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Electrospinning and Drug Delivery

Marilena Vlachou, Angeliki Siamidi and Sotiria Kyriakou

Abstract

A detailed account of the construction, properties, and practical applications of electrospinning for the fabrication of high-quality ultrafine fibers, suitable for drug delivery, is given. With respect to the electrospinning method, various parameters are of crucial importance. The electrospinning parameters are classified as solution properties, process parameters, and environmental conditions. The solution properties include the polymer concentration, molecular weight and viscosity, the solution conductivity and relative volatility, volatility of the solvent, surface tension, and dielectric constant. The process parameters refer to the flow rate, the applied voltage, the needle diameter, and the distance between the tip of the needle and collector and the geometry of the collector. The environmental conditions include the relative humidity and temperature. All these factors are responsible for a flawless electrospinning process, which leads to the formation of the desirable electrospun nanofibers with the requisite characteristics. In this chapter, it has been shown that the electrospinning technology could provide a useful method for modifying drug release behavior and opens new routes for the development of effective and tailor-made drug release carriers.

Keywords: nanofibers, electrospinning, electrospinning parameters, polymers, oral drug delivery

1. Introduction

During the last years, nanofibers have become increasingly attractive as drug delivery systems, mainly because they enhance the delivery of limited absorption drugs by improving the dissolution rates and solubility of drug molecules. Moreover, nanofibrous approaches in preparing stable amorphous drug formulations are extensively profitable [1].

The principal methods used for the fabrication of polymer nanofibers include drawing, template synthesis, phase separation, self-assembly, solvent casting, and electrospinning. However, the latter has become the most frequently used technique because of its ability to afford nanofibers with unique characteristics. These include a very high surface area to volume ratio, a high porosity with a small pore size, improved mechanical properties, degradability, and flexibility in surface functionalities/motifs. All the other fabrication methods have limitations, with respect to the materials used, and moreover, they are laborious and complex processes, resulting in problematic scale-up. Furthermore, compared with the other processing techniques, electrospinning is a simple, user-friendly, reproducible, and continuous

process [1–4], and upon the appropriate selection of the electrospinning apparatus and materials, diverse types of fibers, such as core-sheath, porous or hollow structured nanofibers can be produced.

2. Electrospinning

As already mentioned, electrospinning is a simple, highly versatile and robust technique for the production of polymers and a wide range of materials, including ceramic, metallic, and long fibers with diameters from submicron down to nanometer scale. These fibers are produced by feeding a polymer solution, dispersion or melt in a high electric field. It is worth mentioning that the use of melt in the electrospinning process is costly and leads to more difficult production than using polymer solution [1–6].

2.1 Electrospinning equipment

The main setup of an electrospinning equipment involves three main parts all enclosed within a chamber. A typical electrospinning apparatus is shown in **Figure 1**. It is composed of an electrical supply, for generating a high-voltage power supply, a piece of feeding equipment, which consists of a glass syringe with metallic needle filled with the polymer solution, a pump suitable for controlling the flow rate of the polymer solution, and a grounded collector usually made from aluminum foil. The power supply is used to apply tens of kilovolt to the needle, which works as a spinneret, while the pump extrudes the polymer from the syringe to the collector, which can be either rotatable or static [2, 4, 5, 7–9].

2.2 Electrospinning process and methods

2.2.1 Electrospinning process

The working principle of electrospinning is straightforward: at ambient temperature, a polymer solution or melt is ejected from the tip of a needle to a grounded metal collector by applying high voltage between the needle and the collector [2]. In

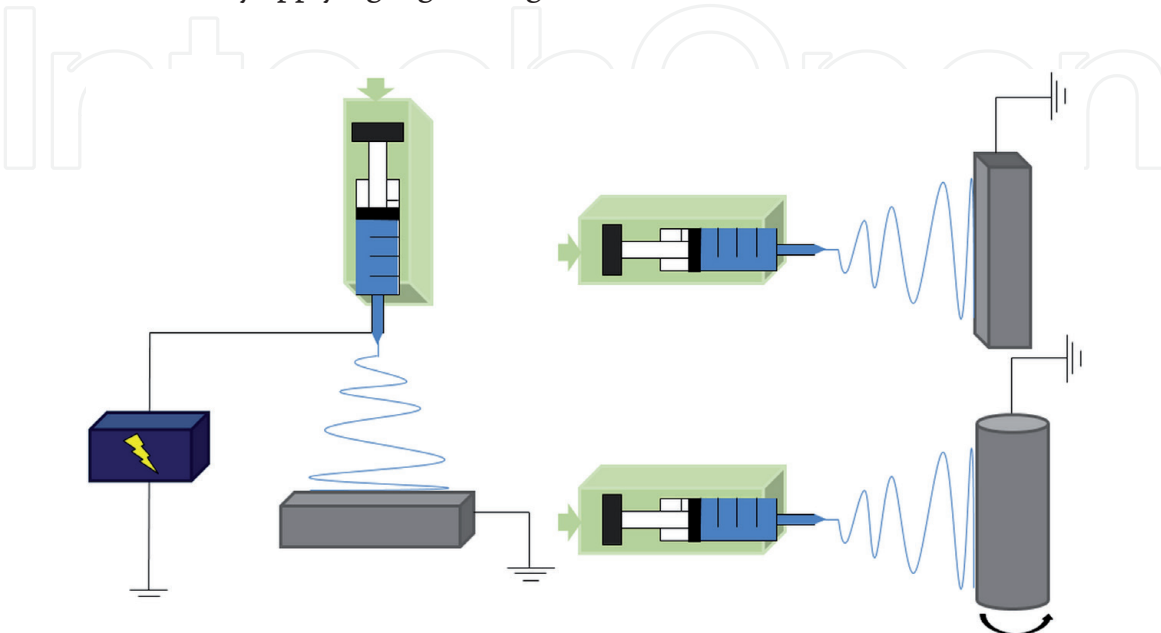


Figure 1.
Typical schematic setup of electrospinning equipment with static (up) and rotatable collector (down).

detail, the electrospinning process starts with the application of high voltage, which creates electric charges that are moving toward the polymer solution in the syringe *via* the metallic needle. The induction of charges on the polymer droplet causes instability within the polymer solution, thus creating an electrically charged jet of polymer solution or melt. Concurrently, a force that opposes the surface tension is produced, by the mutual repulsion of charges, and as a result, the polymer solution flows in the direction of the electric field and is extruded from the needle of the syringe with the aid of a pump [4]. Specifically, the solution jet is ejected from the nozzle of the needle when the voltage exceeds a threshold value because the electric force overcomes the surface tension of the droplet. Each droplet is exposed to a high voltage, and a cone-shaped droplet is formed. This is known as the Taylor cone and is caused due to the electrical voltage, which is the difference voltage between the nozzle and the collector with the counter charge [8]. Subsequently, the charged jet of solution is evaporated or solidified before reaching the metallic collector, where the solid material is collected as a solid interconnected continuous network of small fibers [1, 8, 10]. Regarding the electrospinning process, a stable charge jet can be formed only if the polymer solution has adequate cohesive force. During the process, the internal and external charge forces cause the whipping of the liquid jet, thus permitting the polymer chains to stretch and slide into the solution pushing the jet toward the collector [4]. As a result, the created fibers have enough small diameters to be characterized as diversely functionalized nanofibers because of their surface structure and their potential to modify their morphology and their internal bulk content [1, 4, 11, 12].

2.2.2 Electrospinning methods

The electrospinning technique is very useful for the incorporation of drugs in drug delivery systems. This technique can be reproducible under controlled parameters and is used in many formulations for the creation of new and innovative drug carriers because of their efficiency of transporting the bioactive agents to the target without causing secondary effects in the body. There are different methods for incorporating therapeutic drugs into drug delivery systems with electrospinning, which can greatly influence the properties of the resulting drug-loaded fibrous system. These methods involve blending, coaxial, emulsion, and surface modification electrospinning, which have discrete advantages and disadvantages. According to the physicochemical properties of the drug, the polymeric characteristics and the application of the drug-incorporated fibers, such as the target zone and the required drug release rate, the appropriate method is being selected as not all drugs can be loaded with all of these methods [3, 13, 14].

2.2.2.1 Blending electrospinning

Blending of the therapeutic agent with the appropriate polymeric solution remains the most predominant method for drug loading into nanofibers [3, 13]. This method is simple, compared to others, but some requirements should be met in order to gain the desired results. The polymeric blend improves the mechanical and physicochemical properties equilibrium of the drug-loaded nanofibers and increases effectively the formulation design for drug release, resulting in the manipulation of the release rate by changing the proportion of polymer in the blend [3, 15]. The insufficient solubility of the drug in the polymeric solution, where the drug molecules can shift to a nearby surface of fiber during electrospinning, can trigger the isolate release of the drug into the solution. Thus, the equilibrium among hydrophilic and hydrophobic properties between drugs and polymers is

very important during blending electrospinning [3, 7]. The drug release behavior is highly contingent on the distribution of the drug molecule into electrospun nanofibers as well as on the morphology of the nanofibers. In order to achieve perfect encapsulation of the drug inside the electrospun nanofibers, the hydrophobic polyester polymers should interact very well with the hydrophobic or lipophilic drugs, such as rifampicin and paclitaxel, while the hydrophilic polymers, such as gelatin, polyethylene glycol (PEG), and polyvinyl alcohol (PVA), can dissolve hydrophilic drugs, such as doxorubicin. It has been cited that amphiphilic copolymers like the PEG-b-PLA diblock copolymer could significantly enhance drug-loading efficiency and subsequently reduce the burst release of drugs [13]. With the blending electrospinning method, the drug is dissolved or dispersed into the polymer solution to achieve drug encapsulation through a single-step electrospinning, and as a result, fibers are obtained with single phase only [3, 13].

2.2.2.2 Coaxial electrospinning

The coaxial electrospinning method is regarded as one of the most significant breakthroughs, and it is mainly useful for multidrug delivery systems, where the individual drug release behavior is controlled [2, 3, 13]. In this method, there are two liquids inside the spinneret, which minimize the interaction between aqueous-based biological molecules and the organic solvents, in which the polymer is mainly dissolved, and as a result is used for obtaining fibers with core-shell structures [2, 3, 13]. These structures are used in cases where the therapeutic agent is sensible to the environment [3]. Moreover, this method can be used for generating novel structural nanomaterials, such as preparing nanofibers from materials without filament-forming properties enclosing functional liquids within the fiber matrix and encapsulating drugs or biological agents in the core of the polymer nanofibers leading to sustained and controlled drug release [2, 3]. The functionality of biomolecules is improved in coaxial electrospinning because the inner jet is formed by the biomolecule solution, and the outer jet is formed by the polymer solution, which is the co-electrospun. Moreover, the polymeric shell contributes to the sustained and prolonged release of the therapeutic agent as well as protecting the ingredient in the core from direct exposure to the biological environment [3, 13]. In this method, the coaxial fibers have successfully loaded proteins, growth factor, antibiotics, and other biological agents for drug delivery purposes [3, 13]. In coaxial electrospinning, there are a lot of factors, which should be considered in the design step, such as shell and core polymer concentration, molecular weight, and drug concentration [13, 14]. Nevertheless, only a limited portion of the produced fibers can form the proper core/shell structure and this system improves the sustained release of drugs and allows the bioability of unstable biological agents to be maintained [3, 14].

2.2.2.3 Emulsion electrospinning

The emulsion electrospinning method is an important and flexible method for the encapsulation of several drugs into nanofibers as well as a cost-effective and efficient manner for preparing core-shell electrospun nanofibers [3, 14]. In the emulsion electrospinning method, the oil phase is created by the emulsion of the drug or aqueous protein solution in the hydrophobic polymer solution. At the end of the electrospinning, the biomolecule-loaded phase can be distributed within the fibers, if a low molecular weight drug is used, or a core-shell fibrous structure can be configured as macromolecules in the aqueous phase [3, 13, 14]. It has been reported that the ratio of hydrophilic (aqueous) to hydrophobic (polymer) solution is one of the parameters that affect the distribution of the biomolecules within

the fibers. Moreover, it plays an important role in regulating the release profile, structural stability, and bioactivity of the encapsulated drug or proteins [3, 13, 14]. It is worth mentioning that the main advantage of emulsion electrospinning against blending electrospinning is the elimination of the need for a common solvent as the drug and the polymer are dissolved in applicable solvents. Numerous hydrophilic drugs and hydrophobic polymeric combinations can be used while maintaining minimal drug contact with the organic solvent during the procedure [3, 13, 14, 16]. However, the emulsion electrospinning would still cause damage or degradation of unstable macromolecules, like nucleic acids, mainly because of the shearing force and tension between the two phases of the emulsion, compared to coaxial electrospinning. Therefore, further modifications, like condensation of the carrier gene in gene therapy might be useful for more protection. Furthermore, during the emulsification or ultrasonication procedures in emulsion electrospinning, the contact of core materials with the solvent is increased, which may cause probable damage to the drug contents. Although extremely hydrophobic polymers can be used in emulsion electrospinning, the affinity or compatibility between drug and polymer might also influence the distribution of drugs within the fibers. It is cited that the copolymerization of hydrophobic polymers with hydrophilic polymers, such as PEG, ϵ -caprolactone (6-hexanolactone) (PCL), and poly(3-hydroxybutyric acid-co-3-hydroxyvaleric acid) (PHBV), affects drug distribution [3, 13, 14].

2.2.2.4 Surface modification electrospinning

The surface modification electrospinning is another promising method for introducing biofunctionality into nanofibers. In the surface modification electrospinning, a specific conductive surface can be chemically altered and changed aiming at modifying the external properties of a coated device, such as the tissue, which encircles the implanted material [3]. In this strategy, the release of the therapeutics is weakened and the functionality of the surface, where the immobilized biomolecules are located, preserved [13, 17]. Thus, this method is applied to avoid fast initial burst release and to slow down the rate of immobilization of the biological molecules on a particular surface. Therefore, the surface modification electrospinning is more applicable for gene or growth-factor delivery where slow and prolonged release of the therapeutic agent is required [13, 17]. Moreover, having a good electrospinning system and a well-standardized method, it is possible to coat 3D surfaces with nanoparticles or homogeneous surfaces [3, 16]. In cases where the drug cannot be immobilized, either because the drug is required to be endocytosed or interact with the nucleus of the cell, its release rate could be accurately controlled by introducing responsive materials to local external cues. This can happen by introducing hydrophobic functional groups onto the nanofibers surface [13].

2.3 Electrospinning parameters

The fabrication of nanofibers *via* electrospinning is affected by many different, but interlinked parameters as shown in **Table 1** [1]. These parameters modulate both the electrospinning process and the morphology of nanofibers [1, 4]. The electrospinning parameters can be classified as solution properties, process parameters, and environmental conditions [1, 4, 8]. The solution properties include the polymer concentration, molecular weight and viscosity, the solution conductivity and relative volatility, volatility of the solvent, surface tension, and dielectric constant. The process parameters refer to the flow rate, the applied voltage, the needle diameter, the distance between the tip of the needle and collector, and the geometry of the collector. The environmental conditions include the relative humidity and

Electrospinning parameters	Symbol	Effects on nanofiber morphology, diameter and its structure	
		Effects the morphology and structure	Effects on the diameter
Solution properties			
Concentration	$C\uparrow$	Increasing concentration leads to increase in fiber diameter.	Nanofiber diameter \uparrow
Viscosity	$\eta\uparrow$	Increasing viscosity leads to thicker nanofibers without beads, but too high viscosity causes generation of beads.	Nanofiber diameter \uparrow
Solution conductivity	$\sigma\uparrow$	Increasing conductivity leads to thinner nanofibers.	Nanofiber diameter \downarrow
Surface tension	γ	No conclusive correlation has been established between the surface tension and the nanofiber morphology.	-
Molecular weight of polymer	$M_r\uparrow$	Increasing polymer molecular weight leads to formation of a nanofiber with fewer beads.	-
Volatility of solvent	α_{solvent}	Higher volatility requires higher flow rate and leads to formation of a nanofiber with fewer beads.	-
Solution relative volatility	α	Porous microstructure appears because of higher volatility.	-
Dielectric constant	E_v	Sufficient dielectric constant of the solvent is needed for successful electrospinning.	-
Process parameters			
Flow rate	$Q\uparrow$	Higher flow rate results in thicker nanofibers. Too high flow rate causes the generation of beads.	Nanofiber diameter \uparrow
Applied voltage	$V\uparrow$	Higher applied voltage leads to thinner nanofibers.	Nanofiber diameter \downarrow
Needle diameter	D_{needle}		
Needle tip to collector distance	$D\uparrow$	Minimum distance required to obtain dry nanofibers. Beaded morphology occurs when the distance is too short and the electric field is too strong.	Nanofiber diameter \downarrow
Geometry of collector	-	Metal collectors with conductive frame or rotating drum are preferred.	-
Environmental conditions			
Relative humidity	ϕ	Porous microstructure appears due to evaporation-cooling effects. Lower humidity enables higher flow rate and the generation of beads is reduced.	-
Temperature	$T\uparrow$	Higher temperature leads to thinner nanofibers.	Nanofiber diameter \downarrow

Table 1.
Parameters that affect the electrospinning technique.

temperature [1, 4, 7, 8, 18]. The solution properties and the process parameters have predominant influence on the formation and morphology of the produced nanofibers, while the environmental conditions do not have a significant effect [1]. Moreover, all these factors are responsible for a flawless electrospinning process, which leads in the formation of the desirable electrospun nanofibers with the requisite characteristics [8]. Consequently, the careful monitoring of these factors can ensure the formation of smooth, highly porous nanofibers without beads [4, 8].

2.3.1 Effects of polymer concentration

The electrospinning method relies on the creation of electric charges in the polymer solution, which generate a charged jet [4]. When the polymer concentration is low, then the entangled polymer chains break into fragments before reaching the collector, due to the applied electric field and surface tension [4, 9, 12]. The entanglement of the polymer is necessary for fiber formation, but in the state of low polymer concentration. In this state, the phenomenon of electrospraying will take place and particles, instead of fibers, are formed [8, 19]. It has been reported that the boundary concentration between electrospray and electrospinning is solvent-dependent [8, 20]. Moreover, these polymer fragments cause the formation of nanofibers with beads [4]. In turn, if the polymer concentration increases, the

chain entanglement among polymer chains will increase because of the increase in solution viscosity. As a result, these chain entanglements overcome the surface tension and uniform electrospun nanofibers devoid of beads are formed [4, 21]. If the concentration increases beyond a critical value, then the flow of the jet will be blocked as the droplet will dry out at the tip of the metallic needle, and the polymer jet would not be initiated. In this case, the clog should be removed to let the electrospinning process continue [4, 12, 18] and obtain beadless nanofibers with increased diameter [1, 4, 18, 22, 23].

2.3.2 Effects of polymer viscosity

With respect to the electrospinning method, the polymer viscosity is included in the solution properties. It has been reported that a change in polymer viscosity can affect the morphologies of the beads in nanofibers [4, 24]. If the viscosity of the polymer solution is low, the shape of the produced nanofibers will be round droplet like, but if the viscosity of the polymer solution is sufficient, then stretched droplet or eclipsed shapes fibers will be formed [4, 22–25]. Moreover, an increase in polymer concentration causes increase in polymer viscosity, and as a result, an increase beyond a critical value will block the flow of the jet and the droplet will dry out at the tip of the metallic needle. In conclusion, the determination of the critical value of viscosity is essential, as an increase in the polymer viscosity leads to thicker and bead-free nanofibers with increased diameter [4, 21]. Conversely, if the increase of viscosity is too high, beads will be generated in the nanofibers [1, 7].

2.3.3 Effects of solution conductivity

The solution conductivity is another solution parameter, which affects the electrospinning process and as a result the formation of nanofibers and their diameter distribution [7, 8]. The solution conductivity has a significant role on the formation of the Taylor cone and in controlling the diameter of the nanofibers [4, 8]. Poor conductivity solutions are not capable of producing electrospinning results, as the surface of the droplet will have no charge to form the Taylor cone. Conversely, an increase in the solution conductivity will lead to the Taylor cone formation because of the increase of the charge on the surface of the droplet. This will also lead to the reduction of the fiber diameter [4, 8, 26]. It has been reported that if the solution conductivity increases beyond a critical value, the formation of the Taylor cone will be prevented. This can be attributed to the Coulombic forces between the charges on the surface of the fluid and the force due to the external electric field [4]. It has been well documented that a highly conductive polymer solution is unstable and leads to a wide diameter distribution when a strong electric field is applied [4, 7, 27]. However, the polymer solution conductivity could be adjusted by the addition of a suitable salt [4, 7]. The addition of the salt affects the electrospinning process by increasing the number of the ions in the polymer solution resulting in the increase of surface charge density of the fluid and the electrostatic force produced by the applied electric field [4, 7, 22, 28, 29]. Moreover, the addition of the salt increases the polymer solution conductivity resulting in the reduction in the tangential electric field along the surface of the fluid [4]. Concluding, the increase of the solution conductivity leads to ultrafine nanofibers with reduced diameter [1, 7, 8, 26].

2.3.4 Effects of surface tension

The surface tension is included in the solution parameters, which affect the electrospinning process and the nanofiber morphology, but there is no conclusive

correlation [1]. Nevertheless, it has been reported that there is a delicate balance between the surface tension and the electric field (conductivity, concentration, and viscosity), which affects the ultimate morphology of the nanofibers [4, 7]. Particularly, the surface tension and the applied electric field cause the disentangling and breaking of the perplexed polymer chains into fragments before reaching the collector, which cause the formation of beads in the nanofibers [4, 9, 12]. Another case refers that the surface tension influences the surface of the polymeric nanofibers, and in the case of poor conductivity of polymers, charges accumulate onto the surface and as a result, beaded formation is prompted [7].

2.3.5 Effects of molecular weight of polymer

The molecular weight of the polymer is included in the solution properties, and it is a parameter that affects the viscosity of the solution. Ordinarily, an increase in molecular weight, until a critical value, leads to increase in solution viscosity and the formation of nanofibers with fewer beads [1, 7]. In general, polymers with high molecular weight are preferred as they cause extensive chain entanglement, which facilitates the nanofiber formation during the spinning process. On the contrary, polymer solutions with lower molecular weight may lead to the formation of beads or break up into droplets [30]. Overall, the molecular weight is one of the most important parameters, which affect the outcome nanofibers and as a result the electrospinning process.

2.3.6 Effects of solvent volatility

The solvent volatility is another parameter of solution parameters, which affects the electrospinning process and as a result the formation of smooth and beadless electrospun nanofibers. The solvents that are preferred in the electrospinning process should be polymers that are entirely soluble, and they should have moderate (appropriate) boiling point, which is related with the volatility of the solvent [4, 8]. Common volatile solvents, with high evaporation rates, which ensure the facile evaporation of the solvent from the tip of the needle to collector, are used in the electrospinning process [4]. The rate of solvent evaporation from the polymer solution jet leads to phase separation and creation of secondary structures on fibers [4, 7, 31]. It has been reported that highly volatile solvents absorb the heat from the jet, thus lowering the temperature of the liquid jet; this temperature drop decreases the thermodynamic stability of the nonsolvent phase. These phenomena result in high evaporation rates, which cause the drying of the jet at the tip of the needle, block the needle tip, and hence hinder the electrospinning process or else the early solidification of the polymer jet. Overall, highly volatile solvents are avoided in the electrospinning process because fiber formation will not be completed [4, 7, 8]. Similarly, solvents with low volatility should not be used, because they have high boiling points, which prevent the drying during the nanofiber jet formation or else the solidification process could be retarded because the solvent evaporation is low [4, 8]. Conclusively, the type of the solvent and especially their volatility profile, and the rate of evaporation are very important parameters for the formation of nanofibers. It is cited that higher volatility demands and higher flow rates result in the formation of electrospun nanofibers with fewer beads [1, 4, 7].

2.3.7 Effects of solution volatility

Relative volatility is a measure of the differences in volatility between two components and is used in the design of separation or absorption processes. The

solution relative volatility is a solution parameter that has similar effect with the volatility of the solvent. Solutions that are prepared from solvents of very low volatility may deliver wet and cross-linked nanofibers or even no nanofibers, at all [4, 8, 30]. Conversely, the usage of highly volatile solvents for the solution preparation may result in intermittent spinning because of the solidification of the polymer jet at the tip of the needle [4, 7, 30]. It has been reported that an increase in relative volatility of polymer solution causes the appearance of porous microstructure due to higher volatility, and this affects fiber's porosity and morphology [7].

2.3.8 Effects of dielectric constant

The dielectric constant, sometimes called relative permittivity or specific inductive capacity, is the ratio of the permittivity of a substance to the permittivity of free space. It is an expression of the extent to which a material concentrates electric flux. The dielectric constant of the solvent(s), used in the successful electrospinning and the formation of electrospun nanofibers, has to be sufficient, but not high [1]. It has been reported that an increase in the dielectric constant of the solution leads to an increase of the number of jets. On the contrary, a reduction in the value of the dielectric constant to a single digit leads to the formation of a single jet. Furthermore, the value of the solution dielectric constant may influence the stability of the jet, as bending instability may be reduced with a lower charge density resulting in a longer and stable jet [30]. Overall, the solution dielectric constant has to be sufficient for the successful electrospinning and the formation of electrospun nanofibers [1].

2.3.9 Effects of flow rate

The flow rate is an important parameter belonging to the process parameters, which influences the diameter of the electrospun fibers and subsequently the charge density and the morphology of the nanofibers [4, 7]. It is reported that there is a critical point depending on the polymeric solution, in which the critical flow rate leads to the formation of uniform electrospun nanofibers [4, 8]. In the case of increasing the flow rate, beyond the critical value, nanofibers with larger diameter and pore size are produced and the formation of beaded structures is enhanced [4, 7, 8, 18, 31]. This bead formation is caused due to the incomplete drying of the polymeric jet. When the delivery rate of the polymeric jet to the needle tip exceeds the rate at which the polymeric solution is removed from the tip by the electric force in the metallic collector, a mass balance shift results, which leads to a sustained but unstable jet and bead formation [4, 7, 32]. In the case of decreasing the flow rate, beyond the critical value, smooth, fine, and thinner nanofibers are formed [1, 18]. It is cited that increases and decreases in the flow rate affect the nanofiber formation, and as a result, a minimum flow rate of the polymeric solution is preferred in order to replace the solution that is lost with a new one, during jet formation, as the solution will have enough time for polarization, stretching, and drying [4, 31]. Overall, lowering the flow rate causes the formation of thinner nanofibers instead of too high flow rates in which the nanofiber diameter increases and the continuity of the fiber interrupts bead formation [1, 7].

2.3.10 Effects of applied voltage

The applied voltage is an important process parameter, which affects the strength of the electric field and therefore influences the diameter and the nanofiber morphology [7, 8]. Moreover, an increase in the applied voltage causes a change

in the shape of the Taylor cone, and as a result, a critical voltage, which depends on the polymeric solution, is needed for the formation of ultrafine nanofibers given a certain distance between the needle tip and collector [4, 5, 7, 8]. An increase in the applied voltage leads to the formation of thinner nanofibers because of the stretching of the polymer solution in correlation with the charge repulsion within the polymer jet [1, 4, 7, 18, 33]. A higher applied voltage, above the critical value, may lead to an irregular increase of the diameter and the formation of beaded, nonuniformity nanofibers [4, 7, 8, 22]. This situation is attributed to the decrease in the size of the Taylor cone and increase in the jet velocity, keeping the same flow rate [4, 22, 34]. However, there are studies that have shown that the increase in the applied voltage leads to increase in the diameter of the nanofibers [4, 18, 21]. This phenomenon may be explained as the increase of the voltage leads to the decrease of the volume of the drop at the tip of the needle causing the receding of the Taylor cone resulting in increase in the jet length and fiber diameter because of the increase in the amount of the ejected fluid and the flow rate of polymer solution [4, 18, 21]. In conclusion, in general, the increase of the applied voltage, until a critical value, causes the formation of thinner nanofibers, but this depends on the type of the polymeric solvent [1, 4, 7, 8, 18]. It is worth mentioning that the problem of bead formation was not solved by varying the applied voltage [18].

2.3.11 Effects of needle tip to collector distance

The distance between the metallic needle tip and the collector could be easily affecting the morphology of nanofibers because it is dependent on the deposition time, evaporation rate, and the whipping or instability interval [4, 7, 8, 35]. Therefore, a critical distance is needed to be fixed for the preparation of dry, smooth, and uniform electrospun nanofibers [1, 4]. A decrease in the distance between the tip and the collector leads to the enlargement of diameter of nanofibers and the generation of beads, while an increase in this distance leads to the formation of nanofibers with decreased diameter [1, 7, 8, 21, 35]. However, there are cases that the morphology of nanofibers is not affected by the distance between the metallic needle and the collector [4, 32]. Increasing the distance between the needle tip and the collector, the nanofiber diameter decreases and there is a minimum distance required to obtain dry, smooth, and uniform electrospun nanofibers, but when the distance is too short or too large, beads are formed [1, 7].

2.3.12 Effects of relative humidity

The relative humidity is a factor belonging to the environmental conditions of the electrospinning, which affects the diameter and the morphology of the electrospun nanofibers [4, 8, 36, 37]. The relative humidity is crucial for the production of ultrafine nanofibers with acceptable morphology, because it affects the formation of pores on the fiber surface *via* solvent evaporation or else controlling the solidification process of the charged jet [4, 7, 8]. The appropriate amount of the relative humidity depends on the chemical nature of the used polymer. A high relative humidity suppresses the evaporation rate as long as the surface area of the jet increases and the charge per unit area on the surface of the jet decreases resulting in the capillary instability and the beaded structure formation [1, 7, 8]. It has been cited that humidity controls the evaporation rate of the fluid jet when the water is used as a solvent component [7]. Overall, lower relative humidity enables higher flow rate, and as a result, the formation of beads is reduced, while higher relative humidity leads to the appearance of porous microstructures due to evaporation effects and/or phase separation [1, 7, 8].

2.3.13 Effects of temperature

The temperature is another factor belonging to the environmental conditions of the electrospinning, which is crucial for the production of ultrafine nanofibers with acceptable morphology, because it affects the diameter of the fibers [4, 8, 36, 37]. Moreover, temperature causes changes in the average diameter of the nanofibers resulting in modification of the electrospun nanofibers size by causing two opposing effects; first, it increases the evaporation rate of the solvent and secondly, it decreases the viscosity of the polymer solution. These effects have the behavior of two opposite mechanisms, but both of them lead to a mean fiber diameter decrease [4, 8]. In general, an increase in the temperature leads to thinner nanofibers formation [1, 4, 8].

3. Electrospinning in *per* oral drug delivery

With the appearance of nanotechnology, researchers have become more attracted in studying the characteristic properties of nanoscale materials. Electrospinning, a method of electrostatic fiber fabrication, has established more attention in recent years due to its usefulness and potential for applications in diverse fields, like tissue engineering, biosensors, filtration, wound dressings, drug delivery, and enzyme immobilization. The nanoscale fibers are generated by the application of strong electric fields on polymer solution and mimic better the extracellular matrix components as compared to the conventional techniques, offering various advantages, like high surface area to volume ratio, tunable porosity, and the ability to manipulate nanofiber composition in order to get desired properties and function [38]. The use of electrospun nanofibers, as formulation systems for oral drug delivery, has been studied extensively over the past decades in fast/immediate release systems and more recently in modified release systems.

Numerous researchers have been studying orodispersible or fast-dissolving drug delivery formulations produced from nanofiber-loaded systems that rapidly disintegrate in the oral cavity due to nanofibers' large surface area, which causes immediate disintegration in water solutions and fast drug release [18, 39–46]. Applications of the electrospinning technique on modified *per* oral drug delivery are summarized in Table 2.

3.1 Electrospinning in controlled *per* oral drug delivery

Oral controlled drug release systems are characteristic in formulation, and researchers have developed electrospun nanofibers for usage in treatment and management of disorders that need special drug release patterns. Scientists have developed amyloid-like bovine serum albumin with ampicillin sodium salt nanofibers by electrospinning, and the *in vitro* results showed controlled release behavior [47]. Electrospun fiber mats were also investigated as drug delivery systems using tetracycline hydrochloride as a model drug. The nanofibers were made either from poly(lactic acid), poly(ethylene-co-vinyl acetate), or from a 50:50 blend of the two. The release of the tetracycline hydrochloride from these new drug delivery systems followed controlled release behavior [48]. Moreover, polyvinyl alcohol nanofibers loaded with curcumin or its β -cyclodextrin inclusion complexes were prepared using an electrospinning process. *In vitro* dissolution tests showed that the drug release profiles of polyvinyl alcohol/curcumin and polyvinyl alcohol/complex fibers were different, with release from the latter occurring more rapidly [49]. In addition, electrospun gelatin nanofibers were prepared by sequential crosslinking

drug release behavior	delivery system	API	excipient (s)	electrospinning technique	ref
controlled	mats	ampicillin sodium salt	amyloid-like bovine serum albumin	blending	47
	mats	tetracycline hydrochloride	poly(lactic acid), poly(ethylene-co-vinyl acetate)	blending	48
	mats	curcumin	polyvinyl alcohol, β -cyclodextrin	blending	49
	multilayered gelatin mesh	piperine	gelatin (type A), acetic acid	multiple blending with sequential crosslinking using glutaraldehyde	50
	mats in hard gelatin capsules	melatonin	cellulose acetate, polyvinylpyrrolidone and hydroxypropylmethylcellulose	blending	51
	mats in 3-layered tablets	melatonin	cellulose acetate polyvinylpyrrolidone	blending	52
delayed	mats	5-fluorouracil	Core: poly(vinylpyrrolidone), ethyl cellulose, methacrylic acid copolymer S100 or drug alone Shell: methacrylic acid copolymer S100	coaxial	53
	gelatin nanofibers	piperine	gelatin (type A), acetic acid	sequential crosslinking using glutaraldehyde	54
	nano-fiber packed capsules	uranine and nifedipine	methacrylic acid copolymer S100	blending	55
	mats in tablets	acetaminophen	methacrylic acid copolymer S100	blending	56
colon targeted	mats	diclofenac sodium	methacrylic acid copolymer L100-55	blending	57
	mats	ferulic acid	Core: shellac Shell: N,N-dimethylformamide	coaxial	58
	mats	indomethacin	methacrylic acid copolymer RS100 and S100	blending	59
	mats	indomethacin	methacrylic acid copolymer RS100 and S100	blending	60
	mats	celecoxib	pectin, methacrylic acid copolymer RS30D, polycaprolactone	blending	61
	milled mats	budesonide	methacrylic acid copolymer S100	blending	62
	nanofilm	bovine serum albumin	Core: chitosan Shell: alginate	coaxial	63
	mats	doxorubicin	polydopamine, poly- ϵ -caprolactone	blending	64
biphasic	mats	ketoprofen	Core: ethyl cellulose Shell: polyvinylpyrrolidone	coaxial	65
	mats	ketoprofen	Core: zein Shell: polyvinylpyrrolidone	coaxial	66
	tri-layered mesh	ketoprofen	Core: zein Shell: polyvinylpyrrolidone and graphene oxide	sequential coaxial	67
	gelatin coated	ciprofloxacin	Mg-Ca alloy	blending with crosslinking using glutaraldehyde	68
	mats	resveratrol	polycaprolactone	blending	69
	mats	ampicillin	Core/Shell: polycaprolactone	coaxial	70
	mats	piroxicam	hydroxypropylmethylcellulose	blending	71
dual	mats	aceclofenac/pantoprazole	zein/methacrylic acid copolymer S100	blending	72

Table 2.

An overview of the electrospinning technique applications in modified *per* oral drug delivery.

using piperine as a hydrophobic model drug by sandwiching the drug-loaded gelatin nanofiber mesh with another gelatin nanofiber matrix without drug (acting as diffusion barrier). The results indicated controlled and sustainable release of the drug for prolonged time [50]. Researchers have also prepared melatonin-loaded nanofibrous systems based on cellulose acetate, polyvinylpyrrolidone, and hydroxypropylmethylcellulose. The electrospun nanofiber mats that were inserted

in hard gelatin capsules exhibited variable release profiles in the gastric-like fluids, ranging from 30 to 120 min, while the electrospun nanofiber mats that were inserted in DRcaps™ capsules released melatonin at a slower pace [51]. In another study, nanofibers of cellulose acetate and polyvinylpyrrolidone loaded with melatonin were prepared and compressed at various pressures into monolayered tablets. The nanofiber mats were then incorporated into three-layered tablets, containing in the upper and lower layer combinations of lactose monohydrate and hydroxypropylmethylcellulose, as modifying accessories, and their *in vitro* dissolution profiles have showed promising results in modified *per oral* drug delivery [52].

3.2 Electrospinning in delayed *per oral* drug delivery

Besides controlled drug release, researchers have investigated electrospun nanofibers as oral delivery systems for delayed release systems. In a study, both fast dissolving and sustained release drug delivery systems comprising mebeverine hydrochloride embedded in either povidone K60 or Eudragit RL 100–55 nanofibers have been prepared by electrospinning. The *in vitro* dissolution tests of the povidone K60 fiber mats revealed dissolution within 10 s, while the Eudragit fibers revealed pH-dependent drug release profiles, with only very limited release at pH 2.0, but sustained release over approximately 8 h at pH 6.8. As a result, it can be stated that the Eudragit nanofibers have the potential to be developed as oral drug delivery systems for localized drug release in the intestinal tract, whereas the povidone materials may find application as buccal delivery systems or suppositories [53]. Various researchers have synthesized gelatin nanofibers by electrospinning, using piperine as a hydrophobic model drug. The electrospun gelatin nanofibers were cross-linked by exposing to saturated glutaraldehyde vapor, to improve their water-resistive properties. The results illustrated good compatibility of the hydrophobic drug in gelatin nanofibers with promising controlled drug release patterns by varying cross-linking time and the pH of the release medium [54]. In another scientific report, a solvent-based electrospinning method was used to prepare nanofiber-based capsules including drugs (uranine was used as a water-soluble drug and nifedipine as a water-insoluble drug) for controlled release delivery systems using methacrylic acid copolymer as a polymer. The *in vitro* release of uranine or nifedipine from the nanofiber-packed capsules and milled powder of nanofiber-packed capsules showed controlled release of uranine or nifedipine, as compared to capsules of a physical mixture of methacrylic acid copolymer and each drug. The *in vivo* pharmacokinetic evaluation in rats, after intraduodenal administration of nanofiber-packed capsules or milled powder of nanofiber-packed capsules including uranine and/or nifedipine, clearly demonstrated that the application of the nanofibrotic technique, as a drug delivery system, offers drastic changes in pharmacokinetic profiles for both water-soluble and water-insoluble drugs [55]. Furthermore, nanofibers made from methacrylic acid copolymer S, containing acetaminophen, were prepared using a solvent-based electrospinning method. The *in vitro* dissolution rate profiles of acetaminophen showed that the tablets based on methacrylic acid copolymer S nanofibers did not disintegrate in the intestine in the lower pH region and could regulate the drug release in a pH-dependent manner [56].

3.3 Electrospinning in colon-targeted *per oral* drug delivery

In addition to the previously described drug delivery systems, many scientists have demonstrated that the electrospinning method could be regarded as a modern approach for the preparation of colon drug delivery systems leading to marketable products. Eudragit L 100-55 nanofibers loaded with diclofenac sodium were

successfully prepared using an electrospinning process. *In vitro* dissolution tests verified that all the drug-loaded Eudragit L 100-55 nanofibers had pH-dependent drug release profiles, with limited release at pH 1.0, but a sustained and complete release at pH 6.8, indicating the potential of oral colon-targeted drug delivery systems development [57]. Researchers prepared medicated shellac nanofibers providing colon-specific sustained release of ferulic acid using coaxial electrospinning. The *in vitro* dissolution tests demonstrated that there was minimal ferulic acid release at pH 2.0, and sustained release in a neutral dissolution medium [58]. Another group of researchers have prepared electrospun nanofibers of indomethacin aimed for colon delivery using Eudragit S and Eudragit RS as polymers. It was shown that the ratio of drug:polymer and polymer:polymer were pivotal factors to control the drug release from nanofibers. A formulation containing Eudragit S:Eudragit RS (60:40) and drug:polymer ratio of 3:5 exhibited the most appropriate drug release, as a colon delivery system with a minor release at pH 1.2, 6.4, and 6.8 and a major release at pH 7.4 [59]. Electrospun nanofibers were also successfully prepared using indomethacin as a drug and Eudragit RS100 and S100 as polymers for colonic drug delivery [60]. Moreover, celecoxib-loaded electrospun nanofibers were developed using a combination of time-dependent polymers with pectin to achieve colon-specific drug delivery systems. The drug release was limited in the acidic media; while, in the simulated colonic media, it was higher from formulations containing the excipient pectin [61]. Likewise, electrospun fibers loaded with budesonide were prepared with the aim of controlling its release in the gastrointestinal tract using Eudragit RS 100, a polymer soluble at pH > 7, commonly used for enteric release of drugs. The dissolution rate measurements using a pH-change method showed low drug dissolution at pH 1.0 and sustained release at pH 7.2, representing an effective method for drug targeting to terminal ileum and colon with the aim of improving the local efficacy of budesonide for the treatment of some inflammatory bowel diseases [62]. Researchers have developed a novel core-shell-structured nanofilm for colon delivery by coaxial electrospinning using bovine serum albumin as protein model. First, the protein-loaded chitosan nanoparticle was prepared by ionic gelation, and then, the coaxial nanofilm was fabricated using alginate as shell layer and the protein-loaded chitosan nanoparticle as core layer. The protein release in different simulated digestive fluids revealed that the electrospun nanofilm is a promising colon-specific delivery system for bioactive proteins [63]. Another group of scientists reported in their work that the pH-responsive drug delivery systems could mediate drug releasing rate by changing the pH values at specific times as *per* the pathophysiological need of the disease. Their study demonstrated that a mussel-inspired protein polydopamine coating can tune the loading and releasing rate of charged molecules from electrospun poly(ϵ -caprolactone) nanofibers in solutions with different pH values. The *in vitro* release profiles showed that the positively charged molecules led to a significantly faster release in acidic than in neutral and basic media, while the results of specialized assays showed that the media containing doxorubicin released in solutions at low pH values could kill a significantly higher number of cells than those released in solutions at higher pH values. The pH-responsive drug delivery systems based on polydopamine-coated poly(ϵ -caprolactone) nanofibers could have potential application in the oral delivery of anticancer drugs for treating gastric cancer and in vaginal delivery of antiviral or anti-inflammatory drugs, which could raise their efficacy, deliver them to the specific site, and minimize their toxicity [64].

3.4 Electrospinning in biphasic and dual *per* oral drug delivery

More to the point of modified drug delivery systems, researchers have designed and fabricated nanostructures using electrospinning for providing biphasic drug

release profiles. A research work investigated the biphasic release profile of ketoprofen of core/sheath nanofibers prepared using as polymers polyvinylpyrrolidone for the sheath and ethyl cellulose for the core matrix by coaxial electrospinning. The *in vitro* dissolution tests showed that the nanofibers produced could provide a biphasic drug release profile consisting of an immediate and a sustained release [65]. In another work, core-sheath nanofibers were also prepared using ketoprofen as a model drug, and polyvinylpyrrolidone and zein as the sheath polymer and core matrix excipient, respectively, by coaxial electrospinning. The *in vitro* dissolution tests showed that the nanofibers could provide an immediate release of 42.3% of the drug followed by a sustained release over 10 h of the remaining drug [66]. Other researchers have used simple sequential electrospinning to create a triple layered nanofiber mesh with biphasic drug release behavior. The mesh was composed of zein and polyvinylpyrrolidone as the top/bottom and middle layers, respectively. Ketoprofen was used as a model drug, and polyvinylpyrrolidone was blended with graphene oxide to improve the drug release functionality of the nanofiber as well as its mechanical properties. The *in vitro* release tests demonstrated time-regulated biphasic drug release [67]. In another study, gelatin-ciprofloxacin nanofibers containing various amounts of ciprofloxacin were fabricated on the surface of Mg-Ca alloy *via* an electrospinning process. Prolonged drug release was attained from gelatin-ciprofloxacin nanofibers coating along with initial rapid drug release of around 20–22% during 12 h, followed by a slow release stage that can effectively control the infection [68]. Moreover, resveratrol (a promising natural substance for periodontal disease treatment due to its anti-inflammatory and antioxidative effects) was successfully incorporated into polycaprolactone-nanofibers and enabled a biphasic-release kinetic pattern [69]. In a recent study, it was demonstrated that the production of core-shell fibers via modified coaxial electrospinning achieved controlled release of ampicillin-loaded polycaprolactone nanofibers covered by a polycaprolactone shield. The *in vitro* release studies showed that the drug release kinetics of core-shell products is closer to zero-order kinetics, while the drug release kinetics of single electrospinning of the core resulted with burst release [70]. Scientists have also used piroxicam as a low-dose, poorly soluble drug and hydroxypropyl methylcellulose as an amorphous-state stabilizing carrier polymer in nanofibers to produce biphasic-release drug delivery systems [71].

Dual drug delivery systems have also been successfully developed by researchers. In a recent study, aceclofenac/pantoprazole-loaded zein/Eudragit S 100 nanofibers were developed using a single nozzle electrospinning process. The *in vitro* release studies ensured the efficiency of the nanofibers in sustaining the release of both drugs up to 8 h, while the *in vivo* experiments confirmed that the co-administration of pantoprazole and aceclofenac reduced the gastrointestinal toxicity induced by nonsteroidal anti-inflammatory drugs [72].

4. Conclusions

The fabrication of electrospun ultrafine fiber meshes from biodegradable and biocompatible polymers has opened new horizons in the biomedical field. Electrospinning, being a simple, highly versatile, and robust technique for the production of fibers with diameters from submicron down to nanometer scale, could provide a useful method for the development of novel drug carriers capable of affecting the drugs' modified release. By careful selection of polymers, it is now possible to deliver drugs, with diverse stereoelectronic and physicochemical properties, in a required manner using electrospun nanofibers. *Mutatis mutandis*, in order to make further progress in the drug delivery field, it is necessary to identify ways that

will allow fabrication of nanofibers with the desired morphological and mechanical properties in a reproducible manner. Thus, organic solvent mixtures, drug content, and electrospinning parameters, which will influence nanofiber properties, such as morphology, applicability, and quality, are currently under intense investigation.

Conflict of interest


The authors declare no conflict of interest.

Author details

Marilena Vlachou*, Angeliki Siamidi and Sotiria Kyriakou
Department of Pharmacy, Division of Pharmaceutical Technology, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece

*Address all correspondence to: vlachou@pharm.uoa.gr

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