ELECTROSPINNING FOR DRUG DELIVERY SYSTEMS: POTENTIAL OF THE TECHNIQUE

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Abstract

Electrospinning is a technique used to manufacture nano- and submicron fibers based on synthetic or natural polymers. Additionally, biomaterials used in the electrospinning procedure can be modified by bioactive compounds, e.g. peptides or growth factors. The microstructure of the obtained fibrous scaffolds mimics natural extracellular matrix (ECM) environment. The size and the microstructure of the fibrous scaffolds are considered to be suitable for cells adhesion and proliferation.

Various design features of the electrospinning device (e.g. the shape of the collector, the shape of the nozzle, the direction of the applied voltage) or electrospinning conditions (e.g. humidity, temperature) allows to control properties of the fibers (their shape, diameter, porosity). Novel structures, such as core-shell fibers, porous fibers attracted wide attention due to their properties and functionalities. Porous fibers or fibers with nanoscaled structures can be obtained in several ways. These methods are mainly focused on using high humidity and highly volatile solvent applied in the electrospinning process. The core-shell structure can be obtained by coaxial electrospinning. That binary fiber has ability to control the release rate of drug enclosed within the shell or core. The drug release profile can be also modified by loading the pharmacological agent either directly to the spinning solution or its post immobilization.

This diversity of the electrospun fibers is a reason for non-woven materials to be considered for application as drug carriers. The review of electrospinning methods presented here proves that the control over fibers surface area, morphology and the choice of polymer enable modelling of drug release kinetics.

Keywords: *electrospinning, drug carrier, DDS, nanofibers, polymer*

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Introduction

The main challenge in designing drug carriers is an effective biodistribution of the pharmacological agents in the body. Thus, the form of a carrier plays an important role in the drug release process. There are many types of carriers such as micelles, microcapsules, microspheres, liposomes, proteins, and DNA. Lately, scientists have been paying particularly great attention to (nano)fibers. Such form of the material can be obtained by several techniques like template synthesis, self-assembly, phase separation method, airbrush spray, melt blow technology, and the most popular one – electrospinning. In the last one, the polymeric solution is transformed into solid fibers by application of electrical force [1]. There are numerous critical factors, including process parameters, solution parameter, and ambient parameters, that have an influence on the morphology of the fibers and the whole membrane. These variables determine fibers morphology which, in consequence, affects the drug release profile. The electrospun mats have fiber diameter ranging from several dozen of nanometers to microns. These materials are characterized by high porosity and high surface area to volume ratio which allow efficient drug loading. It is also possible to create porosity within a single fiber. That can further enhance surface development and increase the functionality of the fibers. Furthermore, the drug release can be controlled by loading the pharmacological agent either directly to the spinning solution or by its post-immobilization. There are also other techniques for drug incorporation. In the case of less stable drugs, use of emulsion electrospinning or co-axial strategies is recommended.

This review summarizes current possibilities of producing fibrous drug carriers.

Parameters determining the properties of the fibers

A typical electrospinning setup consists of 3 main components: high voltage power supply, syringe pump with attached metal nozzle (needle) and grounded collector (metal shield, plate, rotating drum). The polymer solution is introduced via a syringe pump. When a high voltage (typically 1-30 kV) appears between the metal nozzle and the collector, the polymer solution inside the syringe becomes electrically charged. When the electrostatic force is greater than the surface tension of the polymer drop at the end of the metal nozzle, the droplet is pulled out of the needle. The shape of the drop resembles a cone, known as the Taylor's cone. The thin stream of fiber is accelerated to the collector with opposite polarity. During the passage of the fiber stream from the needle to the collector, the solvent present in the polymer solution evaporates allowing the polymer fiber to solidify on the collector [2-4].

A number of processing parameters can be adopted to obtain the desired diameter and morphology of the nanofibers. They can be divided into three groups: process, polymer, and ambient parameters. Process parameters include applied voltage, the flow rate of the solution, the distance between the tip of the needle and the collector and the type of the collector [5]. The most common collector design is the single static plate collector. The plate can be changed to the rotating drum. This modification allows to obtain parallel fibers by increasing the rotation speed of the drum. Dual collectors can be obtained as well when a gap is left between them. As a result, the electrospun fibers are suspended in the air. A similar solution can be found in a ring collector, which has an empty interior. It is also possible to co-electrospun fibers onto a rotating collector (two separate syringe pumps and nozzles sets are needed) or electrospray and electrospun simultaneously. These numerous permutations of the collector design have an effect on the final morphology of the fibers [6]. The rest of the process parameters affect mainly fibers diameter. Increase in applied voltage causes a decrease in fibers diameter. The same effect is observed when increasing distance between the needle and the collector or decreasing the flow rate [5] (TABLE 1).

TABLE 1. Effects of electrospinning prameters on fibers microstucture.

Paramters	Effect on the fiber morphology
Supplied voltage	↑voltage ↓fiber diameter
Flow rate	↓flow rate ↓fiber diameter
Distance between needle and the collector	↑distance ↓fiber diameter
Polymer concentration	↑concentration ↑fiber diameter
Polymer viscosity	↑viscosity ↑fiber diameter
Polymer molar mass	↓molar mass provides bead formation
Solvent volatility	↑volatility – porous fiber ↓volatility – fibers stick together on the collector
Solution conductivity	↑conductivity – homogeneous fibers diameters
Temperature	↑temperature ↓fiber diameter
Humidity	↑humidity ↓fiber diameter

Also, polymer solution parameters, such as polymer concentration, solution viscosity, the molar mass of polymer, solvent volatility and solution conductivity have an impact on the electrospinning process. Spinnability of the solution is the most important factor which is determined by the polymer concentration. It has to be high enough to allow forming fibers. On the other hand, too high concentration and viscosity impedes passing of the solution through the needle and may cause dropping of the solution from the needle prior to the actual electrospinning process. A highly concentrated solution results in a greater number of entangled polymer chains, which translates into a larger fiber diameter of uniform thickness. At gradually lower polymer concentrations, the resulting fibers become thinner and may contain a large number of beads. Too low concentration and too low viscosity cause lack of spinning or interruption of the beam and the formation of droplets. In this way, the electrospinning process can transform into electrospray. Thus, there are critical concentration and viscosity values at which the concentration of polymer chains entanglements allows the formation of a continuous polymeric stream. It is worth underlining that by increasing these two parameters, the diameter of the resulting fibers may be increased. A suitable viscosity of a polymer solution is provided by a molar mass. Lower molar mass leads to the formation of beads. The role of a solvent is not only to dissolve a polymer but also to transfer the polymer solution towards the collector. Solvent parameters like surface tension, conductivity and vapour pressure are of equal importance. Low vapour pressure and thus high volatility are desirable properties of the solvent. As a result, the entire solvent evaporates completely when the jet is transferred to the collector. When using a solvent with low volatility, the fibers on the collector stick together or flatten. The increased volatility of the solvent also gives a greater chance of producing porous single fibers. All these parameters have an influence on a solution surface tension, which determines the amount of charge needed to initiate the jet. With a smaller surface tension, a low value of voltage created by the power supply to remove the drop from the needle is needed. In the case of high surface tension, the electrospinning process is more difficult [5,7-9].

The ambient parameters are also very relevant. The thickness of the fibers can be controlled by temperature and humidity. The increase in temperature is associated with a reduction in fiber diameter. This is due to the drop in polymer viscosity at elevated temperature. Humidity affects the electrical conductivity of the ambient atmosphere/air. The increase in humidity causes the tensile forces to be more efficient, facilitating the spinning of the fibers from solutions of high viscosity, and the applied voltage can be significantly lower. Lower humidity results in rapid evaporation of the solvent, resulting in thicker fibers, while higher values cause slower evaporation of the solvent resulting in thinner fibers. Changes in humidity and/or higher temperature may contribute to the formation of pores on fiber surfaces, as these parameters affect the evaporation rate of the solvent [5].

Drug incorporation method

The specific form of fiber provides several options for drug incorporation. The basic approach is blend electrospinning (FIG. 1C). Drug and polymer are co-dissolved in solvents before electrospinning process. In the case of this method, the crucial factor is a proper distribution of the drug in the entire volume of a solution. Preferably, active agents should be evenly distributed within the final electrospun fibers. In practice, most molecules, during the electrospinning process, migrate to the surface of the solidifying fibers due to evaporation of the solvent. The molecules of the drug deposited on the fiber surface can be readily released, causing an undesirable burst effect. It is also worth mentioning that appropriate selection of a solvent, polymer and drug system is challenging for blend electrospinning [4].

This limitation can be overcome by applying emulsion electrospinning (FIG. 1B). This technique is based on two immiscible liquids stabilized by an emulsifier. In this way, biomolecules or hydrophilic drugs are protected from a solvent used in a polymer solution. During the electrospinning process, the obtained droplets may be distributed homogeneously within fibers, locate close to the surface or form a core-shell structure. The core-shell structures are obtained when solvent from the outer part of a polymer jet, the surface, evaporates faster than from the inner part. The viscosity of the surface is much higher compared to the interior. Then, emulsion droplets are induced to move from the outside to the inside of the polymer jet. Under a high-voltage conditions, emulsion droplets are stretched and condensed along the fibers axis. Optimal parameters ensure that a fibrous core-shell structure is obtained without using a specific nozzle. Furthermore, emulsion electrospinning allows the encapsulation of less stable molecules and provides a sustained drug release without burst effect [10].

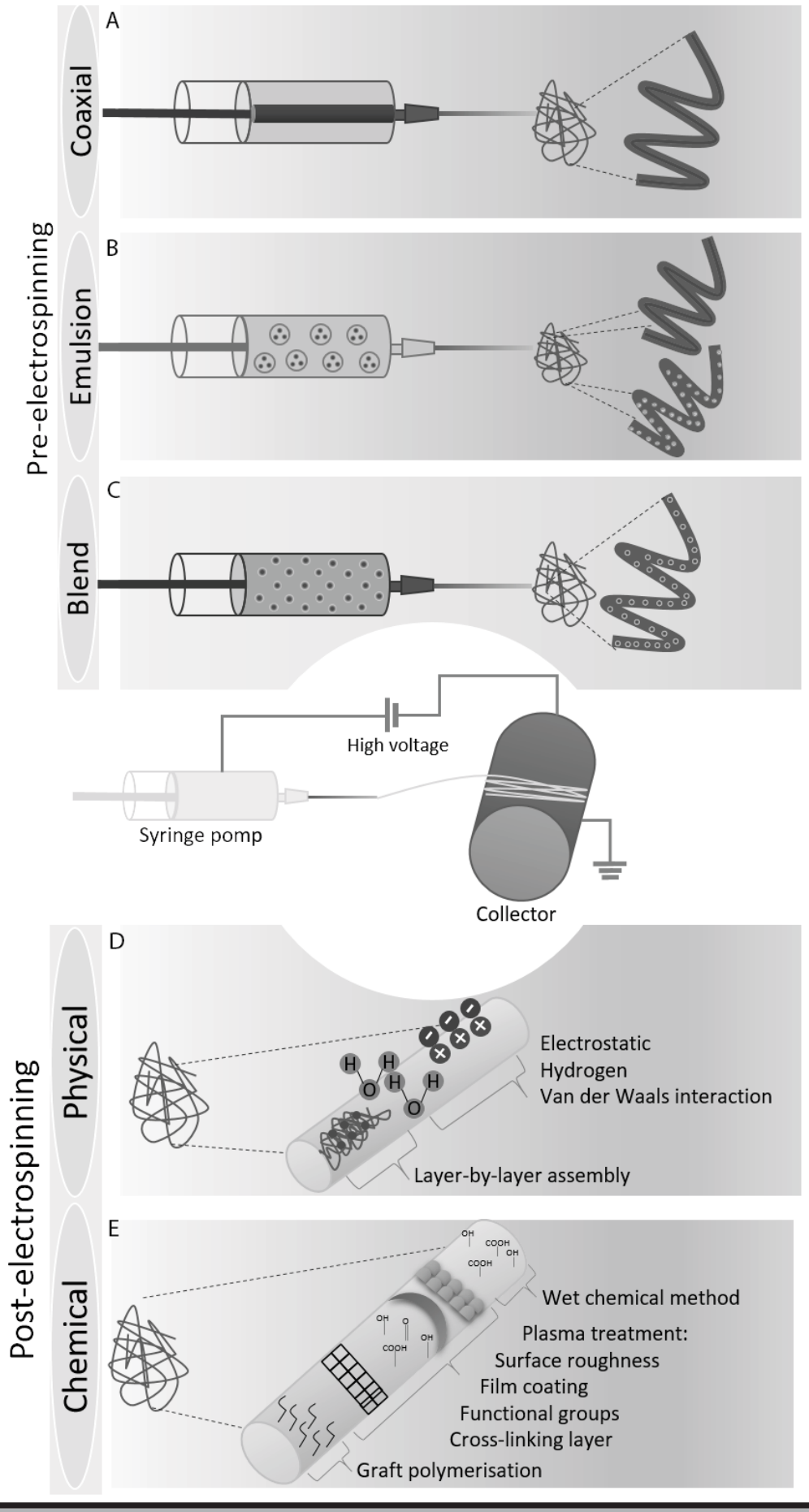

FIG. 1. Strategies of incorporating drug: A - co-axial electrospinning; B - emulsion electrospinning; C - blend electrospinning; D - physical surface modification; E - chemical surface modification.

The core-shell structure can also be manufactured in an intended manner using co-axial electrospinning (FIG. 1A). This strategy is based on simultaneous electrospinning of two kinds of immiscible polymer solutions through two concentrating nozzles. Use of two different solutions increases the difficulty of optimizing process parameters. It is also possible to generate empty space inside the fibers by removing the internal phase of the core. This technique can be used to encapsulate unstable macromolecules [4,6].

The possibility of introducing active molecules into the fibers prior to the electrospinning process is not the only way to combine the drug with a fiber. Active molecules can also be adsorbed onto a surface of the fibers as a result of physical (FIG. 1D) or chemical interactions (FIG. 1E). Simple adsorption is an example of a physical post-immobilization. It is a common method of applying a drug onto a fibrous membrane. Adsorption of molecules onto the fibers is driven by electrostatic interactions, hydrogen bonds, and van der Waals interactions. The fibrous membranes have a higher surface to volume ratio, as a result of which a larger amount of drug can be deposited onto the surface of the fiber than introduced into their volume. For that reason, the immediate release of a very high dose of an active substance may be observed. A similar surface functionalization process takes place in the case of nanoparticles. The method of the physical surface modification can be also realized by a multilayer assembly. The method is based on applying layers of polyanions and polycations to the charged surface by electrostatic forces [4].

Another approach is to modify fibers surface chemically, which causes the formation of reactive functional groups. Such transformation of surface groups allows the immobilization of molecules with covalent bonds. This results in a stronger attachment of a molecule compared to the physical adsorption. As a result, the drug introduced into the fibers remains attached to it for a long time. An example of chemical modification is a plasma treatment. Commonly, plasma is used to optimize wetting properties and adapt adhesion of the surface by changing the surface chemical composition. Polymer surface can be modified by adding different functional groups to improve the biocompatibility [11]. Formation of carboxyl groups or amine groups on the surface of the fibers through plasma treatment with air, oxygen or ammonia, causes immobilization of ECM components on their surface, such as collagen, gelatin, laminin, and fibronectin. This process enhances cell adhesion and proliferation [12]. Moreover, plasma treatment can be also used to coat a surface with a thin film, tailor surface roughness or to induce crosslink formation and graft polymerization. Plasma treatment has also some limitations [11]. Most importantly, only the very surface of the fibrous membrane can be modified due to restricted plasma depth penetration. Other chemical post-mobilization methods which can overcome this restriction is a wet chemical method, based on surface hydrolysis. Surface hydrolysis leads to cleavage of ester bonds in polymer chains. As a result, carboxylic and hydroxyl groups are formed on the surface from degraded, but insoluble, polymer fragments. Plasma treatment and UV radiation cause the formation of free radicals for polymerization on the surface of the fibrous membrane. This operation makes the surface hydrophilic and allows the connection of active agents to a membrane by covalent bonding [12].

Factors affecting drug release

Release of drugs from fibers can be affected by desorption, dissolving, diffusion through water-filled pores and degradation of a polymer matrix. Therefore, the direct factor that affects the release of the drug from the fibers was discussed in the previous paragraph. Blend electrospinning provides drug release through diffusion and degradation of the polymer. This model is characterized by the immediate release of the entire active factor from the fibers. Sustained release with initial burst effect is represented in the case of surface functionalized fibers through diffusion model. Here, the release rate is influenced by the attachment strength of the molecules. The most sustained drug release can be obtained from core-shell or emulsified structures, caused by the degradation of the shell [13,14]. For molecules introduced into the fibers, their diameter has a key role in drug release rate. Thinner fibers have a high surface area to volume ratio that provides larger surfaces for mass exchange and results in a faster release [8]. Also, the distance between a surface and a core of fibers from where active molecules are dissolved is very small [3]. Increasing the contact surface can be achieved by producing porous fibers. Thus, the thicker fibers with high porosity are characterized by faster release when compared to thinner fibers but without pores. Membrane porosity, and hence the orientation of the fibers, also determines the drug release rate. It will be lower in the case of a membrane with parallel, closely arranged fibers than randomly distributed [8]. Moreover, physicochemical drug properties (hydrophilic, hydrophobic), the interaction between a drug and a polymer matrix, molecular weight of a polymer, and degradation rate of a polymer matrix can influence the drug release profile. Polymer degradation is related to its crystallinity. The polymers with amorphous structure degrade faster, providing a faster release of the drug from the matrix. The higher degree of crystallinity, the slower the degradation and the release of the drug. What is more, the degradation depends on the hydrophilic/hydrophobic surface character. The more hydrophilic material, the better water penetration and the faster degradation and desorption of the drug. Hydrophobic material swells in the aqueous environment, releasing small doses of the drug over a long period of time. Combining the drug with the matrix by covalent bond results in sustained release or sustained release with the burst effect in the first days. On the other hand, second-order interactions (hydrogen, van der Waals) ensure the immediate release of the drug [13].

Formation of porous fibers

The electrospun membranes are characterized by high surface area. This property can be further increased by producing porous fibers. Careful solvent selection and appropriate ambient conditions allow to achieve surface or internal porosity. This unique microstructure may be observed as wrinkles, nanopores, porous or hollow interiors. Two mechanisms can explain pore formation in polymer fibers, i.e. based on phase separation or breath figures. By selecting volatile solvents that are immiscible with water and have low dielectric constants, the pores are obtained using the breath figures mechanism. During electrospinning process in a humid environment (above 50%) evaporation of volatile molecules of solvents, causes a decrease in the temperature on the surface of the fiber. As a result of high humidity, water vapor droplets condensate on the fibers. Those droplets leave circular imprints and pores of the same shape are formed after water evaporation from the surface.

In the case of phase separation, a rich polymer phase and the poor one are formed when a polymer solution becomes thermodynamically unstable. The pores are represented by a polymer-poor phase. Three phase separation methods resulting in pore formation have been identified. Firstly, thermally induced phase separation (TIPS) based on a dynamic change of temperature. The decrease of the temperature leads to evaporation of the volatile solvent from the homogeneous solution. Another phase separation mechanism is vapour induced phase separation (VIPS). Water vapour droplets from a humid environment are attracted to the surface of the electrospun jet and penetrate it. The water vapour droplets mix with the solvent and become a non-solvent for the polymer, inducing phase separation. After complete evaporation of the water-solvent solution, highly porous structures are obtained. VIPS, TIPS, and breath figures are mechanisms which explain the formation of the porous fibers in a single solvent system. In the ternary system consisting of two solvents with one non-solvent, a non-solvent induced phase separation (NIPS) takes place. There are also other methods for obtaining porous fibers, like eg. using polymer blends and subsequent removing of one of the components, use of bath collector or appropriate additives, etc. However, there are a few limitations of these methods. Namely, need for: post-treatment of the electrospun membrane, modification of the device, or the optimization of an effect of introduced additives on the properties of the fibers [21,22].

Conclusions

Electrospinning is a simple technique for the manufacturing of nano- and submicrofibers characterized by high porosity and high surface area to volume ratio. These properties of electrospun nanofibers have been highly exploited in biomedical applications such as tissue engineering, regenerative medicine, wound dressing, enzyme immobilization and recently in drug delivery. Manufacturing of the electrospun fibers depends significantly on various parameters: solution parameters, equipment parameters, and ambient parameters. Optimization of these parameters is crucial for obtaining electrospun nanofibers with desirable properties. In the field of drug delivery, different electrospinning methods such as direct method and coaxial electrospinning have been successfully used for fabrication of nanofibers with various drug release behaviour including fast, biphasic, delayed or controlled release. The physical and chemical stability of these polymer-drug fibers systems is a very complex phenomenon, hence the drug release kinetics have not been thoroughly explored yet. Nevertheless, the various possibilities offered by electrospun nanofibers in drug delivery systems guarantee rapid development of this technique for biomedical applications.

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