Review Article

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Electrospinning: A promising technique for drug delivery systems

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Abstract: In the last years, electrospinning has become a technique of intense research to design and fabricate drug delivery systems (DDS), during this time a vast variety of DDS with mainly electrospun polymers and many different active ingredient(s) have been developed, many intrinsic and extrinsic factor have influence in the final system, there are those that can be attributed to the equipment set up and that to the physical-chemical properties of the used materials in the fabrication of DDS. After all, this intense research has generated a great amount of DDS loaded with one or more drugs. In this manuscript a review with the highlights of different kind of systems for drug delivery systems is presented, it includes the basic concepts of electrospinning, types of equipment set up, polymer/drug systems, limitations and challenges that need to be overcome for clinical applications.

Keywords: Electrospinning; drug delivery system; biomaterials, controlled release

1 Introduction

Electrospinning, a term derived from "electrostatic spinning", is a technique for the preparation of ultrafine fibers with high surface area from a variety of materials like polymers, ceramics, and composites. Although, the technique was discovered more than a century ago, the electrospinning process has been intensively studied and gained many adepts during the last 20 years. The first patent solicitation for an electrospinning equipment was made by John Francis Cooley in 1900, after that, several scientists worked in the physics and principles of electrospinning (ES), one of them was Sir Geoffrey Taylor that in the 1960s, following the work of Zeleny [1], made a mathematical model of the cone formed by a droplet under the action of the electrical field [2, 3]. The widespread interest and popularity of the technique is attributed to several facts such as low cost, easy operation, facility to fabricate ultrafine fibers with diameters range from nanometers to several micrometers, control of morphology and versatility of the materials that can be employed. Nowadays, hundreds of papers exhibit the preparation, synthesis, modification, and functionalization of micro and nanofibers, mainly polymers, blends and composites. These publications include a vast number of electrospun materials for applications such as elastic and flexible electronics [4–7] magnetics [8, 9], energy by producing high-performance membranes for fuel cells, thanks to the capability in sustaining proton conductivity and reduce methanol permeability [10], applications in solid oxide fuel cells electrodes [11, 12]. Also, materials fabricated by ES are intensely studied for wastewater treatment such as heavy metal ion adsorption, removal of dye contaminants, water purification, etc. [13–18]. One the other hand, micro and nanofibers obtaining from ES process have properties such as high superficial area, high porosity, and morphology similar to the extracellular matrix (ECM) that make them excellent candidates for biomedical applications. ES has become a key process for the fabrication of biomaterials, mainly for tissue engineering like bone regeneration, skin regeneration, nerve tissue [19–23] and diagnosis for HIV, diabetes, cancer, and others [24–26]. In the field of drug delivery systems (DDS), the research is extremely intense [27]. Therefore, this paper reviews the most relevant advances and perspectives on ESNFs for DDS. It starts with a description of the technique, parameters, and configuration of ES equipment, followed by the most relevant materials and active ingredients for the preparation of DDS.

2 Fundamentals of Electrospinning

Electrospinning consists of a high voltage power supply (HV), a syringe with a needle, metal collector, and a syringe pump as the basic components of the ES system. A schematic representation of a basic set up is shown in Fig-

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ure 1. The HV will make the solution to draw out because of the electric force. The surface tension is overcome by the electric force of the solution and then the fibers emerge from the apex of the conical drop that is known as the Taylor cone. The fiber stretches and elongates in the trajectory to the collector as the solvent evaporates, thereby solid ultrafine fibers reach the collector. Mats randomly oriented or parallel-aligned can be collected by different methods, one of them to obtain aligned fibers is by using a cylinder collector with very high rotating speed [28]. Also, an auxiliary electrode/electrical field putting on the fiber trajectory will help to produced aligned fibers [29] and the use of a thin wheel with a sharp edge and a frame collector are very useful in the production of aligned fibers [30].

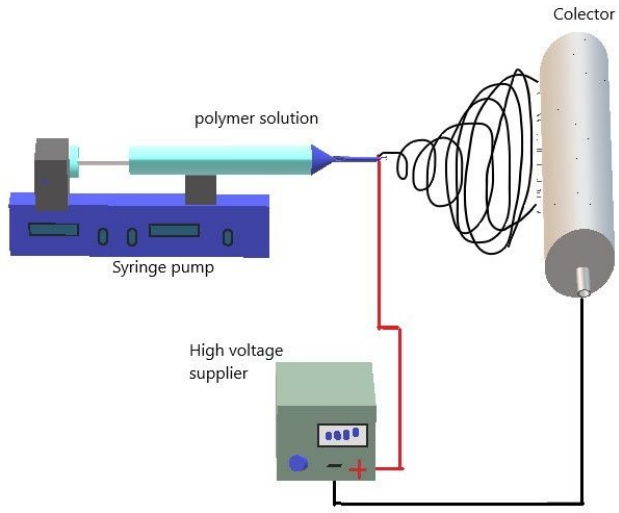


Figure 1: Schematic representation of basic electrospinning set up.

In the process there are several inherent factors to the electrospinning set up that will affect the morphology and structure of the electrospun materials. They are the applied electric field, the work distance between the tip of the needle and collector, flow rate, speed collector if the system has a rotatory drum and the needle diameter. Also, the inherent parameters of the solution have a strong influence in the quality of the fibers, these parameters are solvent type, polymer molecular weight and concentration, conductivity and viscosity. And the third set to be considered is the environmental parameters, temperature and humidity.

3 Influence of the Electrospinning Parameters

3.1 Processing Parameters

Applied Voltage

It is a key parameter in the electrospinning process, the high voltage must be applied and modulated to obtain smooth ultrafine fibers without bead-like defects and others, mostly works report an applied voltage for their systems between 10 and 25 KV. Although several authors coincide that other parameters have more effect on the electrospun materials, there are others that report that increasing the applied voltage, the average diameter of the fiber will increase and also could result in a rough surface and formation of beads [31, 32]. On the other hand, there are authors that suggest that higher applied voltage would generate fibers with a smaller diameter [33, 34], which is a controversial issue that cannot be clarified easily, due to the vast variety of systems that can be formed with a great number of polymers beside the several parameters that should be controlled, but definitely the applied voltage must be considered as a key parameter in ES process.

Flow Rate

Generally, a well-formed fiber will be obtained by an appropriate flow rate that should give the time for a good polarization. There are several papers that present studies about the influence of the flow rate on the morphology and structure of electrospun materials, Zargham *et al.* [35] showed that the droplet size, the trajectory of the jet, and maintenance of Taylor cone varied in the fabrication of nylon 6 NF as the flow rate changed and consequently, the morphology, diameter size, and distribution of the fiber were all influenced by the flow rate of the polymer solution.

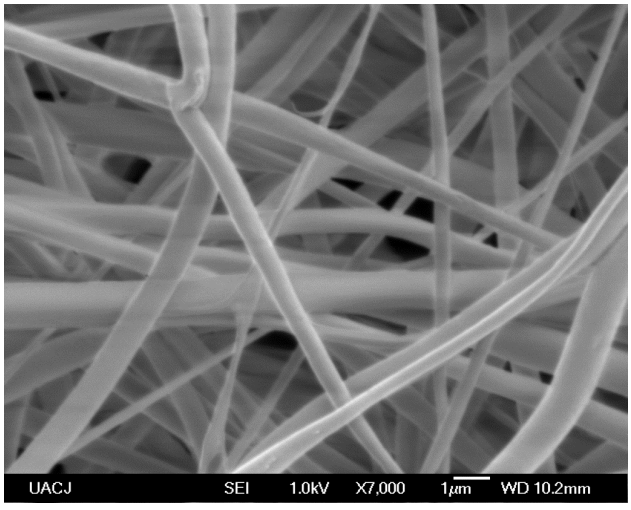
Work Distance – The distance between the needle tip and the collector should be enough to give the time to the polymer solidification before reaching the collector but not too long because beads will appear instead of fibers.

3.2 Solution Parameters

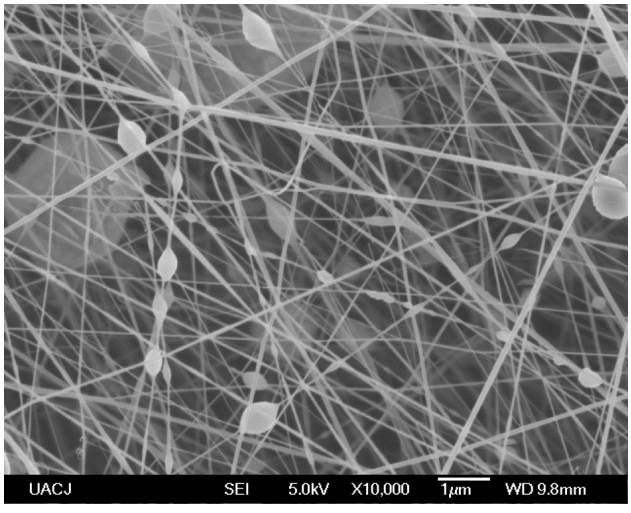
Concentration

Polymer concentration is another parameter that plays a crucial role in electrospinning, if the concentration is lower than a critical value, there will be no formation of fibers due to the tensional surface that cannot be

maintained. When there is an appropriate concentration, smooth fiber without defect will be formed, but below this critical concentration, we can obtain fiber with like-beads defects, also the fiber diameter increases as the polymer concentration increases. Some works report the formation of flat/ribbons morphology by varying the polymer concentration and voltage [36].



(a)



(b)

Figure 2: a) Electrospun PCL fine fibers without defect, and b) Electrospun PCL fibers with like-beads defects.

Polymer Molecular Weight

Polymer MW reflects the entanglement of polymer chains in solutions, namely the solution viscosity. It has a significant effect on the structure of the electrospun polymer, it has found that also affects the jet branching, elongational flow, and bending instability [37].

Viscosity

This is a critical property that offers resistance to flow and consequently in determining the fiber morphology.

Conductivity

The charge carrying ability of the polymer jet, depending on the ions in the solution, adding salt to increase the conductivity can help to obtain defect-free fibers and also fibers with smaller diameters.

3.3 Environmental parameters

The environmental factors like temperature and humidity are also very important and it must be taken under consideration in the fabrication of reproducible fibers. Humidity affects the formation of the fiber in the electrospinning process, lower RH increases the velocity of the solvent evaporation drying the polymer rapidly, whereas higher RH values cause slower solvent evaporation. In a study to determine the influence of the relative humidity on the fiber morphology for poly (ethylene glycol) (PEG), polycaprolactone (PCL), and poly(carbonate urethane) (PCU), the polymers were electrospun under RH from 5 to 75% for PEG and PCL, only broken fibers were produced below the 50% of RH, that increased with the decreased in RH. Meanwhile, for the PCU at 50% RH smooth and uniform fibers were produced, above this RH de fiber deposition decreased considerably, the decreased levels of electrostatic discharged results in fiber breakage [38]. It was expected that high humidity will lead to thick fiber diameter owing to the neutralization of the charges in the jet and the stretching forces become small, also high humidity could increase the surface porosity. However, in the study conducted by Pelipenko *et al.* [39] with electrospun nanofibers of poly (vinyl alcohol) and blended with hyaluronic acid, poly(ethylene oxide) and chitosan, it was found that low RH leads the formation of thicker nanofibers with more heterogeneous size distribution and higher RH produced thinner nanofibers with more heterogenous size distribution independently of the polymer composition, in all the cases the solvent was water. These results were attributed to the driving force for solvent volatilization that in the case of aqueous polymer solutions, the lower the environmental RH the higher gradient, the polymer jet solidifies faster just after left the needle tip and it is exposed to voltage-induced

stretching for a longer time, resulting in the formation of thinner fibers.

It is clear that RH affects the morphology and size of the electrospun polymeric nanofibers, but the influence and the impact can be contrasting for different systems, the material hydrophobicity, solvent properties, and applied voltage must be taken in consideration to hypothesize and predict the influence of the RH in a specific polymer-solvent system.

Another environmental factor that influences the electrospun nanofibers is the temperature that affects the surface morphology, and porous structure, pore size, depth, shape and distribution of the nonwoven mats porous structure [40].

4 Electrospinning for Drug Delivery Systems

Drug delivery systems (DDS) are formulations or systems that enable the introduction of therapeutic agents into the body with improving properties, better efficiency, reliability, and minimal cytotoxicity. The development of ultrafine fibers for delivering therapeutic agents represents a frontier area of nanomedicine, with the possibility to contribute enormously in the different field of targeting several diseases. During the last 15 years when the first publications using electrospinning as potential technique to trap and deliver drugs emerged, the number of publications showing research activity on potential DDS by means of ES has been increased exponentially as can see in Figure 3. This intense activity shows the great expectation that researchers have on ES technique for DDS.

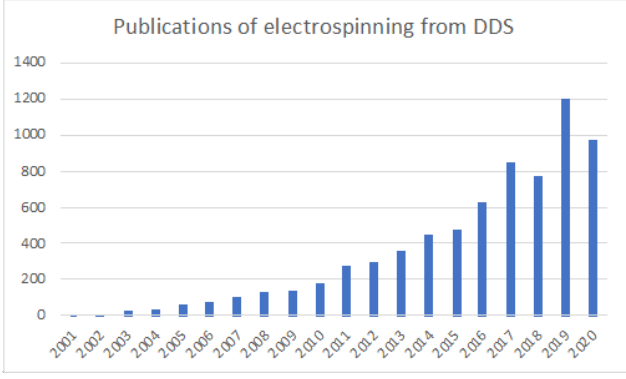


Figure 3: The annual number of scientific publications about electrospinning materials for drug delivery systems (Data analysis was done using science direct database using the words electrospinning and drug delivery, July 15, 2020).

4.1 Electrospinning nozzle configuration in drug delivery systems

Single-needle is the simplest and more used configuration on the electrospinning equipment, for drug delivery is not the exception, but recently, coaxial and multiaxial needle configuration have been gaining adepts, the obtained fibers have features such as core-sheat, hollow, porous, and triaxial-channel fibers for use in various applications. Basically, coaxial electrospinning consists of an arrangement of the inner and outer nozzle where two immiscible liquids are pumping simultaneously through the two concentrically aligned needles, a core-shell droplet at the nozzle is produced, the electric field jets the emerged fluid from the tip to the collector forming fine core-shell fibers. The coaxial electrospinning has advantages over the single electrospinning configuration, such as the encapsulation and drug sustained release, one-step co-encapsulation of multiple drugs with different solubility characteristics, also the damaging effects due to direct contact of the agents with organic solvents are eliminated, the shell layer acts as a barrier to prevent premature release of the water-soluble contents [41]. On the other hand, the coaxial process can be quite complex, and in addition to the basic parameters of the single configuration, other parameters will impact the release of the drugs. Generally, the drug loading is taken on the core polymer, it can be the same or another different polymer in the shell. It has been demonstrated that using coaxial electrospinning the burst and cumulative release can be reduced obtaining a sustained release profile compared with single nozzle electrospinning. Glasmacher *et al.* [42] showed that at higher concentration of Dipyridamole (DIP) led to thinner and more hydrophobic fiber with lower encapsulation efficiency and faster diffusion of DIP through the polymeric matrix. Also, the coaxial technique has been used to co-deliver two different drugs, Wang *et al.* [43] co-delivered a small molecule, acyclovir, and bovine serum albumin (BSA) as model protein encapsulated in electrospun PLGA nanofibers. BSA was incorporated in the core and acyclovir in the shell, several parameters like the core fluid composition, protein concentration, additives in the core fluid, a flow rate of the core and outer solution to tune up the morphology of the fibers and the kinetics release of the molecules [43]. An antitumor protein drug, soluble tumor necrosis factor related apoptosis-inducing ligand (sTRAIL) was first genetically modified and then electrospun into PLGA nanofibers by coaxial electrospinning with the surprising result that the biological activity is maintained during the electrospinning process and a good cumulative release, the potential application for the system is for breast cancer treatment [44].

For triaxial needle electrospinning, a third polymer solution can be incorporated into the system, it can be used to supply and release two different drugs with the dual delivery system [45–48], the intermediate layer can act as an isolation layer between the sheath and core materials. Furthermore, triaxial fiber can be formed with varying hydrophobicity and mechanical strength. Yang *et al.* [49] fabricated core-shell nanostructures in a triaxial arrangement, the inner fluid was ibuprofen-gliadin solution allowing the formation of a core-shell nanostructure of ibuprofen amorphously distributed throughout the gliadin core matrix by means of intermolecular interaction, the outer layer, cellulose acetate (CA) allowed to tune the fiber diameter and the drug release, the CA coating controlled the burst release and increase the time for it. Also, Mania *et al.* [50] incorporated simultaneously three different kinds of anti-cancer drugs in a triaxial setup, Doxorubicin(DOX), Paclitaxel(PTX), and 5-fluorouracil (5-FU), the core made of Chitosan/PVA had encapsulated the 5-FU, The intermediate PLA/Chitosan layer had not drugs, the DOX and PTX were loaded in g-C3N4 and incorporated in PLA/CS solution to form the outer layer. The anti-cancer loaded tri-layer nanofibers showed to be effective against MCF-7 breast cancer cells killing 94% of them.

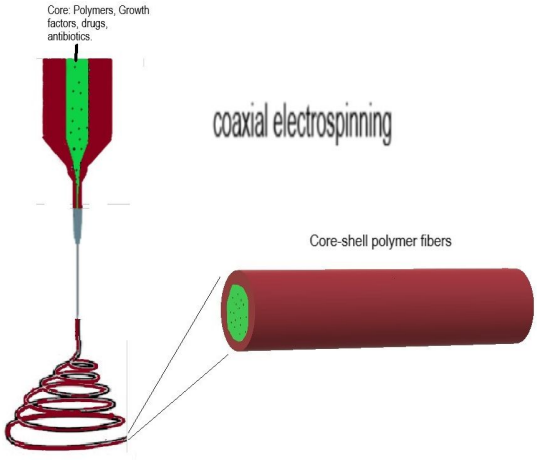


Figure 4: Schematic representation of coaxial electrospinning.

4.2 Electrospun Nanoparticles/polymers systems for DDS

Also, to enhance drug release, several authors have incorporated into the polymer matrix micro or nanoparticles loaded with active ingredients [51], this system includes mesoporous silica nanoparticles in PLGA [52–54], this kind of system has been used to co-encapsulated hydrophilic and hydrophobic drug simultaneously inside the silica particles and electrospun with PLGA [55, 56]. Silica nanoparticles have been very versatile to load different kinds of drugs and then embedded in electrospun polymers. These systems include PCL/silica nps with differents loaded drugs such as allantoin [57], levofloxacin [58], camptothecin [59], gentamicin [60]; also drug-loaded silica nanoparticles have been incorporated in Poly(L-Lactic acid) for doxorubicin release [61], poly(vinyl alcohol) for methylene blue release [62]. To incorporate drug-loaded silica nanoparticles into the electrospun matrix polymer is one of the main methods, but there are other systems of drug-loaded particles/polymer which are widely used in the electrospinning process, like bovine serum albumin (BSA) particles that were loaded with dexamethasone (DEX) and bone morphogenetic protein-2 (BMP-2) and then embedded in poly(caprolactone)-co-poly(ethylene glycol) copolymer, the dual-drug-loaded system was very effective to induce differentiation towards osteoblasts thanks to its synergistic effect of BMP-2 and DEX [63]. Another system, silibinin were loaded to and effectively released from Fe_2O_3 and Au/Ag nanoparticles in a PEG/PLGA fibers [64]. The incorporation of nanoparticles, inorganic, or organic can be very effective for dual or multi-drug delivery with a synergistic effect. Other interesting electrospun materials for drug delivery are those that incorporate inclusion complex (IC) like cyclodextrin, a nontoxic cyclic oligosaccharide that are produced by enzymatic degradation of starch. Their ability to build up non-covalent IC are well known [65]. The formation of IC leads to considerable improvements in the properties of the guest molecules such as protection for evaporation, degradation, oxidation, enhancing solubility, chemical stability, and controlling the release rate. Curcumin-β-cyclodextrin IC was successfully encapsulated in electrospun almond gum/PVA nanofibers and tested in simulated gastrointestinal and simulated saliva medium, in both media the release was governed by diffusion mechanism, higher solubility of curcumin after its complexion with CD lead to higher release in simulated saliva conditions [66]. In another work, α-tocopherol (vitamin E) was complexed with β-Cyclodextrin and then encapsulated in Polycaprolactone (PCL) and compared with electrospun PCL –TC without CD-IC. The results showed that PCL/TC/CD IC has higher antioxidant activity as compared to PCL/TC. This was attributed to the stabilization and solubility increment of TC in the cavity of CD providing higher oxidative stability and stronger photostability of TC, showing the ability of this kind of electrospun system for the release poorly soluble drugs [67]. Searching for new formulation for an effective drug delivery sys-

tem, researchers developed an elastomeric PLLA and PCL copolymer with Aloe Vera, Magnesium oxide nanoparticles, curcumin, and β-cyclodextrin to control the growth of MCF-cells for breast cancer therapy [68]. The biocomposite showed promising results for breast cancer therapy, PLACL/AV/MgO nanofiber support cell adhesion and proliferation but with addition of CUR the inhibition of MCF-7 cells increased 62%.

4.3 Kinetics and Mechanisms

Generally, a controlled release is sought in the electrospinning drug delivery systems, although burst release is unpredictable it could be desirable under certain circumstances such as encapsulated flavors, pulsatile release, target delivery, and wound treatment or in certain applications where a fast release in the initial step followed by a decreased rate of drug administration is required [69]. Polymers fibers for burst release quickly hydrate and dissolve in an aqueous solution and throw out their drug load [70]. On the other hand, the burst release can have the negative effects due to suddenly fast administration such as pharmacologically risks, undesired side effects, ineffective treatments and economically inefficient. Most of the studies focus on sustain release systems, it can be obtained by different routes with tunable results, *e.g.* it has found that highly-aligned fibers release drugs more sustainable than randomly oriented fibers [71, 72]; Eslamian *et al.* [73] incorporated dexamethasone in highly aligned PLGA fibers where almost 11% had burst release in 24 h for randomly oriented fibers compare to almost 9% of sustained releases in 24 days for aligning PLGA fibers. Also, the morphology has been studied to determine its influence in drug delivery systems. Kundrat *et al.* [74] compare the entrap, and release of poly (3-hydroxybutyrate) fibers loaded with levofloxacin, in three different morphologies, sponge, fibers with and without beads, all the models release approximately 32% in 13 days, the difference was in the efficiency to entrap the drug, the sponge morphology entrap 81% compare to 22% and 14% for the fibers with and without beads, respectively; surface erosion mechanism was attributed to the first 24 h followed by a bulk erosion mechanism. Fabrication of ES fibers for sustained drug release requires extensive design considerations depending on the desired release time and type of drug to be supply.

Drug delivery from ESF can be due to desorption of drug from the surface, diffusion from pores, polymers swelling and/or matrix degradation, the latter occurred through an erosion mechanism [75]. All mechanisms can act at the same time and significantly influence the kinetics without a model capable to describe all kinds of mechanisms in DDS. Despite this, several models have been proposed to describe diffusion by solving Fick's second law of diffusion and non-Fickian behavior associated with the swelling of polymers and solvents uptakes [66, 76]. A common approach is to consider time and spatial dependent coefficient diffusion that takes into account the change in solvent diffusivity across the swelling front. In 1961, Higuchi proposed a model based on a pseudo-steady-state of the kinetic release, it was considered a drug homogeneously dispersed in planar devices under perfect sink conditions [76, 77]. Several empirical and semi-empirical models have been proposed, one of the most used is the Peppas equation,

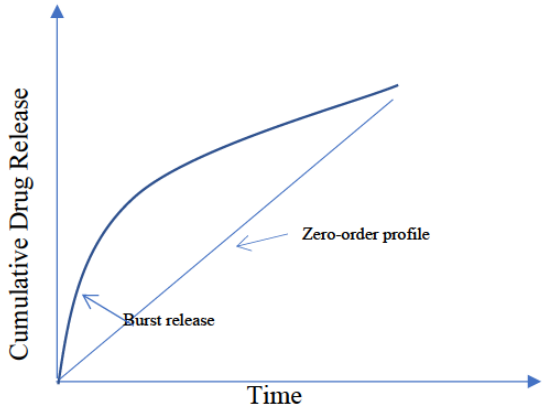


Figure 5: Schematic representation of the cumulative drug release vs time.

Higuchi Equation

$$Mt = K\sqrt{t} \tag{1}$$

Mt is the dissolved drug at time t
K is the kinetic constant for the Higuchi model

Peppas Equation

$$\frac{Mt}{M\infty} = kt^n \tag{2}$$

$M\infty$ is the cumulative drug release at infinite time, k is a constant incorporating structural and geometrical characteristics of the device and n is the release exponent, indicative of the mechanism of release.

4.4 Oral Drug Delivery Systems Prepared by Electrospinning

Oral drug delivery is still the preferred route for drug administration, mainly by capsules or tablet form. There are

several studies that have produced an oral drug delivery system by means of electrospinning technique [5, 78, 79]. It's been used for the fabrication of fast-dissolving systems enabled to increase drug bioavailability and safer excipients when compared to common oral administration systems. One example of these systems is that composed of two active ingredients, choline chloride/mandelic acid, a therapeutic deep-eutectic solvent, encapsulated in electrospun gelatin fibers [80]. Generally, the conventional oral DDS are pH or time-dependent release systems, a combination of pH and time-dependent polymers of Eudragit S and Eudragit ERS were electrospun with Indomethacin as a model drug for colon cancer treatment, resulting in a good candidate for colonic drug delivery due to the suitable morphological characteristics and the formulation was able to protect a major part of the drug in the media simulating the upper gastrointestinal tract [81]. In this context, colon-targeted drug delivery is attractive not only for local delivery to treat disease of the colon, but also for improving the bioavailability of poorly water-soluble drugs as a result of the long retention time and high colonic area [82]. Shellac a natural polymer secreted by female lac beetle was used to produce electrospun colon-targeting nanofibers loaded with ferulic acid, a natural antioxidant reactive toward free radicals. Shellac can protect the drug due to its insolubility in an acidic environment such as the stomach, in vitro dissolution tests showed that fibers morphology are useful for application in oral colon-targeted drug delivery, less than 10% was dissolved in pH 2, while the rest of the active ingredient was released over around 8 h in a neutral phosphate buffer, the mechanism to release the drug from the fibers was through an erosion-controlled mechanism [83]. Another interesting work designed and fabricated various combinations of Eudragit and furosemide nanofibers tablets by electrospinning [84]. Furosemide, a chlorine channel blocker, practically insoluble in water and dilute acids. The authors found that the release of furosemide from these systems was compatible with the gastroretentive and slower intestinal release requirements. Also, formulations acted as furosemide carriers in emergency situations where a relatively fast onset of its action is required.

4.5 Electrospun Patches

Electrospun Patches also have attracted interest in drug release. Several active pharmaceutical ingredients can be incorporated for the fabrication of multifunctional fibrous patches, including, natural ingredients or extracts like Pinus halepensis Barkn that was incorporated in alginate and tested for anti-inflammatory dressings [85]. Also, Plai oil (Zingiber cassumunar Roxb.) has been electrospun into PLA patches for inflammation and pain treatment with very high entrapment efficacy. It was found that the active ingredient could penetrate through the epidermis without irritating the skin making the system an excellent candidate for dermal applications [86]. Patches of poly(vinylpyrrolidone)/Eudragit RS100 carried with lysozyme were prepared by uniaxial electrospinning by Edmands *et al.* [87]. Its systems were designed for drug delivery to the oral mucosa, the protein was released at a clinically desirable rate, reaching 90 ± 13% cumulative release after 2 h. Also, its antibacterial properties were tested against a Gram-positive *Streptococcus ratti*, causing bacterial cell lysis [87]. In the same context, fatty acids in poly(vinylpyrrolidone)/Eudragit RS100 electrospun mucoadhesives patches were effective as antifungal agents against the fungus candida albicans, the results showed that fatty acids could be delivered directly to Candida-infected sites [88].

4.6 Characterization of the Active Pharmaceutical Ingredients

The identification of the morphology of the active ingredients in the final dosage is of utmost importance for electrospun DDS. Stability, solubility, dissolution rate, and bioavailability are some of the physicochemical properties that are affected by the morphology of the APIs. The amorphous and crystalline morphology is the two-state in solids, for one side amorphous state of active pharmaceutical ingredients have important properties like higher water solubility and higher dissolution rate relative to the crystalline form [89].

Thermal analyses such as differential thermal analysis (DTA), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) provide information on melting, crystallization, sublimation and solid-state transitions, also the quantification of volatile components can be characterized. The determination of the melting point (T_m) and glass-transition temperature (Tg) by DSC are used to characterize the crystalline and amorphous state, respectively [90]. Also, is very useful to characterize co-crystallization of two different APIs [91, 92].

X-ray Diffraction (XRD) is a powerful tool for the physical characterization of APIs, XRD is utilized for phase identification and quantification, as well as phase transformation [93]. It can be used to follow and identify the formation of crystals in the co-crystallization process [91].

Table 1: Some examples of electrospun polymers for drug delivery.

Polymer or molecule	Drug delivered	Solvent	Fiber Diameter	Nozzle Type	Potential Application	Reference
Polyhydroxyalkanoate	Paclitaxel	CHCl3 and DMF (4:1)	0.700 µm	single	anticancer	[100]
PCL/Gelatin	Ketoprofen	Cloroform/Methanol/Acetic Acid	0.3 µm	single	Pain reliever	[81, 101]
PLA	Placlitaxel	Chloroform/dimethylformamide (99:1 w/w)	1.4 µm	single	anticancer	[102]
Poly(di(ethylene glycol) methyl-ethermethacrylate/ethyl cellulose	ketoprofen	,1,1,3,3,3-hexafluoro-2-propanol	0.5-0.7 µm	single	Pain reliver	[103]
Eudragit S/RS	Indomethacin	Ethanol	0.6 µm	single	Colon cancer	[53, 81]
Eudragit	Furosemide	Ethanol/ DMF	0.1-2 µm	single	Loop diuretic	[84]
Gelatin	Choline chloride/Mandelic Acid	Water	5 µm	single	Antibacterial	[80]
Shellac	Ferulic acid	Ethanol/DMF	0.6-1 µm	coaxial	Antioxidant Colon-targeting	[83]
Policaprolactone	α-tocopherol	FA/AA	0.2-0.3 µm	single	Antioxidant oral drug delivery	[67]
PCL-PLLA copolymer	MgO / diferuloylmethane/ Aloe Vera	HFP	0.3-0.8 µm	single	Antioxidant/anticancer	[68]
Polycaprolactone	Dipyridamole (DIP)	2,2,2 trifluroethanol (TFE)	0.3-0.9 µm	coaxial	Antiplatelet	[42]
Polycaprolactone	Naringin	DCM/DMF	0.5-0.6 µm	single	Anticancer/antioxidant	[104]
Polycaprolactone	Cilostazol	Chloroform/Methanol	0.8-1.8 µm	single	Vascular implant	[105]
Cellulose Acetate/Giladin(shell/core)	Feluric Acid	HFP/TFAA/AA/Acetone	0.6-0.8 µm	triaxial	Anticancer/Antioxidant	[106]
Poly(methyl vinyl ether-alt-maleic acid) monoethyl ester	Salicylic acid/methyl salicylate/ capsaicin/	Ethanol	0.8-0.9 µm	single	Skin disease	[107]
PLA/PCL	BSA	DCM:DMF	0.8-1.8 µm	single	–	[108]
Poly(methyl vinyl ether-maleic acid)	Montelukast	DMF	0.4-1.2 µm	single	Asthma treatment	[109]
Chitosan/PVA	Tranexamic acid	2% acetic acid in water	0.15-0.2 µm	single	Hemorrhage control	[104, 110]
PCL/PEO	doxycycline	DCM/DMF	0.6-0.8 µm	single	–	[111]
Poly(3-hydroxybutyrate)	Levofloxacin	DCM/Chloroform		single	Antimicrobial	[74]
Almond gum/PVA	curcumin	Ethanol/water	0.09-0.2 µm	single	Gastroinstestinal treatment	[24, 66, 89]
Silk fibroin/PEO	Doxurubicin hydrochloride	Aqueous solution	0.2-0.6 µm	coaxial	Anticancer	[112]
Chitosan/PVA-PLA/Chitosan	Doxurubicin/Placlitaxel/5-fluorouracil	Aqueous solution/Acacid/TFAA	0.2-0.6 µm	triaxial	anticancer	[50]
Poly(vinyl pyrrolidone)-ethyl cellulose	Naproxen	Ethanol	0.4-0.8 µm	single	Pain reliver	[113]
Glicerol/PLA/PCL	Doxorubicin/Apatinib	DCM/DMC	1.3-1.6 µm	triaxial	anticancer	[114]
PLGA/Gelatin/PCL	Rhodamine/Fluorescein isothicyantate-BSA conjugate	HFP	0.8-1.1 µm	Triaxial	Regenerative engineering	[115]
Hydrocortisone/cyclodextrin complex	Hydrocortisone	Aqueous solution	0.5-0.8 µm	single	Oral drug delivery	[5]
Pullulan-gellan gum ratios	–	Water	0.2-0.4 µm	single	Ocular drug delivery	[116]
Celluloce Acetate. Polyvinylpyrrolidinone . Hydroxypropylmethylcellusose.	Melatonin	Acetone Ethanol/DCM. Ethanol	0.7-5.0 µm. 0.1-1 µm. 0.04-0.4 µm.	single	Treat sleep disfunction	[117]

FA FORMIC ACID AA ACETIC ACID HFP 1,1,1,3,3,3-hexafluoro-isopropanol DCM Dichloromethane DMF Dimethylformamide TFAA trifluoroacetic acid

Also, the semi-crystalline and crystalline structure of the excipient have a direct influence upon the drug delivery rate due to the crystalline interrelationship between the excipient or polymer and the active ingredient. XRD is used to characterize this interrelationship [94].

Solid-state NMR (SSNMR) is another technique that is widely used in order to characterize the active ingredient(s), especially ^{13}C SSNMR spectroscopy, however, in formulation with low APIs, the sensitivity of ^{1}H SSNMR under magic angle spinning exceeds that of ^{13}C SSNMR from 1 to 3 order of magnitude reductions in experiment time [95]. SSNMR can also identify the molecular miscibility by measuring the longitudinal the relaxation time. Because the proton distribution represents uniformity of the entire mixture, time relaxation time of protons can sensitively characterize the miscibility between a drug and polymer matrix, The ^{1}H relaxation properties can evaluate it, semi-quantitatively at sub-100 domain size [96–98]. Also, the diffusion in polymer melts also can be characterized by means of high-temperature pulsed-field gradient NMR [99].

In Table 1, it is shown a list of several electrospun materials for DDS, it can be appreciated the great variety of polymers, copolymers and blends that can be electrospinning with different kind of drugs and potential applications.

5 Summary and conclusions

Electrospinning has become a promising technique for DDS due to the capacity for flexible and ease production of inexpensive polymers nanofibers for many applications. The basic knowledge for the fabrication of small fibers with the capability to release a different kind of drugs has been settled, by using different polymers and solvents, by controlling and setting the different parameters of the equipment as well the environmental conditions. The number of ES systems for biomedical research can be countless, although great advances have been achieved, still, there are challenges to be addressed, such as the efficient and uniform production of electrospun materials, environmental safety, reproducibility, and high accuracy as well scalability to industrial production in order to meet the market demand [2, 118]. The standardization of electrospinning set-up and process would facilitate to scale-up and produce DDS at industrial level. That will lead to the production of biomedical products to satisfy the clinical demand of them. However, other issues must be resolved before its clinical use, like regulatory and quality control of the electrospun biomedical products to make it safe for humans. The environmental conditions should be considered in the design and fabrication of industrial electrospinning equipment, temperature and humidity must be kept under control. Safety and health risk due to the used solvents during the electrospinning process must be taken under consideration, not only because the healthy damage but the residual solvent can be trap in the fibers. It should be search for new formulation in aqueous solution to avoid the conventional organic solvents. Interestingly, there are some factors that have been ignored that could affect the release kinetics and bioactivity of drugs or biomolecules at the clinical use. Evrova *et al*. presented a proof-of-concept study of how the sterilization process and period of storage can affect the properties of bioactivity and releases kinetics of a growth factor incorporated in an electrospun polyester urethane block copolymer called DegraPol (DP), it was found that during the storage and UV sterilization there was no visible impact in the morphology and physicochemical properties but UV sterilization affects the release in platelet-derived growth factor significantly, and the release kinetics decreased until 85% [119]. There is not doubt, electrospinning is still a promising technique for DDS and researchers will continue exploring different systems to overcome the limitations until now.

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