1) elimination of high shearing forces (stirring or sonication); 2) high encapsulation efficiency; 3) high loading level; 4) uniform drug distribution in the matrix; 5) efficient removal of residual surfactant; and 6) convenient and easily scalable. Electrospraying, especially the coaxial variant (Figure 2) has the capability to address these requirements. In general, electrospraying is very similar to electrospinning except the fact that the jet breaks down into droplets. Drying effects along with residual charges on the particles prevent aggregate formation once they land on the target. Spheres with a diameter of < 10 nm can be generated using this electrospray technique compared to mechanical atomizers, which typically produce particles with micron dimensions. Especially, the absence of continuous high-energy shearing force is beneficial in protecting sensitive therapeutics like proteins or drugs.

One of the crucial factors for drug effectiveness is the water solubility ratio, especially for the oral route. The electrospraying process can be used to improve solubility of poorly water-soluble drugs. Moreover, different release profiles for the drug can be obtained by using different ratios of different polymers or polymer composites. Electrospraying has also been used for targeted delivery of therapeutics. Through this method, drug release can be predictable in a sustained manner and more importantly the drug can be released to provide enough and exclusive accumulation of the drug at the specific unhealthy location. Especially, this system can protect the drug from degradation and loss of bioactivity effectively compared to other conventional dosage forms.

EHD method can in principle provide a uniform dispersion of a particular drug within the polymeric matrix with high loading capacity and minimal drug loss. Use of multiple electrospinning/electrospraying spinnerets will make the process high throughput. Ease of operation and cost-effectiveness of this process are two major benefits. The aforementioned characteristics along with the ability to spray/spin virtually any soluble polymer into micro/nanoparticles and fibers has made electrosprayed particles and electrospun fibers attractive drug delivery vehicles.

Fabrication techniques

Electrospinning

Monoaxial (one needle) electrospun fibers have been prepared to incorporate and release proteins, antibiotics and other therapeutics in a sustained manner. However, in this version distribution and release of drugs from the fibers are poorly controlled. Moreover, therapeutics like growth factors and cytokines embedded in polymer matrices could lose their bioactivity. The co-axial electrospun fibers offer better delivery systems with better drug stability, efficient drug encapsulation, and well controlled release kinetics compared to monoaxial fibers. Changes made in the shell and core material properties by varying the molecular weight, polymer type and addition of porogens enable us to fine-tune the release profile.

Drug is usually incorporated in the core of core-shell (Figure 2) electrospun fibers as opposed to the random distribution of the drug throughout the fiber matrix in monoaxial fibers. In core-shell design, a higher controlled release barrier can be achieved by using higher molecular weight and concentration of the polymer. The polymer-drug interaction is another variable that significantly influences the extent of drug release. This interaction is governed by charge density, hydrophilicity, and degradability of a polymer. Additionally, increase in encapsulated drug concentration leads to a higher diffusive driving force for drug release.

Electrospraying

Unlike electrospinning, in electrospraying the jet breaks into droplets. Due to surface tension effect the fragments of the jet consequently acquire a spherical shape before reaching the grounded substrate. An increase in voltage, conductivity and surface tension of sprayed solution results in decrease in particle diameter. An increase flow rate, density and viscosity of sprayed solution gives larger particles. The following techniques can be used for loading of drug (s) into the sprayed vehicle.

Adsorption— in this method the drug is adsorbed onto the sprayed particle by exposing them to a drug solution. The major disadvantage associated with this method is that most of the drug is often loosely attached to the particle surface and results in a prominent burst release. In addition to that the period of sustained release also tends to be short for such DDS.

Encapsulation—encapsulation can be achieved by using several methods.

1. collision of droplets of opposite charge: Two adjacent capillaries are used in this process. As droplets emerge from two adjacent capillaries, they attract one another due to columbic forces and subsequently fuse to make a one particle. Therefore, this can be used for drug encapsulation if one charged species is polymer and the oppositely charged species is the drug
2. Electrospraying: The drug-polymer solution/suspension is electrosprayed and the solvent is evaporated as the jet travels towards the collector. Thus, the drug gets encapsulated in the dried polymer spheres.
3. Electrospraying of a drug dissolved/suspended in a polymer followed by solidification by a chemical or ionic cross-linker: The drug-polymer solution/suspension is sprayed into a collection bath containing a cross-linker. Here the drug becomes entrapped in the polymeric network.
4. Coaxial electrospraying: This method offers immense potential as the core-shell structure will reduce any burst release and may follow near zero-order release kinetics. Additionally, this procedure is quick to fabricate and offers high encapsulation efficiency and loading capacity.

Summary and the outlook

Evidently, micro/nanomaterials have the ability to mimic the size range of biological molecules and entities, hence they have a great potential in the medicinal and pharmaceutical field. Biocompatible polymer-based nano/microparticles can be used as vehicles for the controlled delivery of various therapeutics such as anticancer, antidiabetic, antihypertensive drugs, hormones, immunomodulatory agents, vitamins, nucleic acids, proteins, and antibodies. Polymers such as PLGA, PCL, PLA, are approved to be used for the aforementioned purpose by the Food and Drug Administration (FDA).

The main purpose of controlling the release of a drug is to improve the effectiveness of a particular therapy, preventing both deficient and overdosing intake. Moreover, controlled-delivery systems have the ability to maintain the level of the therapeutic agent within the desired range, decrease the frequency of dosage, ensuring better stability of the incorporated substances against degradation (e.g. enzymatic), reduce toxicity, and increase patient compliance. The biggest challenges in adapting electrosprayed microparticles for drug delivery at a commercial level are mass production and reliability of dosage. This will require modern but simple and economical engineering to control the size distribution of the particles precisely. Overall, electrohydrodynamic routes are actually in competition with emerging new technologies such as gyration and microfluidic methods. Therefore, rapid investment is needed to take this perfectly viable laboratory scale method to an industrial scale operation.

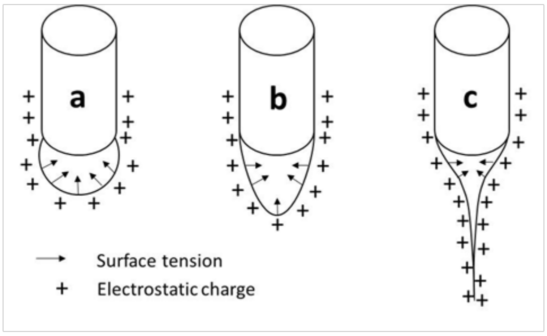

Figure 1: Taylor cone formation at the capillary tip under an applied electric field., (a) primary droplet held by high surface tension, (b) increased electrostatic charge overcomes the surface tension and droplet undergoes deformation (c) at the critical voltage the solution overcomes the surface tension and the electric charge causes the solution to elongate and assume a cone shape, known as Taylor cone.

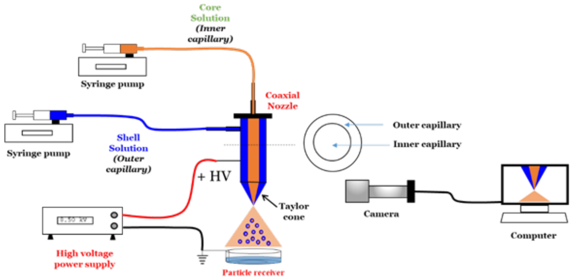

Figure 2: The basic setup for electrospraying consists of several components: syringe pump(s), a metal nozzle connected to a high voltage power source, a grounded substrate as a collector and a monitor

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Guest Articles

Understanding the Relationship Between Protein Structure and Function Using NMR Spectroscopy

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Nuclear magnetic resonance (NMR) spectroscopy uses the magnetic spin properties of certain atomic nuclei within a molecule to enable identification of atoms that are close together in space. NMR is ideal for protein studies, as many structural and motional "spin probes" are uniformly distributed throughout any given protein. These atoms can be nearby either because they are bonded together or because folds of a protein chain bring them together. This information is used to derive a three-dimensional model of a protein in solution phase or a "solution structure". Since protein structure and function are deeply related to one another, several experimental methods have been designed to determine protein structures. An NMR instrument allows the structure of a material to be analyzed by producing atom-atom distances between close atoms of the structure. Important technical improvements of NMR methods for protein structure and dynamic determination have occurred during the past few years.

Many biological processes are in principle driven by protein conformational changes. The polypeptide chain of most proteins fold and fluctuate around an average three-dimensional structure. Understanding the mechanisms of how proteins "morph" their three-dimensional structures into alternative conformations provides a deeper understanding of the protein function. Protein conformational change is a pervasive regulatory mechanism in biology and has recently emerged as a topic of broad appeal to a wide range of biological research areas, including drug design and protein engineering.

The focus of this presentation is understanding how various substrate sequences modulate the affinity and inter-domain dynamics of Pin1, an essential Peptidyl-prolyl isomerase (PPIase). Pin1 is a 163 amino acid polypeptide with an N-terminal binding domain and a C-terminal rotamase (PPIase) domain. A flexible linker of 12 residue connects the two domains. Both domains have binding sites that specifically recognize phospho-Serine/Threonine-Proline motifs. Pin1 catalyzed isomerization supports a major conformational switch between cis-trans isomerization of common pSer/Thr-Pro sequence motif common in cellular response to a variety of signals. However, the binding sites of the two domains are far apart, separated by an inter-domain interface. The diverse number of potential binding sequences for Pin1 made it difficult to interpret its role in pathogenesis in human diseases such as cancer, frontotemporal dementia (FTD) and Alzheimer's disease (AD).