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Electrospinning for Drug Delivery Systems: Drug Incorporation Techniques

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Abstract

Electrospinning is a very versatile technique used for many purposes, such as tissue engineering, textiles, air and water treatment filter, solar cells, and drug delivery systems, among others. This method is cheap, easy to handle, reproducible when ambient parameters are controlled, and can be used for many formulations. The objective of this review is to enlist and emphasize the advantages and disadvantages of different methods for incorporating therapeutic drugs in a drug delivery system with electrospinning. The importance of the research to create new and innovative drug carriers is high, because of their efficiency of transporting the bioactive agent to the target zone, avoiding secondary effects in the body. Nanofibers and nanoparticles have become an important strategy in pharmacology due to their physicochemical and biocompatible properties useful for this purpose. Among the techniques compared are blending coaxial, emulsion and surface modification electrospinning, followed by electrospray and coaxial electrospray. The present review concludes that every technique has advantages and disadvantages and, not all drugs can be loaded with any method, the strategy used will depend on the drug's physicochemical properties, target zone, polymeric characteristics, and required drug release rate. This chapter will serve as a starting point for when to choose one of the drug incorporation techniques mentioned.

Keywords: drug delivery system, drug incorporation, electrospinning

1. Introduction

The electrospinning technique has been widely used for drug delivery system approach. This versatile procedure uses an electrical field to create nanofibers from a conductive solution. These solutions can be prepared from polymeric or composite materials [1–3].

Nanofibers fabricated by the electrospinning approach have been reported to be important in the pharmaceutical industry thanks to its properties, such as degradability, high surface area, variable porosity, and manageability; hence, these structures have been studied as drug delivery systems. The polymers used in this technique usually facilitate the incorporation of different drugs thanks to their chemical composition and physicochemical characteristics. For example, poly(vinyl pyrrolidone) (PVP) scaffolds improve the solubility of some hydrophobic drugs because PVP nanofibers help in the dispersion of these drugs [4].

Drug delivery systems that use the electrospinning strategy possess better control and predictability on drug delivery than the conventional methods. Such is the case of itraconazole used for the treatment of tinea pedis and other infections. This drug has been successfully grafted in electrospun nanofibers showing a lineal dependence to a square root of release rate, indicating that this drug delivery system follows a Fickian release kinetics [4].

In the case of mexofin, a cephalosporin antibiotic used to treat bacterial infections or preventing bacterial infections before, during, or after certain surgeries, it has been reported to be loaded to poly(D,L-lactid acid) (PDLLA) scaffolds showing a complete release of the drug within 24 h with a bulk release within the first 3 h. The researchers proposed that the surface deposition and drug accumulation has an important effect on drug delivery performance of electrospun nanofibers [5].

Other studies reported drug delivery systems using poly(ethylene-co-vinyl acetate) (PEVA)/poly(lactic acid) (PLA) nanofibers loaded with the polyketide antibiotic tetracycline, well known to treat periodontal diseases. Comparing the PEVA scaffolds with the PLA/PEVA nanofibers, the first system proved to have a higher release, delivering 65% of the loaded drug in 120 h [6].

Additionally, not only drugs can be loaded in electrospun nanofibers or microfibers, but also biological agent can be controlled and released with this system. For this approach, it has been reported that nanofibers with lower diameters are effective for delivering genes, proteins, and enzymes in postsurgical treatment of glioma cells [4].

2. Advantages and disadvantages of nanofibers as drug carriers

Material uses for drug delivery systems need to be biocompatible, biodegradable, permit drug loading, possess mass transfer properties, and respond to stimuli, among others. Drugs can be loaded into the polymeric nanofibers from antibiotics and anticancer agents to biomolecules such as DNA, RNA, and proteins [2].

Among the advantages of electrospun nanofibers as drug carriers is the high surface-to-volume ratio, which can accelerate the solubility of the drug in the aqueous solution and improve the efficiency of the drug. Surface morphology and structure of the nanofibers are important factors for controlling the releasing rate and amount of the drug. Furthermore, biodegradable polymers would protect drug from corrosion of gastric acid and enzyme, maintaining the bioactivity of the drug. On the other hand, nanofibers scaffolds can be used as templates for the production of conductive drug-loaded polymer systems [7].

It can be found in the literature that electrospinning is a cost-effective technique capable of producing long and continuous nanofibers. Also, it is useful for the production of aligned nanofiber and tailorable mechanical properties. Despite this, the method possesses several limitations as production of large nanometer to micron-scale fiber requires the use of organic solvents and it is not possible to control the 3D pore structure [8].

Compared with other methodologies, electrospinning is an easy and friendly technique. One-step top-down process in the fabrication of nanoscale fibers is not limited in the coprocessing of polymeric mixtures or chemical cross-linking. The scaffolds made by electrospinning possess various properties such as charged surfaces areas, adequate porosity, elasticity, strength, and weight. The disadvantages of the other techniques for the production of nanofibers such as template synthesis, drawing, phase separation, and self-assembly are material limitation, time consuming, and complex processing [9].

One of the important things to recognize about electrospinning is the demonstration of an enhanced drug release rates using nanofiber formulation than those from original drug substance reported in *in vitro* and *in vivo* studies [7].

3. Electrospun polymeric nanofibers as drug delivery systems

A great variety of polymers have been used to form nanofibers, such as poly(L-lactic acid) (PLLA), poly(L-lactic acid)/hydroxyapatite (PLLA/HA) [10, 11], poly(glycolic acid) (PGA), poly(caprolactone) (PCL), poly(carbonate), poly(urethane) (PU), poly(ethylene glycol) (PEG) [1], poly(D,L-lactide-co-glycolide) (PLGA), PLGA/gelatin [7], poly(lactic acid) (PLA), poly(ϵ -caprolactone) (PCL), poly(ethylene oxide), and poly(L-lactide-co-caprolactone) [12], among others (**Table 1**). But not all of them can be used for drug delivery systems.

Many drugs have been loaded into nanofibers using different methods. Among these drugs, chromazural B was successfully loaded into 5, 10, 15, 20-tetraphenyl-21H, 23H-porphine tetrasulfonic acid tetrasodium (TPPS) fibers; in this work, the scientists concluded that the fiber diameter was inversely proportional to the drug release rate [18] (**Table 2**).

Electrospun polymeric nanofibers	Drug loaded	Type of drug	Ref.
Poly(vinyl alcohol) (PVA)	Sodium salicylate, diclofenac sodium, naproxen (NAP), and indomethacin (IND)	Freely soluble in water, sparingly soluble in water, both insoluble in water, respectively	[13]
Poly(ethylene-co-vinyl acetate) (PEVA)	Actisite®	Antibiotic originally isolated from <i>Streptomyces aureofaciens</i>	[14]
Poly(vinyl alcohol)/poly(vinyl acetate)	Ciprofloxacin HCl (CipHCl)	Antibiotic belong to a group of drugs called fluoroquinolones	[15]
Poly(D,L-lactide-co-glycolide) (PLGA), PLGA/gelatin	Fenbufen	Nonsteroidal anti-inflammatory drug	[7]
Poly(ϵ -caprolactone) (PCL)	Naproxen (NAP)	Non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that relieves pain, fever, swelling, and stiffness	[16]
Poly(vinyl alcohol) (PVA) and sodium alginate (Na-Alg)	Insulin	Pancreas' hormone that allows the body to use sugar	[17]

Table 1. Nanofibers as drug delivery systems.

Fibers/particles	Drug loaded	Observations	Ref.
TPPS nanofibers ^a	Chromazural B	Smaller fibers exhibited rapid drug release in initial stage No significant difference between the total amount of released drug and the fiber diameter or type of drug, fiber diameter between 150 and 290 nm	[18]
PNIPAAm nanofibers ^b	Ketoprofen (KET)	Exhibited fibers largely smooth and cylindrical, with no phase separation	[3]
Gliadin nanoparticles	Cyclophosphamide anticancer drug	Particles are homogeneous and have a narrow distribution, nanoparticles diameter between 218.66 \pm 5.1 nm	[19]
PCL ^c and PHBV ^d nanofibers	Metformin hydrochloride (MH) or metoprolol tartrate (MPT)	Emulsion electrospun nanofibers significantly alleviated the burst release and produced a sustained release of drugs compared to the blended electrospun nanofibers	[3]

^aTPPS: 5,10,15,20-tetraphenyl-21H, 23H-porphine tetrasulfonic acid tetrasodium.

^bPNIPAAm: poly(N-isopropyl acrylamide).

^cPCL: poly(ϵ -caprolactone).

^dPHBV: poly(3-hydroxybutyric acid-co-3-hydroxyvaleric acid).

Table 2. Characteristics of fibers and particles for drug delivery applications.

4. Drug incorporation techniques using electrospinning

Nanofibers are not the only product of electrospinning device useful for drug delivery systems. It can also be applied to the electrohydrodynamic (EHD) technique, which allows the production of nanoparticles of different shapes and sizes. This method employs several techniques such as blending, coaxial process, and surface modulation, which permits the

incorporation of any drug, DNA, and growth factors, depending on the treatment needed to reach the proper material characteristics (**Figure 1**). Depending of the bioactive molecule desirable to be loaded, the polymeric or composite system is carefully chosen, with the purpose of the preservation of the therapeutic effect [12].

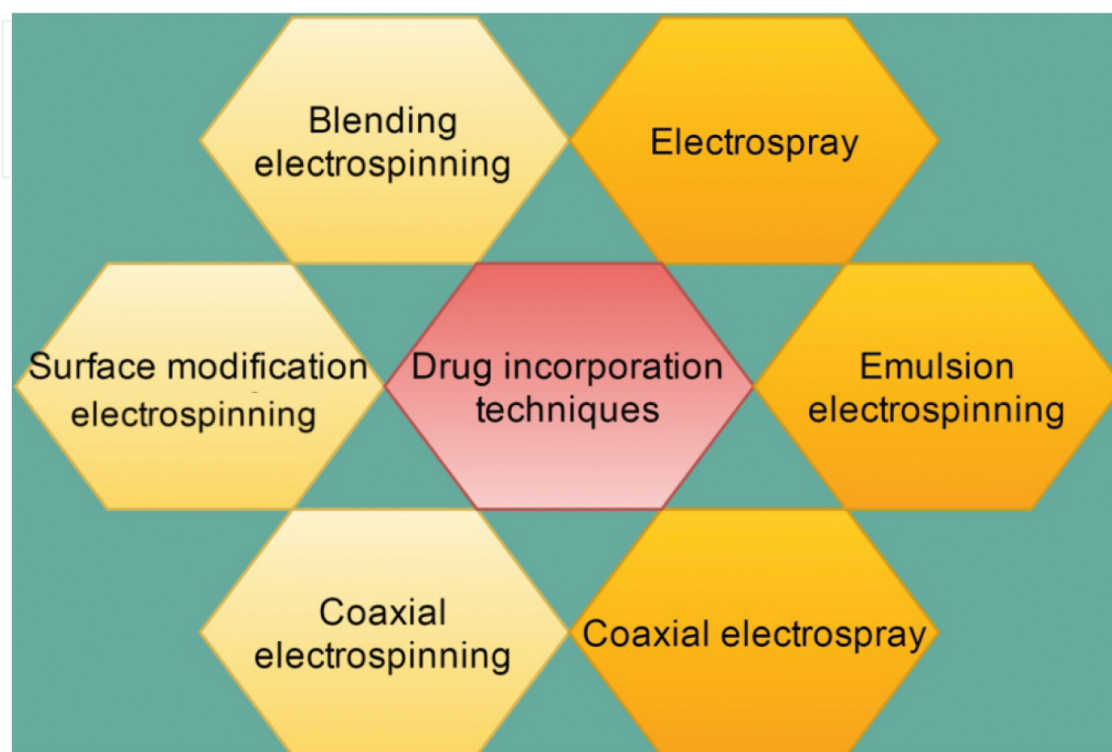


Figure 1. Drug incorporation techniques by electrospinning device. Adapted with permission from Ref. [11].

4.1. Blending electrospinning

The use of polymeric blend improves the equilibrium between mechanical and physicochemical properties of the drug-loaded nanofibers. Also, it effectively increases the formulation design for drug release, where the release rate can be manipulated by altering the proportion of polymer in the blended solution [20].

When using the blending electrospinning method, drug encapsulation is achieved through electrospinning in a single step, because drugs are dissolved or dispersed in the polymeric solution (**Figure 2**). The interaction between polymer solution and drugs is affected by the physicochemical properties of the polymers, because these characteristics act as factors that determine the efficiency in drug encapsulation, drug dispersion into the fibers, and the release rate. The isolated release of the drug into the solution can be triggered by the insufficient solubility of the drug in the polymeric solution, where the drug molecules can migrate to a nearby fiber's surface during the electrospinning process. Researchers have emphasized the importance of the equilibrium between hydrophilic and hydrophobic properties among drugs

and polymers when blending electrospinning is used. For example, thanks to the hydrophobic nature of some polymers, the lipophilicity of drugs becomes easier to get a homogeneous solution, and vice versa. For example, polyester polymers, which are hydrophobic, interact very well with the hydrophobic drug rifampicin and paclitaxel, and gelatin, PEG, and PVA, which are hydrophilic polymers, can dissolve hydrophilic drugs such as doxorubicin [21].

With blending electrospinning fibers are obtained with a single phase only. If the objective is to produce fibers with core-shell structure, which protect the labile biological agents and growth factors, blending electrospinning is not the proper method. For this purpose, coaxial and emulsion Electrospinning can be used [21].

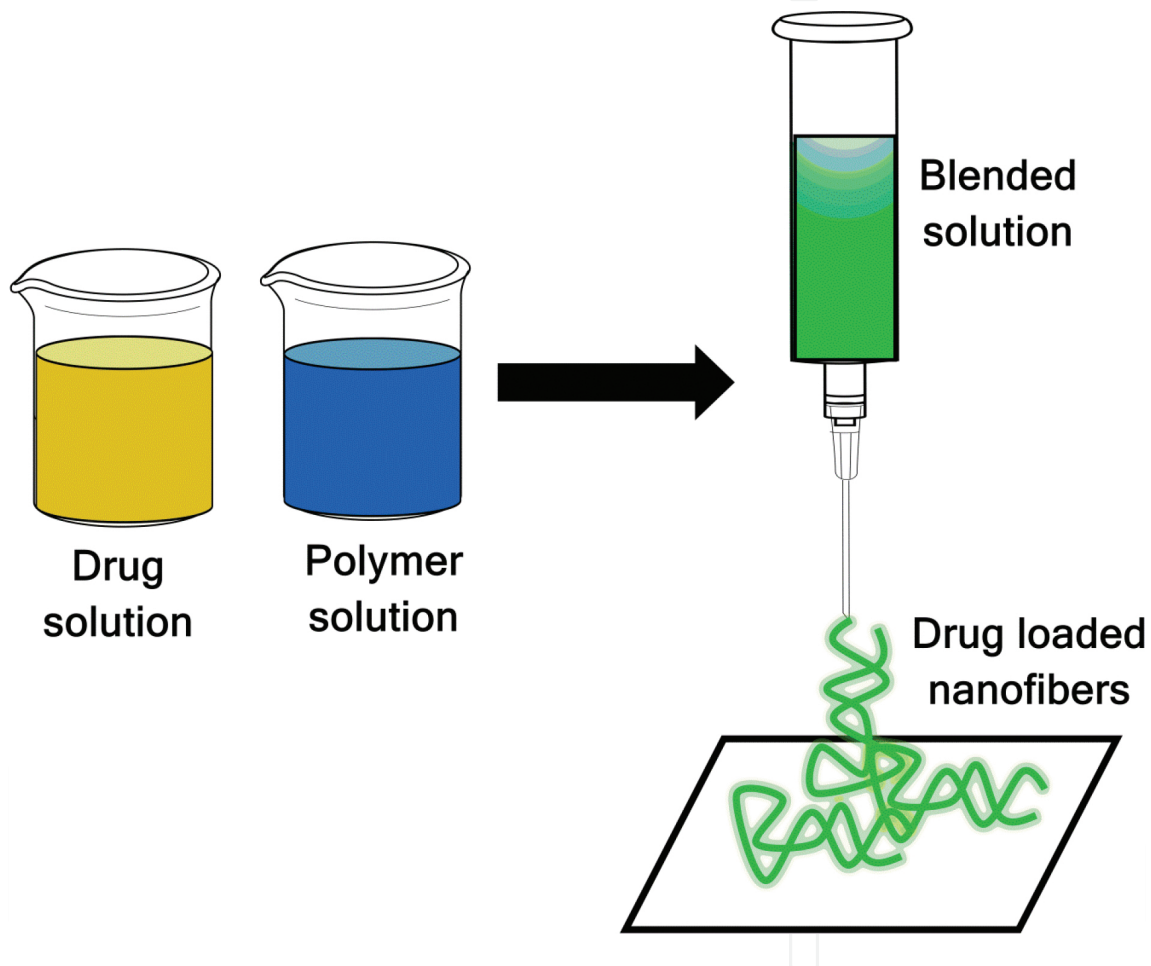


Figure 2. Blending electrospinning principle.

Several reports can be found in the literature where blending electrospinning is used for the loading of drug in a polymeric delivery system. A research, conducted by Lu et al., produced fibers of poly (N-isopropyl acrylamide) (PNIPAAm), which is well known as a smart polymer because it responds to pH and temperature stimuli, mixed with ethyl cellulose (EC), and it was successfully blended by electrospinning, and ketoprofen (KET), a nonsteroidal anti-inflammatory drug, was added into the system. The resulting complexes exhibited fibers that are largely smooth and cylindrical, with no phase separation. In this investigation, it was found

that the drug was present in its amorphous physical form in the fiber matrix, and significant intermolecular interaction between KET and the polymeric scaffold was observed. These systems were not toxic and biocompatible in cell culture [3].

4.2. Coaxial electrospinning

The main purpose of coaxial electrospinning is to obtain fibers with core-shell structure. This technique can be used to obtain fibers with specific drugs encapsulated in the core of the fibers, which lead to a sustained and controlled drug release (**Figure 3**). These kinds of fibers present a high surface area and three-dimensional network. Proteins, growth factor, antibiotics, and other biological agents have been successfully loaded into the coaxial fibers for drug delivery purposes. One of the main advantages of this technique is that the core-shell structure gives protection to the loaded compound and the bioactivities of drugs, for example, remain intact [9].

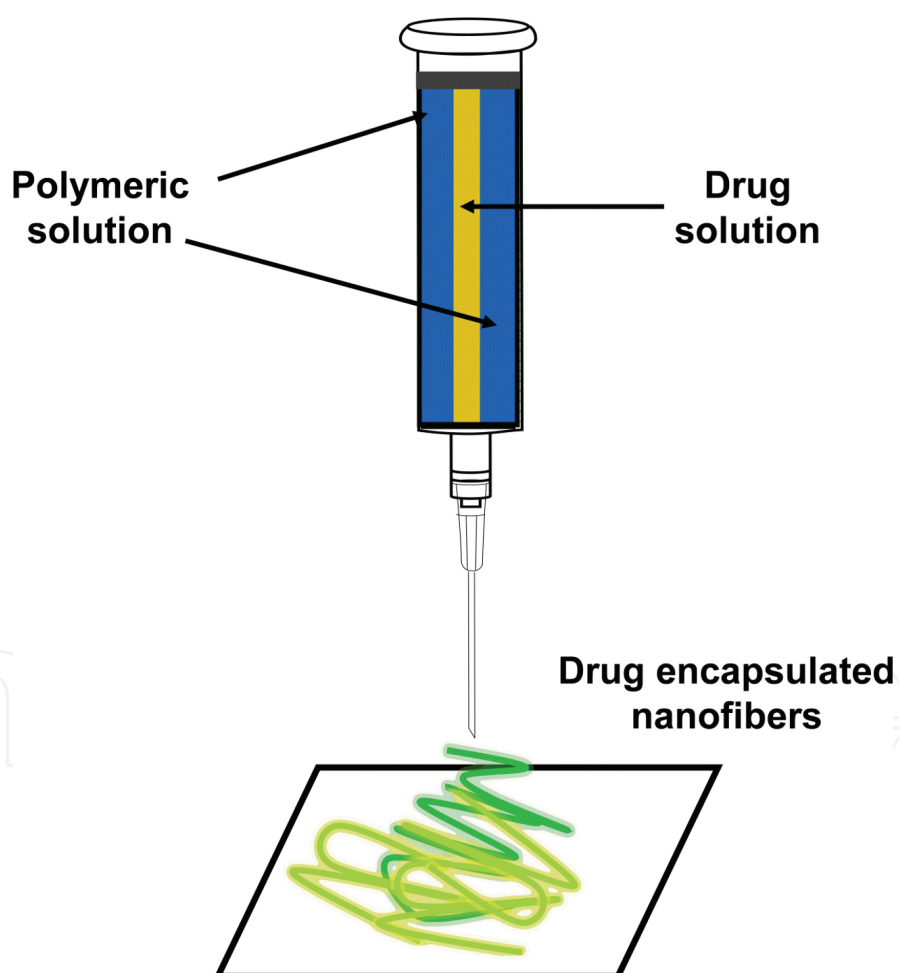


Figure 3. Coaxial electrospinning principle.

Among the coaxial electrospinning method benefits is the enhancing of biomolecule functionality, by having it into the inner jet, while the electrospinning process is working and the

polymeric solution is in the outer jet giving protection to the biomolecule. In this technique, the polymeric shell helps to avoid the direct contact of the biomolecule with the external environment. The core-shell system improves the sustained release of drugs and also allows the bioability of unstable biological agents to be maintained [21].

4.3. Emulsion electrospinning

Emulsion electrospinning is a flexible and potential technique for the encapsulation of several drugs into nanofibers [3] and is one of the most important methods for preparing core-shell electrospun nanofibers in a cost-effective and efficient manner (Figure 4) [9].

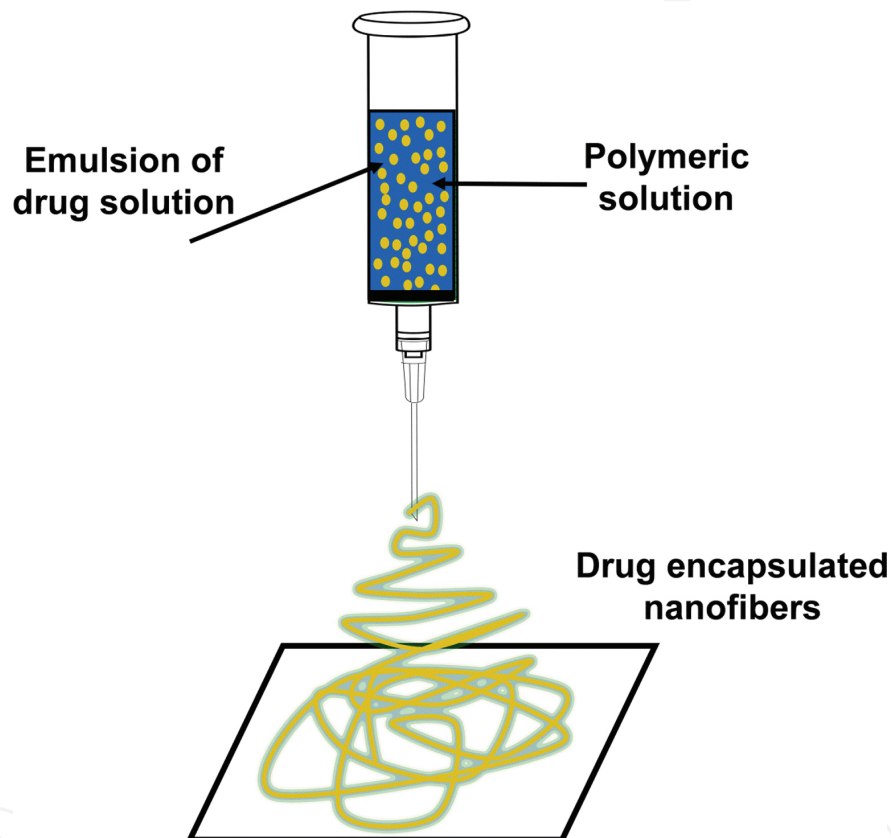


Figure 4. Emulsion electrospinning principle.

Using emulsion electrospinning fibers composed of poly (ϵ -caprolactone) (PCL) and poly (3-hydroxybutyric acid-co-3-hydroxyvaleric acid) (PHBV) were loaded with metformin hydrochloride (MH) or metoprolol tartrate (MPT). In this study, emulsion electrospinning demonstrated to be a better technique than blending electrospinning, especially in the modulation of the drug release rate by regulating the oil phase and water phase of the emulsions for obtaining the desired drug release. Between the two polymers tested, PCL showed better drug delivery properties than PHBV [3].

In the emulsion electrospinning method, the oil phase is created by the emulsion of the drug or aqueous protein solution in the polymer solution, followed by electrospinning. When the

drug to be load has a sufficient low molecular weight, the biomolecule-loaded phase can be distributed within the fiber or a core-shell fibrous structure could be configured as macromolecules amalgamate in the aqueous phase. The 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. Subsequently, a number of formulations of hydrophilic drugs and hydrophobic polymeric solution can be used while maintaining minimal drug contact with the organic solvent during the procedure [21].

4.4. Surface modification electrospinning

In this strategy, thanks to the electrospinning approach, a particular conductive surface can be chemically altered and changed, with the purpose of modifying the external properties of the coated device, by incorporating certain molecules that can camouflage the surface by offering a similar environment than the tissue that will surround the implanted material. Usually this strategy is applied to avoid fast initial burst release and slow the rate of immobilization of the biological molecules on a particular surface. In addition, with a good electrospinning system and with a well-standardized method to create electric field inside a camera, it is possible to coat 3D surfaces with nanoparticles or homogeneous surfaces (**Figure 5**) [21].

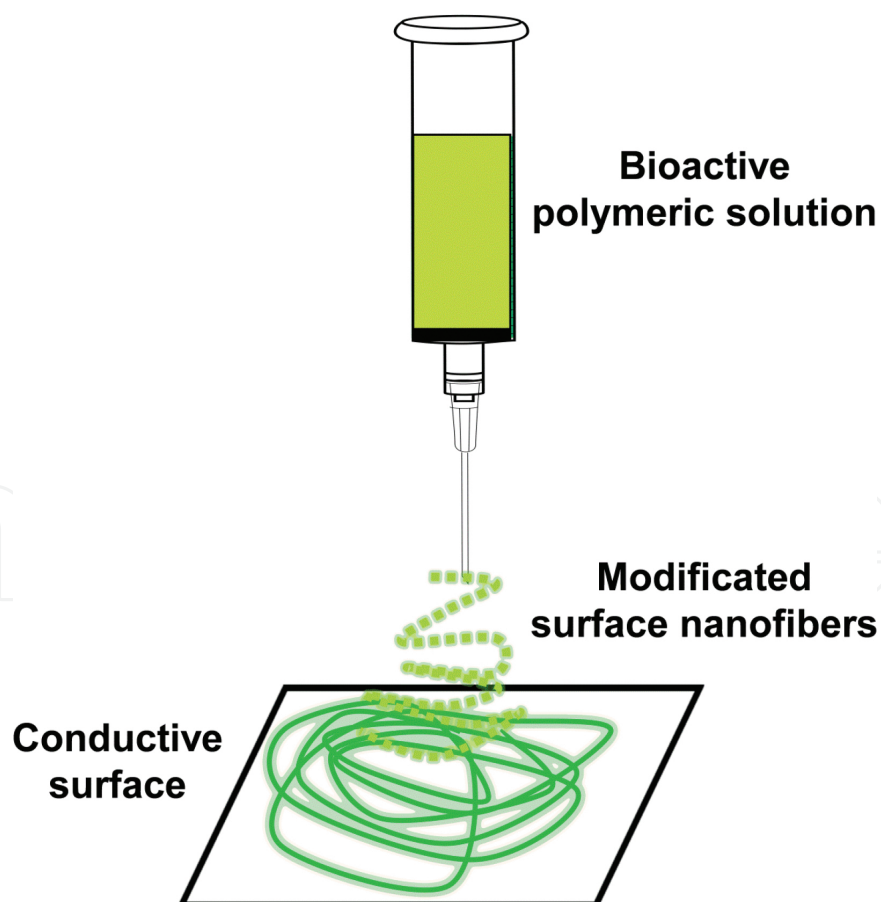


Figure 5. Surface modification electrospinning principle.

4.5. Electropray

Electropray is one of the most effective methods for the synthesis of nanoparticles and nanospheres. This technique is the simplest of all the drug incorporation methods. In this process, the liquid emerging from the nozzle into the electrical field forms the Taylor cone because of the surface tension. Once the electric field increases, the Taylor cone breaks into highly charged droplets, creating suitable conditions for the formation of nanoparticles or microparticles. Solid particles are formed by solvent evaporation (**Figure 6**). Some of the parameters that need to be taken into account are the needle gauge diameter, flow rate, voltage, and distance from the needle to the conductive collector, promoting the right incorporation of the drug [19].

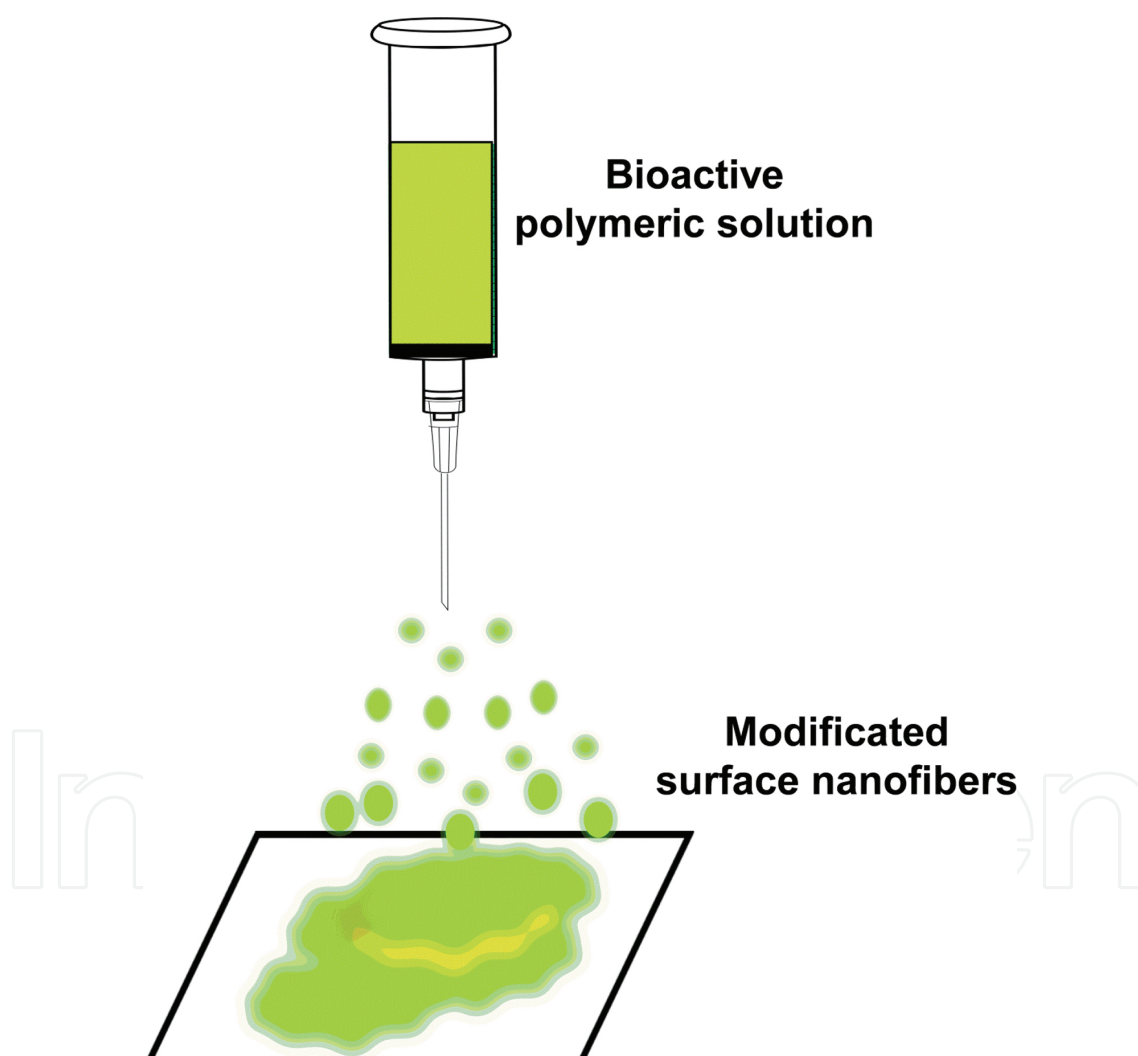


Figure 6. Electropray principle.

Electrospayed nanoparticles can be useful for biological, medicinal, and pharmaceutical applications; hence, it is zero dimensional in nature. The advantages of electrospaying include increased scalable synthesis, reproducibility, and high encapsulation efficiency [19].

In addition, with this technique nanoparticles can be loaded with pharmaceutical molecules like drugs and biomolecules acting as particular transporters due to its active surface absorption, binding capacity, and complexation with drugs and bioactive molecules. Moreover, the particles of a nanoscale size are important in therapeutic treatments, because they improve the drug carrier rate, specificity, adhesion, and reactivity [19].

For this strategy, the use of nanoparticles of natural gliadin loaded with cyclophosphamide anticancer drug has been reported for the treatment of retinoblastoma and certain cancers. In this study, over 72% of drug loading was accomplished; researchers reported homogeneous nanoparticles with average diameters of 218 ± 5.1 nm [19].

4.6. Coaxial electrospay

Coaxial electrospay allows the production of multilayer particles with sizes ranging between 10 and 100 μm by using a high electric field between coaxial capillary needle and ground. In this technique, the resultant electrical shear stress elongates the core and the shell liquid menisci at the needle outlet to form the “Taylor cone”; after this phenomenon, the jet of the liquid elongates enough until it is broken into multilayer droplets owing to the electrohydrodynamic forces (**Figure 7**) [22].

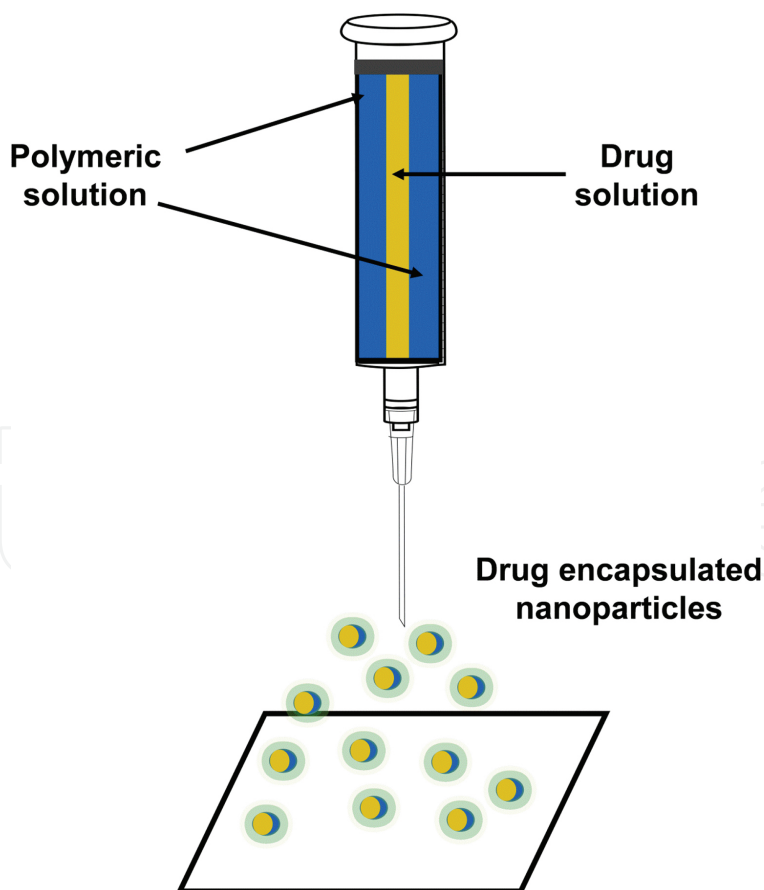


Figure 7. Coaxial electrospay principle.

This method achieves high encapsulation rate, precise control of the core-shell structure, and protection of the fragile therapeutic cargos from process-induced denaturation and aggregation. Also, this process is scalable for mass production of drug-loaded microparticles and nanoparticles [22].

Moreover, coaxial electro spray leads to a microencapsulation and a nanoencapsulation of drugs into polymeric particles. To perform this method it is necessary to use a coaxial capillary needle to deliver two liquids independently. Several liquid materials can be used including glycerol, distilled or deionized water, ethanol, ethylene glycol, etc. For the synthesis of multilayer macroparticles and nanoparticles with a hard shell, polymeric solution, such as PCL, PLA, PLGA, PMMA, PE, among others, can be used [22].

In general, all methods for drug incorporation using electrospinning possess its advantages and limitations (**Table 3**).

Method	Advantages	Disadvantages	Ref.
Blending electrospinning	Improves the tunability of the physicochemical and mechanical properties of the drug-loaded fibers. Benefits the development of controlled drug release formulations, for which the release rate can be modified by altering the ratio of the polymers in the blend	A clear understanding of the phase behavior of the processed polymer blend is essential	[20, 21]
Coaxial electrospinning	Enhanced biomolecule functionality. The core ingredient is shielded by the shell polymer avoiding direct contact to the biological environment	Need a special syringe tip	[21]
Emulsion electrospinning	No need of a common solvent as the drug and the polymer are dissolved in applicable solvents	Not all drugs can be loaded by this method	[21]
Surface modification electrospinning	Resolve the issues of large initial burst release and short release time as the biomolecules are surface immobilized	Depend of the nature of polymers and drugs	[21]
Electrospray	Easy to control the operation parameters. Fast preparation and one-step technique. This involves simple ideology. This technique can be able to extend for bulk production	This technique may induce some macromolecule degradation due to the stress involved in the operation parameters (ex: thermal stress in drying, shear stress in the nozzle)	[19]
Coaxial electropray	High encapsulation efficiency, effective protection of bioactivity and uniform size distribution	Process control in coaxial electro spray is challenged by the multiphysical nature of the process and the complex interplay of multiple design, process and material parameters	[22]

Table 3. Advantages and disadvantages of drug incorporation methods using electrospinning.

5. Conclusion

This chapter summarized reported drug incorporation techniques developed from electrospun nanofibers and nanoparticles, from polymers used to a comparison between the techniques. Coaxial electrospinning and coaxial electrospinning can be used when a core-shell structure is needed, for example, in cases when the therapeutic agent is sensitive to the environment. Blending and emulsion electrospinning do not need special equipment and are the simplest methods to incorporate drugs into nanofibers. Finally, surface modification is necessary when the burst release effect needs to be avoided and a more durable release rate is desired. All techniques are useful, versatile, cheap, and easy for the incorporation of drug in a drug delivery system. The method must be chosen depending on the nature of the therapeutic agents.

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