

Drugs Loaded into Electrospun Polymeric Nanofibers for Delivery

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ABSTRACT - The electrospinning technique is a useful and versatile approach for conversion of polymeric solutions into continuous fibers, ranging from a few micrometers (10–100 μm) to the scale of nanometers (10–100 nm) in diameters. This technique can be used in a vast number of polymers, in some cases after modifying them to the required properties. The high surface-to-volume ratio of the fibers can improve some processes like cell binding and proliferation, drug loading, and mass transfer processes. One of the most important and studied areas of electrospinning is in the drug delivery field, for the controlled release of active substances ranging from antibiotics and anticancer agents, to macromolecules such as proteins and DNA. The advantage of this method is that a wide variety of low solubility drugs can be loaded into the fibers to improve their bioavailability or to attain controlled release. This review presents an overview of the reported drugs loaded into electrospun polymeric nanofibers to be used as drug delivery systems. These drugs are classified by their applications in pharmacy.

INTRODUCTION

One of the main strategies in drug delivery application is the controlled release of important biomolecules using fast dissolution of biodegradable polymers, because the used of these molecules allows the increment of drug solubility and bioavailability and it can be manipulated the rate and site of the drug delivery. It has been reported many drug delivery systems that are administered by enteral routes, such as tablets, capsules, granules; or the administration by parenteral routes, such as intravenous, intra-arterial, intramuscular and subcutaneous. These have some disadvantages, such as first-pass metabolism, discomfort or pain (1).

An alternative method for these types of release is loading pharmaceutical components into fibers by the electrospinning technique, since this is a method that produces ultra-fine fibers with controlled surface morphology. Using polymeric fibers, the different controlled-release administration routes allows the application of pharmaceutical drugs once or twice a day, improving the patient willingness and reducing the toxic plasma peak concentrations that can be

produced by multiple administration of immediate release formulations (2).

Many advantages are obtained when the diameters of the polymeric fiber are reduced to micrometers or nanometers, such as a bigger surface area to volume ratio, elasticity and better mechanical properties (stiffness and resistance to traction), compared to any other known form of the material. These properties make polymer nanofibers the optimum candidates for many important applications in the biomedical areas (1-3).

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Electrospinning

The term electrospinning is derived from "electrostatic yarn" and it is a dry spinning process, which utilizes electrostatic forces to draw small fibers (10–100 μm to 10–100 nm) from a polymer solution, or in its case, a melted polymer (4).

Figure 1 illustrates the basic configuration for the electrospinning device. It consists of three main components: a high voltage source, a syringe pump and a conductive collector.

The dissolved or molten polymer is housed in a syringe and placed in a syringe pump. When a droplet of the polymer solution appears on the tip of the metal needle a high voltage is applied (usually from 5 kV to 50 kV), to the droplet hanging. This droplet will become highly electrified and the induced charges will be evenly distributed over the surface. The liquid drop will deform into a conical object known as the "Taylor cone". This cone appears when the space between the electrical conducting liquid and insulator exceeds a critical voltage, making the liquid drop unstable and transforming from a rounded shape to a conical shape (5, 6). When the voltage exceeds a threshold value, the electric force exceeds the surface tension of the drop and then one or more jets loaded with the solution are expelled from the tip of the drop, depending on the electric field strength. As the jet travels to a metal collector (usually a conductive one,

like aluminum), the solvent evaporates and a nonwoven scaffold is formed on the collector surface (7, 8).

Applications of the electrospinning technique

Various drug delivery systems have been, and are currently being investigated, nanoscale formulations like liposomes, polymer micelles, some complexes, and nanofibers have attracted special attention during these last decades, this is because these systems have the potential to improve the therapeutic effects and reduce the toxicity of conventional dosage forms. Some of the attractive features for an ideal drug delivery system would be high loading capacity, high encapsulation efficiency, simultaneous delivery of various therapies, ease of operation and cost-effectiveness, either for immediate or extended release. Some other uses may also be wound dressing and local chemotherapy. In comparison to other formulations, the electrospinning technique is very versatile in the selection of its materials and pharmaceutical drugs for their application of the release of these, so this makes it an attractive technique for the area of drug delivery systems.

In the case of drug delivery systems, drug-loaded nanofibers deliver continuously the drug meanwhile the nanofiber are in degradation (Figure 2).

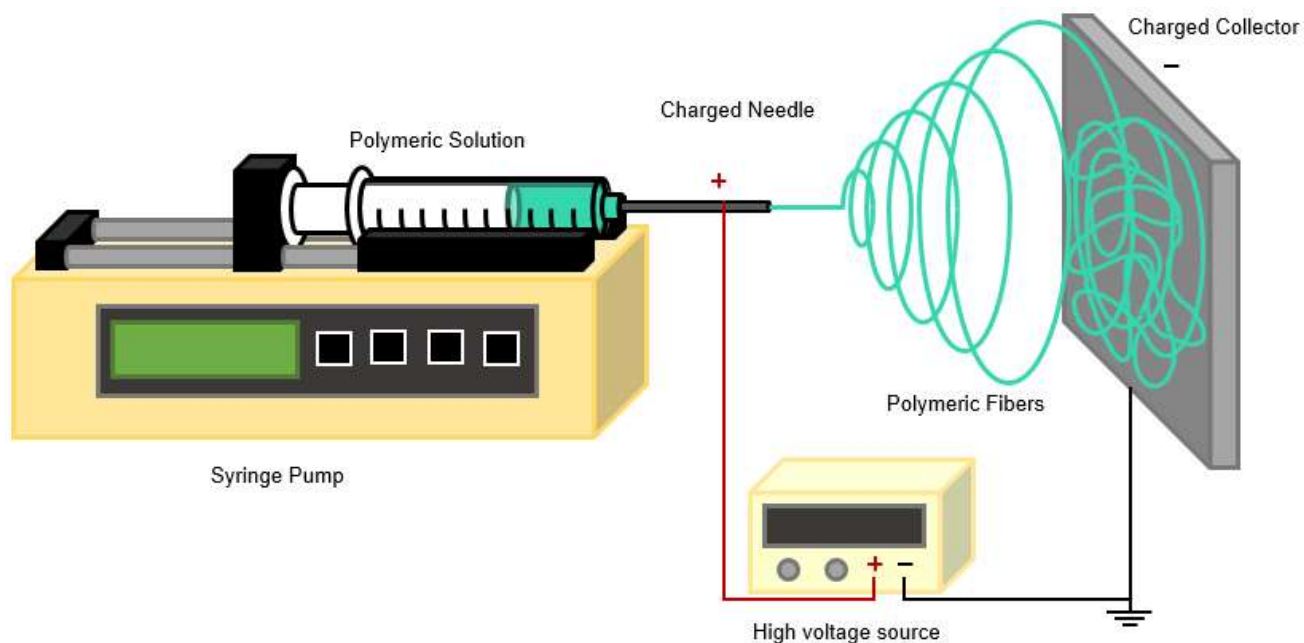


Figure 1. Basic diagram of the electrospinning device.

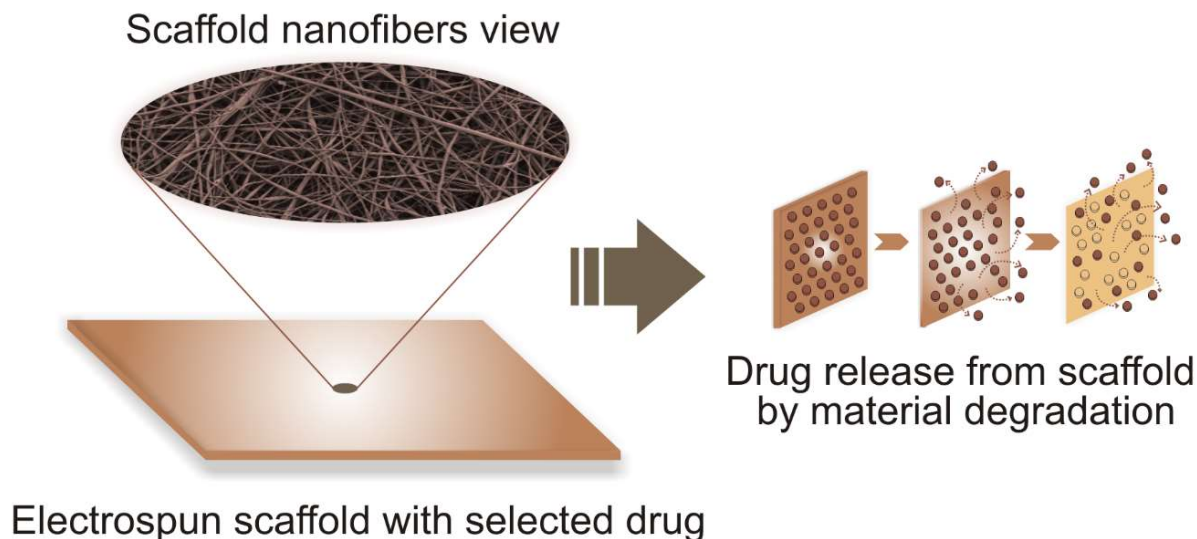


Figure 2. Drug release from electrospun nanofibers.

Polymers

Today, many synthetic and natural polymers have been used as drug carrier materials in a form of micro or nanofibers fabricated by the electrospinning technique. These polymers, must be mainly biodegradable because the releasing of the drug is determined by the diffusion of the bioactive component and degradation of the polymeric fiber. This technique, allows to control the specific distribution of the drug around or inside the fibers leading the improvement of the release kinetics of the pharmaceutical components (9).

Biodegradable polymers, have attracted special attention in the pharmaceuticals industry because avoid the necessity of a second surgery, which its function is to remove an implanted support. Between the polymers that have been extensively investigated as drug delivery systems are poly (ϵ -caprolactone) (PCL), poly (vinyl alcohol) (PVAL), poly (vinyl pyrrolidone) (PVP), and chitosan (CHS), which have been successfully electrospun and its biomedical used have been proved (9).

The mechanism of release of the electrospun fibers is through its degradation; in other words, drug loaded fibers continuously release the biomedical components meanwhile the polymeric fibers go to its complete degradation. It is expected, that the polymer slowly breaks down into smaller, non-toxic fragments, releasing the drug wherever is necessary. This degradation is triggered by metabolic pathways that take effect for the natural elimination of these compounds (into simpler products) (8).

Moreover, the use of certain polymers or the modification of them, can improve the biocompatibility of a drug delivery system reducing body rejection. It has been reported, that using hydrophilic surfaces reduce tissue reaction (3). Between the reported hydrophilic polymers, it can be included alginate (10, 11), chitosan (12), collagen (13, 14), dextran (15, 16) and hyaluronan (17, 18), these polymers resemble natural components of the body improving the disposal of its metabolites (3). Have been established, that several polymeric biomaterials provoke immune evasion through its surface properties, such as hydrophobicity, hydrophilicity, adhesive signal among others, the type of surface will determine the type of cellular response that occurs in the host. Some of the polymers that are able to evade immune system are poly (lactic acid), poly (lactic-co-glycolic acid) (PLGA), poly (ethylene glycol) (PEG) and poly (vinyl alcohol) (PVAL). Another strategy is the active modulation of the immune system through mimicking pathogen-associated molecular patterns (PAMPs), molecules that are detected by pattern recognition receptors (PRRs) located in both the membrane and cytosol of cells. An example, of polymers that do that are poly (ethylene glycol) (PEG) and poly (lactic-co-glycolic acid) (PLGA) (19).

In Table I, is listed natural and synthetic biocompatible polymers used as drug delivery system applications that have been electrospun.

Table 1. Main properties of biocompatible polymers used as drug delivery carriers that have been electrospun (7, 20-60).

Polymer	Properties	Loaded Pharmaceutical component	Ref.
Poly (vinyl pyrrolidone) (PVP)	Biocompatible, biodegradable, increase dissolution of active molecules, good hydrophilization properties	Ibuprofen, naproxen, indomethacin, meloxicam, ketoprofen, acetaminophen, feruloyl glycerol oleyl (FOG), loratadine, spirolactone, griseofulvin, amocycilin, sodium dodecylsulfate	(20-31)
Poly (vinyl alcohol) (PVAL)	Non-toxic, non-carcinogenic, bioadhesive, high degree of swelling in water, rubbery, elastic nature simulates natural tissue	Sumatriptan, aceclofenac, caffeine, riboflavin, docetaxel, ciprofloxacin, donepezil HCl	(7, 31-34)
Poly (ethylene oxide) (PEO)	High binding efficiency, form novel complexes, crosslink ability, emollient, film former excipient, low toxicity, flocculant activity, lubricity, solubility/thickening of many organic solvents, thermoplasticity, wet tack, thickening power (aqueous), viscoelasticity, nontoxic and degradable	Glycerol monolaurate, doxorubicin, paclitaxel	(35-38)
Poly (ϵ -caprolactone) (PCL)	Biocompatibility, higher hydrolyzability, elastomeric properties, high elongation, enhanced solubility in organic solvents, ability to be processed at low temperatures, non-toxic degradation byproducts, slow rate of degradation	Ibuprofen, sumatriptan, naproxen, carvedilol, tetracycline, amphotericin B	(39-43)
Chitosan	Biodegradable, biocompatible, mucoadhesive, oral absorption enhancer	Sumatriptan	(31, 40)
Poly (acrylic acid) (PAA)	Biodegradable, good rheological properties, exists as a liquid at pH 5 and as a gel at pH 7	Sumatriptan	(31, 40)
Ethyl cellulose (EC)	Biocompatible, non-biodegradable, retardant material	Ketoprofen	(26, 27)
Cellulose acetate (CA)	Cellulosic, thermoplastic, soluble in many common solvents, hydrophilic, high surface area	Ketoprofen	(26, 44)
Eudragit S100	Soluble in gastric fluid, low toxicity by the subcutaneous route	Aceclofenac	(45, 46)
Hydroxypropyl methylcellulose	Hydrophilic, biodegradable, biocompatible	Diphenhydramine	(47, 48)
Poly L- (Lactic acid) (PLLA)	Biodegradable, biocompatible, biologically inert	Tetracycline hydrochloride, doxorubicin	(37, 49, 50)

Poly (lactic-co-glycolic acid) (PLGA)	Biodegradable, biocompatible, FDA approved, modified surfaces provide better interaction with biological materials, suitability for export to countries	Metoclopramide hydrochloride paclitaxel	(41, 49, 51)
Poly (acrylonitrile) (PAN)	Low density, thermal stability, high strength and modulus of elasticity, stability to UV degradation, nonfusible, chemical resistance	Acyclovir	(52, 53)
Poly (urethane) (PU)	Good biocompatibility, flexural endurance, high strength, high abrasion resistance, processing versatility	Itraconazole	(54-56)
Cellulose acetate phthalate	Enteric coating, hygroscopic, biocompatible, anti-microbicidal	Tenofovir, disoproxil fumarate	(57, 58)

Electrospun nanofibers as drug delivery systems

Electrospun fibers, possess several characteristics that are useful in pharmaceuticals, such as a large surface area, a possibility of loading large amounts of drug, simultaneous administration in various therapies, ease of operation, and cost-effectiveness have led to its use being expanded in the area of drug administration. These properties make them good candidates for the administration of poorly water-soluble or low-bioavailability drugs. Among the most investigated areas, drug delivery (either rapid dissolution or controlled release), tissue regeneration and local cancer treatments are of the most interest (59, 60). The following are some of the drugs used in the electrospinning area.

Anti-inflammatory

The anti-inflammatory drugs are substances that its main function is to reduce inflammation and swelling, they possess an analgesic and antipyretic activities (61). These kinds of drugs have been extensively loaded into nanofibers using the electrospinning method, because many of them are poorly water soluble, which become an issue for the patient that desired an immediate effect using the conventional pharmaceutical formulations. As shown below, with the electrospinning technique, the electrospun nanofibers are usually developed with an anti-inflammatory and with another pharmaceutical component to have an improved treatment.

One of the most studied drug is ibuprofen, which is a therapeutic agent in the class of nonsteroidal used to treat pain, fever and inflammation. This includes

painful menstrual periods, migraines and rheumatoid arthritis (62). Ibuprofen has been loaded into polymeric nanofibers such as PVP K30 (20, 45) and PCL (40), using the electrospinning technique because of its properties, such as poorly water soluble and high bioavailability (20).

Another drug that has been incorporated in the fibers is naproxen, which is a non-steroidal anti-inflammatory drug that relieves pain, fever, swelling and stiffness (62). Naproxen was incorporated into electrospun sheets through the electrospinning process. Electrophilic anti-inflammatory drugs have been studied in combination with other drugs for a more effective treatment. In this case naproxen was combined with sumatriptan succinate. They were studied alone and in combination. The release of naproxen and sumatriptan with three hydrophilic polymers was tested: CHS, PVAL and poly (acrylic acid) (PAA); and one hydrophobic: PCL. All polymers provided a release of more than 90 % of the releasable drug and it was dissolved in the acceptor phase within 10 min. Interestingly, the membranes that showed fast release of the two drugs was made of hydrophobic PCL. SEM micrographs showed that the nanofibers had the desired homogeneity. Moreover, the resulted membranes turned out to be very flexible and mechanically resistant. With their drug loading capacity of up to 40% membrane mass, which could be very advantageous for the formulation of sublingual drug delivery systems (41).

In another research, coaxial electrospinning was successfully performed to make naproxen-loaded PVP nanofibers. Field emission scanning electron

microscopy (FESEM) showed that higher quality nanofibers could be produced, with a diameter of 270 ± 60 nm, also with linear morphologies, with no beads or spindles and a smooth surface. The XRD patterns verified that the nanofibers were amorphous nanocomposites with the drug distributed homogeneously in the polymer. *In vitro* dissolution tests showed that the medicated nanofibers could release the contained drug all at once while in contact with the dissolution medium, which is considerable faster than the commercially dispersible tablets (42).

PCL was selected as the polymer matrix to create a drug delivery system for naproxen. This drug was complexed with beta-cyclodextrin (BCD) to form an inclusion complex and then electrospun. SEM images showed that the fiber diameter was around 300 nm. The complex drug in the fibers showed a better release than the fibers with uncomplexed drug, this was possible because the complex improved the solubility of the drug (42).

Also, indomethacin, which is a non-steroidal anti-inflammatory drug is estimated to be 20 times more potent than acetyl salicylic acid (62). Several experiments were realized for the optimization of a release system, involving two sets of electrospun PVP fibers loaded with indomethacin, using an acetone/dimethylacetamide solvent system. It was possible to obtain loadings up to 33% w/w. SEM images showed that the fibers were smooth and uniform. It was also found by XRD and DSC that the drug exists in amorphous physical state in the fibers.

The amorphous form of the drug was found to be stable after storage of the fibers for 8 months in a desiccator (relative humidity <25%). Finally, the functional performance of the fibers was studied. In all cases, drug-loaded fibers released their components quickly, offering accelerated dissolution over the pure drug (22).

Meloxicam has also been electrospun into nanofibers for immediate release. This formulation is from oxycodone derivatives, which are enolic acids that inhibit COX-1 and COX-2 with anti-inflammatory, analgesic, and antipyretic activities. Meloxicam has a similar efficacy to aspirin, indomethacin and naproxen, for the long-term treatment of rheumatoid arthritis or osteoarthritis (60). Despite this, poor absorption of the drug occurs after oral administration because of its low solubility. Samprasit, W, et al. (2015), PVP fibers were loaded with meloxicam. The creation of PVP fibers and the incorporation of BCD and sweeteners were carried

out to improve the solubility, disintegration time and release, as well as the taste of the dosage forms. The created drug delivery system of meloxicam shown to be viable for drug release (23).

Ketoprofen is another non-steroidal anti-inflammatory drug that it is derived from propionic acid and has analgesic and antipyretic effects. In addition to the inhibition of the COX, it can stabilize the lysosomal membranes and antagonize the actions of bradykinin. PVAL nanofibers containing ketoprofen have been developed as a drug delivery system. Researchers were successfully to prepare PVAL fibers stabilized against the disintegration in water by treatment with methanol. Fibers were analyzed by UV spectrophotometer at body temperature (37 °C), and at room temperature (20 °C). The results showed that fibers treated with methanol do not present accelerated release, but a controlled release fashion. This may be beneficial for certain treatments that need more controlled release (33).

In another research, the production of electrospun ethyl cellulose (EC), cellulose acetate (CA) and PVP nanofibers loaded with ketoprofen were presented, in conjunction with their *in vitro* drug release profiles. SEM images showed clear formation of duplicate nanofibers that appear to be affected by the solvent and amount of drug used. The *in vitro* drug release studies showed that nanofibers having hydrophilic polymer had a high drug loading percentages but shows faster drug release compared to those hydrophobic polymeric nanofibers, which presented lower drug loading percentages (24).

On the other hand, acetaminophen is used for the relief of a mild to moderate pain because acetaminophen increases the threshold to painful stimuli and therefore exerts an analgesic effect against pain due to various causes (62). Acetaminophen it's another low water-soluble drug that has also been electrospun. Yu, D.-G. et al. (2010), prepared solid dispersions of acetaminophen to produce PVP loaded nanofibers. Solid dispersions of electrospun fibers were compared to those prepared from three traditional dispersion system processes: By freeze drying, vacuum drying and heating drying. Using SEM, DSC, XRD, and FTIR techniques, the surface morphologies, drug physical status, and drug-polymer interactions were investigated, as well as an *in vitro* dissolution. The tests demonstrated that electrospun nanofibers released 93.8% of the acetaminophen content within

the first 2 min and that the acetaminophen dissolution rates of the different solid dispersions and solid dispersions that were electrospun into nanofibers showed better dissolution effects in comparison to the other solid dispersions due to their large surface area, high porosity and homogeneous distribution of acetaminophen in the fibers (25).

Feruloyl glycerol oleyl (FOG) is poorly soluble in water due to the long chain of the acyl group, which may limit its use, even with its excellent properties. FOG has also been successfully eluted for the creation of fast dissolving drug release membranes PVP, as base polymer matrix, these being dissolved in chloroform/ethanol. The FTIR spectra revealed a good compatibility between FOG and PVP, as well as a good FOG distribution within the fibers. It was observed that the diameter of the fibers was influenced by the concentration of PVP and voltage. In this case, fibers with a diameter of 700-800 nm were obtained. The release assays confirmed that the fibers were indeed of rapid dissolution with mean dissolution time of 2.0 ± 1.5 s. These results demonstrated the potential of solid dispersion electroplating to improve the dissolution profile of hydrophobic drugs (64).

In a study, diclofenac sodium (sparingly soluble in water), naproxen and indomethacin (both water insoluble) were electrospun with PVA as the drug carrier. These drugs were non-steroidal anti-inflammatories with different water solubility's. The morphological appearance of the drug-loaded fibers depended on the compositions of the drugs. The study proposed that the chemical composition of the drugs was not affected by the electrospinning process, these conclusions were supported with a ^1H NMR spectra analysis. DSC and TGA analyzed the thermal properties of the fibers mats. Also, the molecular weight of the drugs used in their research played an important role on the rate and the total amount of the drugs release, both decreasing when the increase of the molecular weight of the drugs. They also compared the release characteristics of drug loaded fibers and films, and conclude that the fibers exhibited much better release characteristics of the model drugs than the drug-loaded film (65).

Finally, aceclofenac was electrospun with pantoprazole. This combination has the purpose of restricting and compensating adverse effects of non-steroidal anti-inflammatory drugs, so the co-administration of proton pump inhibitors may be beneficial to arthritis patients. These drugs were

simultaneously electrospun by using a composite solution of zein/Eudragit S100. The physical-thermal characterization of the nanofibers showed the drugs with the polymers had a molecular integration, and so the drugs were evenly distributed in the nanofibers in the amorphous state. *In vitro* release studies maintained the release of both drugs until 8 h, making it a good candidate for a controlled release treatment. Co-administration of pantoprazole together with aceclofenac reduced gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs; this was confirmed by animal experiments *in vivo*. The researchers successfully developed a dual drug delivery system comprising polymers with different release characteristics and achieved oral administration of aceclofenac with reduced side effects (45).

Antihistamine drugs

An antihistamine is a type of pharmaceutical drug that opposes the activity of histamine receptors in the body. These are subclassified according to the histamine receptor. The two largest classes of antihistamines are H1 antihistamines and H2 antihistamines. This study focused on H1s, which target the histamine H1 receptor and are used to treat allergic reactions in the nose (e.g., itching, runny nose and sneezing), as well as for insomnia. They are also sometimes used to treat dizziness or vertigo caused by problems with the inner ear.

Loratadine is useful to relief symptoms of allergies, such as fever, urticaria, chronic idiopathic, urticaria, and other skin allergies. For allergic rhinitis, loratadine is effective for both nasal and ocular symptoms: sneezing, runny nose, itching or burning eyes (42). This drug has also been successfully electrospun in PVP nanofibers. A study observed that using a low polymer concentration, low feed rate in the injection pump, and high applied voltage nanofibers with a smaller diameter and greater uniformity were created. The study concluded that the smaller the diameter of the fiber and the amount of drug, the faster its dissolution, and the time of release of this pharmaceutical component (26).

Another antihistamine is diphenhydramine, which decreases or prevents the histamine effects on smooth muscle and immune cells, as well as antagonizes muscarinic receptors and α -adrenergic receptors. This drug is normally used for insomnia, common cold symptoms and nausea (66, 67). Diphenhydramine has been electrospun directly onto

a polymeric film of hydroxy propyl methyl cellulose (HPMC), and glycerol to improve the mucoadhesive system. Their effects on the measured responses: disintegration time, adhesion work, adhesion strength, the area under the curve (at 1 min), and the area under the curve of the permeation (at 3 min) were used to calculate the dependent variables of the process: the filling volume, HPMC and the glycerol concentration. The physicochemical and physicomachanical properties of the developed system were studied with the following methods: rheology, FTIR, determination of tenacity, mucoadhesion and nanotensile tests. The data obtained from the physical-mechanical characterization confirmed the suitability of the systems for the application in the delivery of drugs. The optimized system showed drug entrapment of 2.3 mg/1.5 cm² with disintegration time of 12.8 s (47).

Drugs for the treatment of gastrointestinal diseases

Not many studies have been done, using the electrospun scaffolds as drug delivery system of gastrointestinal drugs. Metoclopramide is one of the oldest real prokinetic drugs. Its administration results in coordinated contractions that intensify the intentional transit. Its effects are largely confined to the upper portion of the digestive tract, where it increases the tone of the lower esophageal sphincter and stimulates antral and small intestinal contractions. Although it has *in vitro* effects on contractility of smooth muscle colonic, metoclopramide has no clinically important effects on the motility of the large intestine (68).

Liu, H., et al. (2007), suggest a possible approach to the controlled release of metoclopramide hydrochloride using core-shell electrospinning. Using various polymers (PCL, PLLA and PLGA 80/20). The strategies were proposed for the control of the distribution of the release. The fibers consisted of two layers, the polymer on the outside and the drug inside. By varying the physical and chemical properties of the core and shell solutions, it was shown that the rate of release of this hydrophilic drug was controllable. The study discusses the importance of controlled release of hydrophilic molecules, such as peptides, proteins and even pDNAs (plasmid DNA), and their difficulty in being administered. The results showed a clear difference in the release pattern between monolithic fibers made from

hydrophilic and hydrophobic polymers and various core-shell fibers with PCL, PLLA and PLGA 80/20 as shell polymers (44).

Drugs for the treatment of cardiovascular diseases (CVD)

Nicorandil is a vasodilator therapeutic agent that can hyperpolarize muscle tissues, and is an effective coronary vasodilator. It seems to be active in all types of angina pectoris, including advanced coronary artery lesion (70). Polymeric fibers were electrospun for the sublingual administration of nicorandil in an attempt to reduce mucosal ulceration and improve bioavailability of the drug. Polymeric nanofibers were obtained using vitamin B12, and a mixture of hyaluronic acid and PVAL. The morphology, drug loading, XRD, DSC, *in vitro* drug release, degree of swelling and their pharmacokinetic behavior of the resulting fibers were characterized. Nanofibers were found to be homogeneous with a diameter of 200-450 nm. Histopathological studies showed no evidence of mucosal ulceration at the site of application. Preclinical safety was checked and maintenance of an effective therapeutic level over an extended period was demonstrated. The study showed that the biocompatible nanofiber become a perfect carrier system for the sublingual administration of antianginal drugs (71).

Moreover, PVP K90 nanofibers loaded with a lipophilic spironolactone were prepared, which is a drug that is mainly used to treat fluid accumulation due to heart failure, liver scarring, or kidney disease, and for the treatment of high blood pressure. However, temporary precipitation was observed. Vigh, T. et al. (2013), used beta-cyclodextrin to improve the immediate release of the drug. A small addition of beta-cyclodextrin provided sufficient for a dramatic increase in the rate of release, even at high concentrations of drug. This approach ensured the near-total release of the drug in one minute, making the system a suitable formulation for rapid release (28).

Potrč, T. et al. (2015), studied the cardiovascular drug carvedilol, which is a drug that is indicated in the treatment of congestive heart failure. It is indicated in the treatment of hypertension and to reduce the risk of mortality and hospitalizations in a subset of people after a heart attack. It may be used alone or with other antihypertensive agents. It was observed that the incorporation of this drug into PCL

electrolyzed fibers reduced its crystallinity. By DSC studies, the study demonstrated that the incorporated drug in the nanofibers were partially molecularly dispersed in the polymer matrix, and partly in the form of dispersed nanocrystals. The incorporation of the drug into PCL nanofibers significantly improved their dissolution rate. PCL nanofibers released nearly 77% of the incorporated carvedilol in 4 h, indicating the influence of drug properties, such as molecular weight and solubility, on their release from the polymer matrix (40).

Contraceptives

In the case of contraceptive drug, not many studies have been done, due of the difficulty of the *in vivo* or application studies. Contraceptives drugs are applied to prevent pregnancy. Estrogen and progestin are two female sex hormones that in combinations avoid ovulation. These hormones also modify the lining of the uterus (womb) to prevent the development of pregnancy, and modify the mucosa of the cervix to prevent sperm from entering (62).

In a study, electrospun PVAL nanofibers were loaded with progestin levonorgestrel, the system was stacked on tissue paper and studied the release kinetics of the drug and measured its cytotoxicity. It was observed that the *in vitro* release of levonorgestrel was affected by the composite microarchitecture, thickness and drug content, whereby the electrospinning process was optimized (73).

Anticancer

Docetaxel is a well-known mitotic inhibitor for oral cancer. It faces problems of extravasation, inflammation of the veins, and other side effects of chemotherapy (7). Singh, H. et al. (2015), design a mucoadhesive nano-carrier system that is maintained at the site of application and maximizes the therapeutic potential of the anticancer drug, as well as attenuate its systemic side effects. In the study, PVAL/docetaxel fibers were prepared using the electrospinning method. The resulting fibers were characterized by surface morphology, drug loading, *in vitro* drug release, tensile strength, mucoadhesivity, drug permeability, degree of swelling, and anticancer activities against selective cell lines, to establish their therapeutic potential, demonstrating polymeric nanofibers can be successfully used for local administration of anticancer drugs (7, 70).

An electrospun system of five layers was developed, using cisplatin and PLA nanofibers. The first, third and fifth layer are made from polymer and the second and fourth layer, drug was incorporated. This for a prolonged release of cisplatin to prevent local cancer recurrence after a surgery. Cisplatin is used in the treatment of cancer, mostly liver cancer, but one of the main issues of this drug is that tends to accumulate on the liver and has a poor intake after intravenous administration. The *in vivo* studies of 24 h showed that the multilayer fiber mat had a prolonged release and the retention in the tissue was more stable. The authors observed, in the studies with mice, that liver cancer had been retarded; mice had a prolonged survival time, and there was a reduced toxicity, compared with other groups with different treatments (73).

Also, doxorubicin is a chemotherapy medication used in some numerous types of cancer. This includes leukemia, lymphoma and many types of carcinoma (solid tumors), and soft tissue sarcomas. It is usually given by injection into a vein. The electrospinning of fibers loaded with doxorubicin has been extensively studied. In one report, the authors developed fibers using a water-in-oil emulsion. The polymers used were poly (ethylene glycol) and poly (L-lactic acid) (PEG-PLLA), these were dissolved in chloroform which constitute de oily phase. Doxorubicin was contained in the aqueous phase, with the purpose of encapsulate the drug in the fibers. The diameter of the electrospun fibers was in the range of 300 nm -1 μ m. The content of doxorubicin in the fibers was 1-5% by weight, and it was fully encapsulated within the fibers. Release was controlled by the combined diffusion and enzymatic degradation mechanism. In the initial stage, the diffusion mechanism was predominant and sometime later, the mechanism of enzymatic degradation became predominant. The antitumor activity of doxorubicin incorporated into PEG-PLLA fibers versus mouse glioma cells (C6 cell lines) was assessed by the MTT method. The results showed that doxorubicin could be released from the fibers without losing cytotoxicity (37).

Xu, X. et al. (2009), studied the drug release behavior of drug-loaded nanofibers prepared by an emulsion method. Confocal microscopy images indicated that the drug was incorporated in the PEG-PLLA copolymer nanofibers, forming drug-loaded structural fibers. Drug release behavior of this system showed a three-stage diffusion controlled

mechanism, in which the rate of release of the first stage was slower than the second stage, but both followed the second law of Fick. Hence, it was concluded that the rate of doxorubicin release decreases when is present a higher concentration of fibers (38).

Salehi, R. et al. (2013), fabricated stimuli sensitive poly (N-isopropylacrylamide-co-acrylamide-co-vinyl pyrrolidone) (P(NIPAAM-AAm-VP)) nanofibers loaded with doxorubicin. The prepared systems were characterized by XRD, SEM and FTIR. The cytotoxicity of the samples was evaluated by MTT test using a A549 lung cancer cell line. The *in vitro* cytotoxicity assay showed that P(NIPAAM-AAm-VP) fibers did not affect the growth of A549 cells. The antitumor activity of DOX-loaded fibers against cells was maintained, whereas DOX disappeared within 48 h (74).

In the case of paclitaxel, which is a drug that acts as a toxic substance for the mitotic spindle through its binding of high affinity to the microtubules with the intensification of tubulin polymerization (75). A study was performed incorporating a system of two drug: doxorubicin and paclitaxel. These drugs were successfully loaded onto the PEG-PLLA fibers. The release behaviors of both drugs from the same fiber mats were attributed to their solubility and distribution status in the fibers. Due to its high hydrophilicity, doxorubicin was easy to diffuse from the fibers, and its release rate was always faster than that of the hydrophobic paclitaxel. In addition, the rate of release of paclitaxel was accelerated by the release of doxorubicin. *In vitro* cytotoxicity against rat C6 glioma cells indicated that the dual drug combination showed greater inhibition and apoptosis compared to single-drug system, suggesting the promise of multiple drug delivery in therapy that combines pharmaceutical components (38, 76).

Antimicrobials

Lopez, F. L. et al. (2014), prepared PVP/griseofulvin electrospun fibers, with the purpose of treat mycotic diseases of the skin, hair and nails due to *Microsporum*, *Trichophyton* or *Epidermophyton* infections. SEM images showed that the fibers comprised to a large extent in being smooth and uniform. It was also found that the drug existed in amorphous physical state in the fibers with the XRD technique and DSC. The amorphous form of the drug was found to be stable after storage of the fibers for 8 months in a desiccator (relative humidity <25%).

Finally, the functional performance of the fibers was studied. In all cases, drug-loaded fibers released their components fast, offering accelerated dissolution over the pristine drug (22).

The permeability of the electrospun PVAL fibers with ciprofloxacin has been studied, this drug inhibits DNA replication by binding to DNA gyrase and topoisomerase IV. The research focused on examining the permeability of ciprofloxacin from PVAL nanofibers through different biological membranes. The researchers indicated that the fibers had greater drug permeability than the drug alone. These studies also reported that there was a steady-state release of the drug, which has not been seen with the current presentations of the drug (which has a high degree of fluctuations). As a conclusion, fibers provide numerous advantages for its use as a support system for encapsulating drugs and thus enhancing current therapies (75, 77).

Ball, C. et al. (2012), evaluated the viability to release the glycerol monolaurate (GML) drug, which has been proposed as a microbicide component by blocking transmission-facilitating innate immune response to vaginal exposure. The purpose of the study was to create a multipurpose prevention technologies that simultaneously prevent sexually transmitted infections (STIs), and prevents unwanted pregnancy. It was demonstrated that GML scaffolds designed for topical administration can function as a combination of chemical and physical barrier for a prevention technology. The authors used FDA-approved polymers (PLLA-PEO) to prepared controlled-release fibers that facilitate the simultaneous release of multiple agents against HIV-1, HSV-2 and sperm. In this work, it was observed that drug-loaded fibers inhibited HIV-1 infection *in vitro* and physically obstructed the penetration of spermatozoa. In addition, previously unknown activity of GML is reported to potently inhibit the motility and viability of spermatozoa. Application of nanofibers eluting drugs for HIV-1 prevention and sperm inhibition can serve as an innovative platform for drug delivery in the lower female reproductive tract (36).

Also, tetracycline, chlorotetracycline hydrochloride and amphotericin B were loaded into PCL-PLA nanofibers. Their release properties and antimicrobial efficacies were studied. By forming PCL-PLA fibers, the surface and release characteristics could be modified to conform to a sensitive drug delivery. With the obtained results of

this work, electrospun system can be adapted to the physiological conditions of the human body, and how they have become increasingly important for clinical applications in recent years. Electrospun fibers offer special advantages because of their large surface area and their sorption/release properties. If loaded with drugs, the administration properties can be adapted to a specific release rate (50).

He, C. et al. (2006), fabricate core-shell PLLA/tetracycline hydrochloride (TCH) fibers for drug delivery application, using a coaxial electrospinning method. The results indicated that a reservoir-type drug delivery device can be conveniently obtained by the encapsulation of tetracycline hydrochloride in the PLLA fiber. A sustained release of TCH from these nanofibers was observed in the research, so drug-containing hydrophilic fibers can be used as drug delivery vehicles or transformed into biomedical devices such as sutures and wound dressings (78).

Other fibers, that have been investigated are the cellulose acetate/PVP-amoxicillin/cellulose acetate fibers. In these fibrous complexes, mechanical characterization of the fibers showed that the tensile strength of the membrane is not affected by the presence of amoxicillin inside the fiber. The amount of amoxicillin release increased with increasing pH, from 61% for a pH 3 to 79% at pH 7.2. It was proposed that amoxicillin release is due to a diffusion mechanism. These composites are recommended to resolve the problem of possible drug loss during the matrix entrapment process with potential local application in biological media to treat dental or cutaneous infections (29).

On the other hand, HIV still affects the health of millions of people around the world and a lot of effort is being put into developing methods to prevent infection or eradicate the virus after infection. The use of cellulose acetate phthalate (CAP) electrospun fibers with tenofovir disoproxil fumarate as a tool to prevent transmission of HIV have been proposed. Interestingly, because of the pH-dependent solubility of the CAP, the fibers are stable in the vaginal fluid (healthy vaginal flora has a pH below 4.5), while the addition of small amounts of human semen (pH between 7.4 and 8.4) immediately dissolves the fibers that give rise to the release of the encapsulated drugs. The pH-dependent release properties have been carefully studied and it is shown that the antiviral drugs released along with CAP, which have been reported to have intrinsic

antimicrobial activity, efficiently neutralize HIV *in vitro* (55).

In another study, acyclovir was selected as a model drug, PVP as a hydrophilic filament-forming polymeric matrix, sodium dodecyl sulfate as a transmembrane enhancer and sucralose as a sweetener. The study, successfully prepared the core-shell nanofibers, with the shell part consisting of PVP, sodium dodecyl sulfate and sucralose, and the core part composed of PVP and acyclovir. In the results, the authors reported that the core-shell nanofibers had an average diameter of 410 ± 94 nm with a uniform structure and a smooth surface. Through DSC and XRD was determined that acyclovir, sodium dodecylsulfate and sucralose was well distributed in the amorphous matrix of the PVP. *In vitro* dissolution and permeation studies demonstrated that solid dispersions of core-shell nanofibers could rapidly release acyclovir in one minute, with an increased permeation rate six-fold across the sublingual mucosa compared to that of the crude acyclovir (30).

In a comparative research, three methods were tested to produce a copovidone/itraconazole drug delivery system, using casting films, spray-drying, electrospinning, and high-speed electrospinning. The formulations were evaluated in terms of improvement in the dissolution rate of itraconazole and were analyzed by SEM, DSC and XRPD. Despite the significant increase in productivity of high speed electrospinning, the morphology obtained was very similar to the fibrous material of simple electrospinning. The results of the DSC and XRPD showed that the drug was transformed into an amorphous form in most cases, except for the film casting samples. The limited solution of crystalline itraconazole could be highly improved: rapid dissolution (> 90% in 10 min) occurred in the case of both high-speed and single-needle electrospun fiber types. This work proved, that using the high-speed electrospinning system to produce fibers with the amorphous solid dispersions it's a good alternative for the single-needle electrospinning, this because the fibers were flexible, the process was scalable, and easy to be set in a continuous manufacturing line (54).

Finally, itraconazole and ketanserin were loaded into poly (urethane) (PU) fibers. It was obtained an amorphous nanodispersion for ketanserin with dimethylformamide (DMF), and ketanserin with dimethylacetamide (DMAc). It was demonstrated that the collected fibers release the drugs at various

speeds and profiles based on the morphology of the nanofibers, and the content of the drugs. The data were generated using a specially designed release apparatus around a rotating cylinder. The authors found that loading a small amount of itraconazole, the fibers released as a linear function of the square root of time, Fick kinetics, and that the drug did not have an initial burst release (57).

Drugs used in palliative medicine

In this area, not many studies have been done, despite this, a nanofibers loaded with donepezil-HCl were prepared as a dosage form so that it was dissolved orally. This research aimed to create a removable scaffold using an ultrafast release electrospinning device, using PVAL as the matrix polymer, and donepezil-HCl as the drug to be loaded. Kadajji, V.G. et al. (2011), found diameters between 100 nm and 300 nm in their resulting nanofibers. The *in vitro* tests showed that it had an immediate release, less than 30 s, regardless of the drug content in the fibers, this is because of the large surface area the nanofibers. The study, compared the scaffolds and the commercial tablets and conclude that the electrospinning technology was a promising method to produce alternative effective dosage forms, especially with patients, children, and elderly people with dysphagia (32).

Miscellaneous

Caffeine temporarily prevents or alleviates drowsiness, and therefore maintains or restores alertness. Between the uses of caffeine as a pharmaceutical drug it can be include in bronchopulmonary dysplasia in preterm infants, for both prevention and treatment, apnea of prematurity as primary treatment, treatment of orthostatic hypotension and general vasodilation. Usually used for vasodilation to relieve headaches, or even migraine. In contrast, riboflavin (vitamin B2) is used in individuals with protein depletion and infections that complicate it.

Li, X. et al. (2013), prepared PVAL electrospun nanofibers loaded with caffeine and riboflavin. SEM images showed that nanofibers had an ultrafine morphology with an average diameter in the range of 260-370 nm. Also, PVAL/caffeine and PVAL/riboflavin nanofibers had almost the same dissolution time (approximately 1.5 s), and wetting time (approximately 4.5 s). Both drugs can be released in an accelerated manner (caffeine in an

extent of 100%, and riboflavin up to 40% in 60 s) (34).

In the case of preclinical studies, have mainly focused on formulation methods to enhance the dissolution of active compounds, in many cases without considering that the formulation matrix affects not only dissolution but also influences the transport of the molecules of the drug through membranes. It has been reported a study that test an electrophilic formulation based on cyclodextrin of aripiprazole, with an apparatus (μ Flux) which monitors the permeation along with the dissolution, and by this means a better *in vitro-in vivo* correlation. It has been demonstrated that an electrospinning formulation based on cyclodextrin-aripiprazole has the potential to ensure rapid delivery of drug through the oral mucosa due to the rapid dissolution of the drug in the formulation and the improved flow through the membranes, as shows by the result of the new *in vitro* dissolution and permeation test (79).

In vivo studies in animal models

In the case of *in vivo* application of drug loaded electrospun nanofibers, the literature has reported only animal models, most frequently rodents. Depending on the drug, the animal model is prepared for the experiments, but just after the samples showed good results in *in vitro* test, and a bioethical committee have approved the assays. Because of the nature and morphology of the fibers, *in vivo* tests are usually implanted subcutaneously and intramuscularly at the back of the rodent, depending of the study fibers are left hours or days respectively (Figure 3).

Until now, not many literature can be found about the *in vivo* application of drug loaded electrospun nanofibers, but between the most studied pharmaceutical applications it can be found anti-inflammatory, gastrointestinal, anti-cancer and anti-microbial activities (91-84) (Table 2), and no *in vivo* studies have been performed on anti-histamine, contraceptive, palliative and miscellaneous drugs, these can be due to the difficulty of the study.

In vivo studies in human volunteers

Electrospun nanofibers meant to be used as drug delivery systems have been documented extensively with clear advantages over bulk materials thanks to their large specific surface and short diffusion path length. However, in order to take these scaffolds to the market, they have to pass through *in vivo* studies

before clinical applications. Most of the reported systems requires further investigation, and extensive experimental campaigns are needed before making products fully ready for commercialization (85). Some examples electrospun systems that have gone through studies using human volunteers are listed in Table 3.

CONCLUSION

The electrospinning method have gaining importance in the pharmaceutical industry, as an

alternative strategy to developed a new form to administrate and transport pharmaceutical drugs. Nano or microfibers produced by this technique possess such some interesting advantages over the other methods of administration. Its intrinsic high surface-volume ratio, its versatility of fibers composition, its surface bioactivity, the manipulation of the drug release rate, its easy fabrication and cost-effectiveness operation are all attractive features for its drug delivery application.

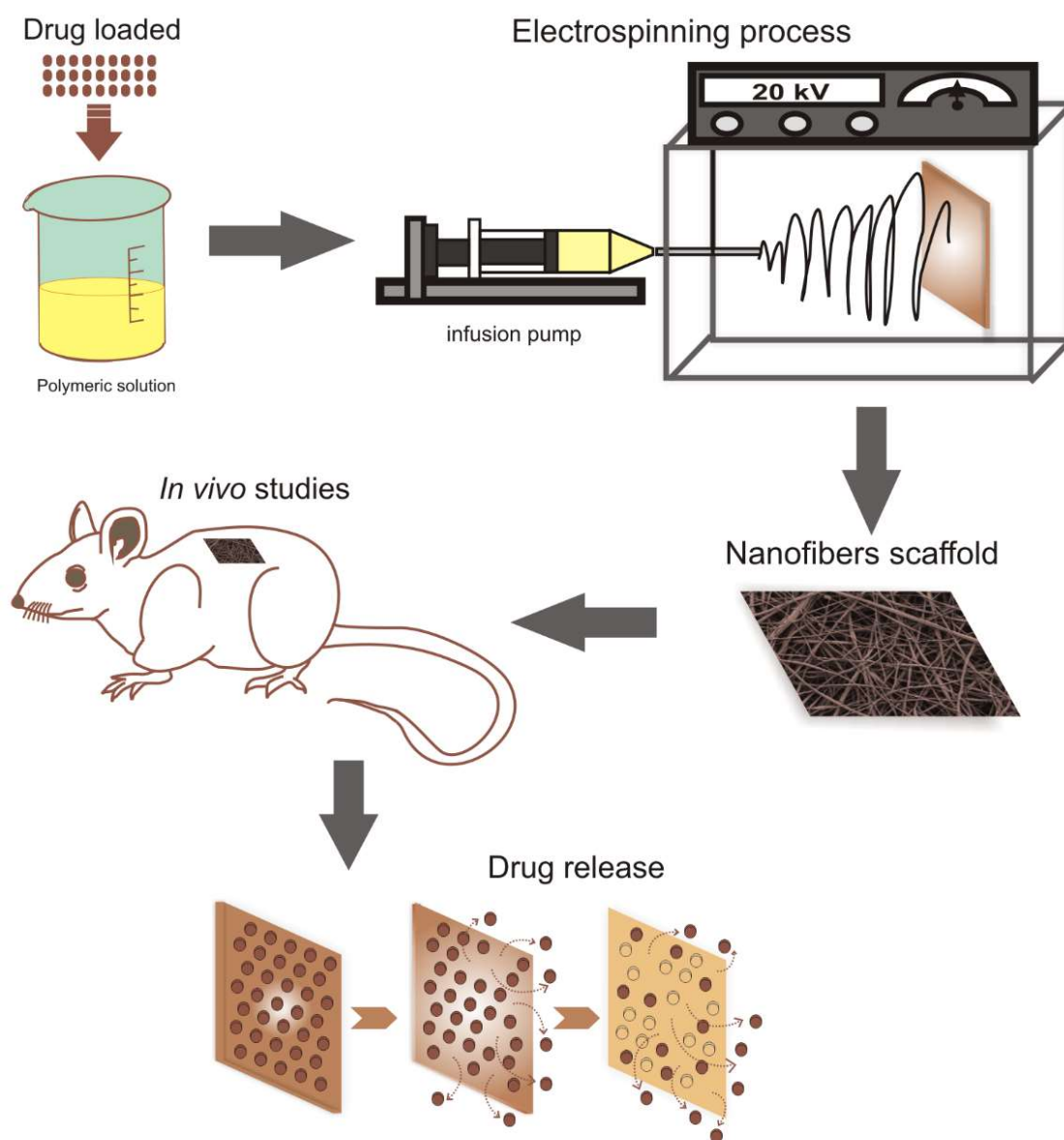


Figure 3. *In vivo* analysis of drug loaded electrospun nanofibers

Table 2. Examples of drug loaded electrospun nanofibers studied with animal models.

Polymeric fiber	Drug	Application	Animal model	Ref.
Methacrylic acid copolymer (EUDRAGIT® S100, MAC)	Uranine (UN), nifedipine (NP)	Anti-inflammatory	Pharmacokinetic study in rats after intraduodenal administration	(81)
Ethylcellulose (EC)-core/Eudragit S100-shell nanofibers	Budesonide (BUD)	Gastrointestinal	Gastrointestinal (GI) tract in rats	(82)
Poly (lactide) (PLA)	Dichloroacetate (DCA)	Anticancer	Cervical carcinoma tumor-bearing mice	(83)
Poly (vinyl alcohol) (PVAL) and sodium alginate (NaAlg)	Ciprofloxacin (CIP)	Antimicrobial	Transdermal tissue of male rabbits	(84)

Table 3. Examples of drug loaded electrospun nanofibers studied with human volunteers.

Polymeric fiber	Drug	Application	No. of volunteers	Characteristics tested	Ref.
Thiolated chitosan (CS-SH) blended with poly (vinyl alcohol) (PVAL)	α -Mangostin	Oral care and prevention of dental caries	6	Antibacterial activity, mucoadhesive property, and taste and mouth feel of the nanofiber mats.	(86)
Poly (vinyl pyrrolidone) (PVP), Poly (ethylene oxide) (PEO), poly (caprolactone) (PCL)	Clobetasol-17-propionate	Treatment of oral lichen planus (OLP) and recurrent aphthous stomatitis (RAS)	26	Patch adhesion	(87)
Poly (methyl vinyl ether-alt-maleic ethyl monoester) (PMVEMA-ES)	Salicylic acid, methyl salicylate, and capsaicin	Psoriasis treatment	3	Functionality of the encapsulated TRPV1 agonists by analyzing its responsiveness	(88)
Poly (vinyl-alcohol) (PVAL)	Donepezil HCl	Dysphagia	1	Time of disappearance of the web	(89)
Poly (ethylene oxide) (PEO)	Chitosan	Treatment of II, IIIa, and IIIb degree burns	19 (II), 10 (IIIa), 10 (IIIb)	Wound-healing behavior	(90)

The electrospinning technique has gained importance in the pharmaceutical industry as an alternative strategy to develop a new form to administrate and transport pharmaceutical drugs. Nano- or microfibers produced by this technique possess some interesting advantages over the other methods of administration. Their intrinsic high surface area-to-volume ratio, the versatility of fiber composition, their surface bioactivity, the manipulation of the drug release rate, their easy fabrication and cost-effectiveness operation are all attractive features for their drug delivery application.

This review presented many examples of poorly water soluble drugs being loaded into hydrophilic

polymeric fibers, which were successfully incorporated and released at desired times. Some of the presented works reported time stable drug loaded fibers, focusing on the importance of drug administration system storage and transport.

It has been demonstrated that hydrophilic fibers increase drug dissolution, and for instance bioavailability. In the case of electrospun scaffolds, fast release formulations for oral absorption are specially of interest to avoid first pass metabolism and degradation in gastric fluids. Moreover, the present review summarizes most of the anti-inflammatory, anti-histaminic, gastrointestinal, cardiovascular, contraceptive, anti-cancer, anti-

microbial, palliative and miscellaneous drug that have been loaded into nanofibers.

Besides electrospinning, other techniques have been tested to produce drug loaded mats for oral distribution, but electrospun nanofibers have demonstrated to be the most efficient. In the case of electrospinning, this technique possesses different configurations as single needle electrospinning, high speed electrospinning, coaxial electrospinning and electrospraying, that allow for the production of versatile fiber configurations that can improve the release and protection of the pharmaceutical drug.

Until now, most studies on the release of pharmaceutical agents are carried out *in vitro*. In the case of *in vivo* studies, few literature have been reported. Most of the nanofibers have been implanted in rodents. It is for sure that in-depth systemic studies are necessary before any clinical marketing is considered, especially those on the kinetics and dynamics of drug release *in vivo*, the effects of drug dosage and release kinetics on therapeutic efficacy, and the biodistribution of the released drugs. Full studies are indispensable about toxic effects over long periods of time, as well as pharmacokinetics of the polymeric transporters.

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