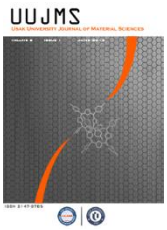
Usak University Journal of Material Sciences
journal homepage: http://uujms.usak.edu.tr



Research article

Functionalization Techniques for Electrospun Nanofibers for Drug Delivery Applications: A Review

[a]*Ramazan Erdem and* [b*]*Erhan Sancak*

[a]*Textile Technology, Serik Gülsün Süleyman Süral Vocational School of Higher Education, Akdeniz University, Antalya, Turkey*
[b]*Textile Engineering Department, Technology Faculty, Marmara University, Istanbul, Turkey*

Received 16 March 2014 Revised 25 December 2014 Accepted 29 December 2014

Abstract

Electrospinning has been defined as an efficient technique for the fabrication of polymer nanofibers. In this method an electrical charge is applied to polymer melt or solution to draw very fine fibers. The properties of nanofibers are influenced by polymer characteristics, process parameters and ambient conditions. Electrospun polymer nanofibers have high reputation as drug release systems due to their unique characteristics such as large surface area to volume ratio, high porosity and very small pore size. The small diameter of nanofibers with a high surface area is useful for mass transfer and efficient drug release. For drug delivery systems biocompatible and biodegradable polymers can be used for drug loading. Encapsulated drugs or biological factors can be burst released or delivered over a long period of time by modifying nanofibers and/or the system. This paper discusses the functionalization techniques of electrospun nanofibers mainly used in drug delivery systems. These include surface functionalization (post electrospinning), blend electrosinning, co-axial electrospinning and emulsion electrospinning. Each technique has different advantages allowing fabricating novel nanofibrous structures. Drug release kinetics of the structures are dependent on the appropriate selection of the techniques, solution properties, the type of drug used and proper set up of the process parameters.

©2014 Usak University all rights reserved.

Keywords:*Surface functionalization, blend electrospinning, co-axial electrospinning, emulsion electrospinning, drug delivery.*

1. Introduction

Electrospinning can be defined as the fiber forming in submicron range by applying electrostatic forces. During the process following operational events occur such as; charging of the fluid (polymer solution or melt), formation of the cone-jet, thinning of the instable jet in an electric field and finally collection of the jet on a proper collector. Diameter and morphology of electrospun nanofibers are influenced by several parameters such as solution properties (viscosity, conductivity, molecular weight, surface tension, polymer concentration and solvent type), process parameters (applied electric

*Corresponding author:
E-mail:esancak@marmara.edu.tr
DOI: 10.12748/uujms.201429447

©2014 Usak University all rights reserved.

field, tip to collector distance and feeding rate) and ambient conditions (humidity and temperature of the environment) [1].

In the last few decades, electrospinning process has gained remarkable popularity in scientific and commercial fields because it provides efficient and simple method for fabricating nanofibrous structures from a wide variety of natural and synthetic polymers [2]. Nanofibrous scaffolds exhibit promising characteristics, such as considerably large surface area-to-volume ratio, high degree of porosity with a very small pore size and their 3D structure are similar to extracellular matrix [3]. Thus, electrospun nanofibers are claimed as candidate materials for many biomedical applications, such as wound dressing, drug delivery and scaffolds for tissue engineering [4-6].

Drug delivery systems have attracted the attention of many researchers recently due to its numerous advantages compared with conventional dosage forms, such as improve therapeutic effect, reduce toxicity and provide convenience, by delivering drugs at a controlled rate over a period of time [7,8].

Electrospun nanofibrous matrices were investigated as new type of mechanisms for drug delivery. The main reason to choose fibrous carriers for drug loading is that they offer site-specific delivery of drugs to the body. In addition, it is possible to integrate more than one drug directly into the fibers [9-13].

There exist plenty of non-degradable and degradable polymers that can be used for producing drug delivery materials by electrospinning technique. In the case of non-degradable materials, drugs are mainly released and driven by a concentration gradient; however, in the delivery system made from degradable materials, drug release is occurred with both diffusion and scaffold degradation. In tissue engineering applications and drug delivery systems, biodegradable materials are widely preferred due to the reason that the scaffold replacement is eliminated during tissue regeneration [14].

In this review, drug loading and functionalization of electrospun fibers, such as; surface functionalization, blend electrospinning, co-axial electrospinning and emulsion electrospinning were mainly discussed. Novel studies and recent developments in drug delivery field were presented. Functionalization of nanofibers is not an easy task and it has considerable challenges, because many bioactive molecules are incompatible with the organic solvents necessary to process polymers that are commonly used in tissue engineering such as poly(caprolactone) (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA) etc [15]. In order to sort this problem out various approaches are currently defined to modify the electrospinning process. Factors influencing the drug release of the mechanisms depending on the electrospinning techniques were discussed in the following sections.

2. Functionalization Techniques for Electrospun Nanofibers

2.1. Surface Functionalization

Surface functionalization of the nanofibers can be performed with physical or chemical immobilization of the bioactive molecules (Fig. 1). By doing this, biologically functional nanoparticles or drug encapsulated polymeric nanoparticles are adsorbed on the fibers or layer-by-layer assembly of polyelectrolytes is applied on the surface of the fibers. In these cases, polymer properties are usually modified by plasma treatment, wet chemical

treatment or surface graft polymerization for the realization of surface functionalization [16].

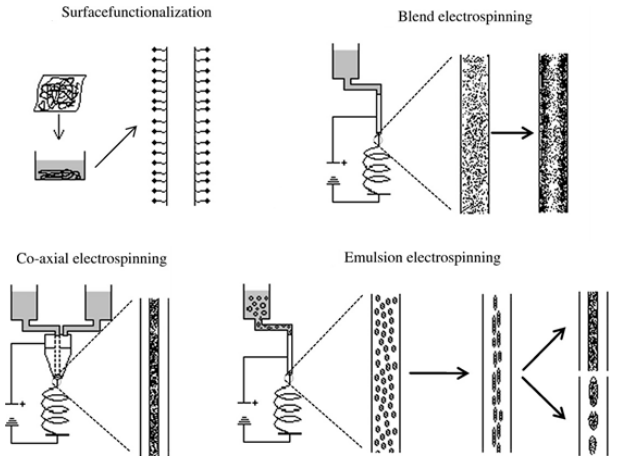


Fig. 1 A schematic illustration of the different techniques for functionalization of electrospun fibers[15]

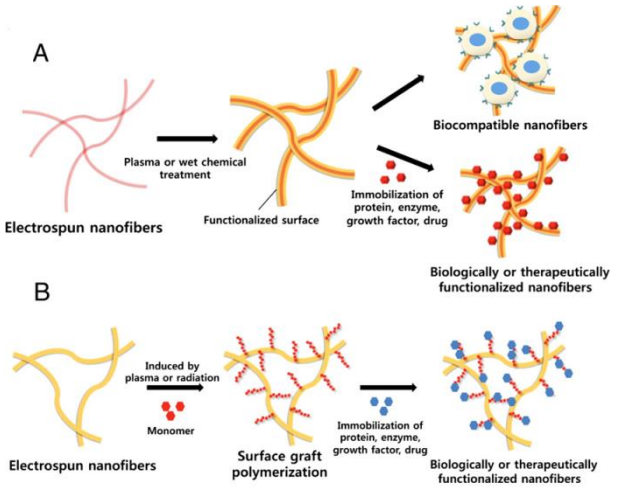


Fig. 2 Surface functionalization of electrospun nanofibers (a)Plasma or wet chemical treatment, (b) Surface graft polymerization[16]

Plasma treatment of polymer substrates is generally applied to customize the surface adhesion and wetting characteristics by altering the surface chemical structure (Fig. 2). Proper preference of the plasma source provides opportunity for the introduction of functional groups on the target surface to permit covalent immobilization of various bioactive molecules. Mostly oxygen, ammonia, or air are utilized through plasma treatments to generate carboxyl groups or amine groups on the surface. Wide range of extracellular matrix protein components such as gelatin, collagen, laminin, and fibronectin can be immobilized onto the fiber surfaces, which are activated by plasma treatment, to promote cellular adhesion and proliferation. It was reported that Poly(glycolic acid) (PGA), poly(l-lactic acid) (PLLA), or poly(lactic-co-glycolic acid)

(PLGA) based electrospun nanofibers were modified successfully with plasma glow discharge by using oxygen and gas-phased acrylic acid [16-19].

On the other hand, plasma treatment for nanofibrous mats has a critical disadvantage that the mat surface cannot be effectively modified due to the some nanofibers located deeply in the mat, hence, plasma is not always be able to affect all the fibers equally. In this situation, wet chemical treatment may be an alternative method that possibly covers the limitations related with plasma technique especially for the surface modification of thick nanofibrous mats [20].

In wet chemical treatment, surface generation of carboxylic and hydroxyl groups occurs through random chemical scission of ester linkages on the polymer backbones which are mostly located on the surface (Fig. 2). One of the examples for wet chemical treatment is partial hydrolysis. It has been recently reported that the surfaces of biodegradable aliphatic polyester films and scaffolds have been successfully customized by partial hydrolysis under acidic or alkaline condition in order to change wettability property or generate new functionalities [16,21-23].

When the surfaces of biodegradable polymeric nanofibers are modified, the partial hydrolysis process must be conducted carefully. Because, the bulk property of the nanofibrous mesh may be changed extremely. Therefore, the duration of the hydrolysis and the concentartion of hydrolyzing agents must be determined accurately [20].

Another application of wet chemical treatment is the surface aminolysis method which uses diamine species as an alternative hydrolyzing agent for especially polyester nanofibers. Within this technique, positive surface charges as well as amine functionalized surfaces are generated [20,24]. It was announced that electrospun poly(L-lactide-co-caprolactone) copolymer (PLLC) nanofibrous scaffolds were surface-modified satisfactorily via aminolysis, followed by immobilization of a cell adhesive protein, human plasma fibronectin [25].

Surface graft polymerization is another alternative method that is commonly applied to increase the surface hydrophilicity of the nanofibers as well as to introduce multi-functional groups on the surface for covalent immobilization of bioactive molecules to allow enhanced cell adhesion, proliferation, and differentiation (Fig. 2). The surface graft polymerization is frequently triggered with plasma and UV radiation treatments to create free radicals for the polymerization [16,26].

Electrospun polyethylene terephthalate (PET) nanofibers that were modified with poly (methacrylic acid) by graft polymerization in a mild condition were reported. According to findings, there was not any structural damage in the bulk phase [27]. First of all, the PET nanofibers were treated with formaldehyde to create hydroxyl groups on the surface. The subsequent oxidization of surface hydroxyl groups by Ce (IV) produced free radicals, thereby initiating the polymerization of methacrylic acid monomers from the surface. The carboxylic acid moieties on the surface were then conjugated to immobilize gelatin on the nanofibers. The increment in surface density of carboxylic acid was observed as the reaction time and the monomer concentration was increased.

Electrospun polyurethane (PU) nanofibers were also modified by surface graft polymerization technique. Following electrospinning process, PU based nanofibers were firstly treated with argon plasma which created oxide and peroxide groups on the surface. Then PU fibers were immersed in a 4-vinylpyridine monomer solution with exposure of UV irradiation, finally poly(4-vinylpyridine) grafted PU fibers were

successfully produced. After that the grafted prydine groups were quarternized with hexylbromide in order to make nanofibers highly antibacterial. Antibacterial test results proved that modified PU fibers exhibited significant inhibitory effect against Grampositive Staphylococcus aureus (S. aureus) and Gram-negative Escherichia coli (E. coli) bacteria [28].

One of the major advantages of fiber surface functionalization as a post-spinning modification is the prevention of destabilizing during the electrospinning process. In addition, it enables easy loading of various types of mixtures of drugs to electrospun matrices. However, when sustaining high concentrations of drugs locally and controlling drug release over extended time periods, post spinning modification techniques may not perform well enough to meet the requirements [29,30].

2.2. Blend Electrospinning

For combined functionalization effect, bioactive molecules can be added into the polymer solution before electrospinning (Fig. 1). Through this technique, it is possible to form fibers with a wide range of drug releasing functionalities. For example; *Zhang et.al.* prepared drug-loaded nanofibers by blend electrospinning of biodegradable aliphatic polyesters such as [Poly(l-lactic acid) (PLLA), poly(lactic-co-glycolic acid) (PLGA), and poly(lactic lactic-co-ε-caprolactone) (PLCL)]. Captopril, which is a vasodilator and inhibitor of certain renal functions, was chosen for the application. They found that the morphology and diameters of fibers were influenced and decreased by drug loading. Also, *in vitro* dissolution test results proved that drug release from the fibers is dependent on the release medium, temperature and the polymer type [31]. *Chen and Yu* [32] produced Acyclovir (ACY)-loaded Polyacrylonitrile (PAN) fibers from dimethyl sulfoxide solutions of PAN and ACY by elevated temperature electrospinning at 80 ◦C. As the temperature increased, the viscosities and the surface tensions of the blend solutions decreased, whereas conductivities increased, which improved electrospinnability. High quality nanofibers were obtained without any beads or imperfections. *In vitro* dissolution tests presented that fibers could provide sustained drug release profiles over a time period of 16 hrs. *Toncheva et. al.* [33] obtained microfibrous electrospun matrices based on poly(L-lactide-co-D,L-lactide) (coPLA) and coPLA/poly(ethylene glycol) (PEG) containing a fluoroquinolone antibiotics: ciprofloxacin hydrochloride (Cipro), levofloxacin hemihydrates (Levo) or moxifloxacin hydrochloride (Moxi). Infrared spectroscopy and flourescence microscopy analysis proved one-step incorporation of antibiotics into the fibers. It was observed that release behavior of the antibiotics was dependent on the fiber composition, and presence of PEG in the fibers speeded up the antibiotic release within the first 2 hrs. Antimicrobial test results confirmed that existence of antibiotics in the matrices caused a substantial decrease in the adhesion of the pathogenic micro-organisms. *Huang et.al.*reported the potential use of cellulose acetate phthalate (CAP) based electrospun fibers loaded with antiviral drugs such as TMC 125, Viread and Rhodamine 6G to prevent HIV transmission. CAP is known as an accelerator that induces conformational changes in HIV glycoproteins (gp 41 and gp 120), which are the main substitutes that bind the human CD4 receptor and CCR-5 and CXCR-4 co-receptors. Findings exhibited that the morphology of fibers was not affected remarkably by drug loading. *In vitro* studies presented that CAP fibers themselves and drug loaded ones were both found to be powerful inhibitors against HIV infection [34].

Electrospun nanofibrous biodegradable scaffolds are potential candidates for biomedical applications due to their mechanical barrier properties and the capabilities of local delivery of drugs.

The successful incorporation and sustained release of a hydrophilic antibiotic drug (MefoxinR, cefoxitin sodium) from electrospun poly(lactide-co-glycolide) (PLGA) scaffolds without the loss of structure and bioactivity was presented. It was found that drug concentration was the main factor for establishing the morphology and density of the electrospun scaffold. Drug release behavior of the scaffolds was also investigated and it was observed that themaximum dosage of drug was released after 1 h of incubation at 37 ^{0}C in water. In addition, it was claimed that usage of the amphiphilic block copolymer (PEG-b-PLA) reduced the cumulative amount of the released drug at earlier time points and prolonged the drug release rate at longer times (up to a 1-week period). The released antibiotic inhibited substantially the growth of Staphylococcus aureus (>90%)[35].

For the controlled drug delivery, *Karuppuswamy et. al.* prepared Polycaprolactone (PCL) nanofibers with different concentrations of tetracycline hydrochloride (TC) by blend electrospinning technique. TC is preferred to be used as skin and bone ointments to control infections. Also, it is believed that TC may boost faster regeneration of osteoblasts and fibroblasts. Chloroform and methanol (3:1) were used as solvents for the fabrication of PCL/TC nanofibers. According to the test results, the highest resistance to deformation was observed for 5% drug loaded nanofibrous membrane. It was also found that 2% drug loaded membrane showed the greatest tensile strength at 3.9 MPa. Porosity of the membrane increased with the increasing amount of the drug. UV-Visible Spectrometry analysis revealed that the minimum level of burst release recorded within the first hr and controlled release action continued within the following eight days [36].

Nanofibers can be functionalized through blend electrospinning for very specific applications. For example;*Luu et.al.*used blend electrospinning method to fabricatesynthetic polymer/DNA composite scaffolds for therapeutic application in gene delivery. Scaffolds were consisted of poly(lactide-co-glycolide) (PLGA) random copolymer and a poly(D,L-lactide)–poly(ethylene glycol) (PLA–PEG) block copolymer. It was noticed that the release of plasmid DNA from the scaffolds continued over 20 days. However, most of the plasmid DNA was released within first 2 hrs. Cumulative release profile exhibited that the amount of released substitute was approximately 68–80% of the initially loaded DNA. It was emphasized that morphology and drug release profile of the scaffolds were remarkably affected by PLGA to PLA–PEG block copolymer ratio [37].
Generally, drug delivery systems should optimize the delivery mechanism of bioactive agents. Through this optimization it is possible to decrease systemic side effects and to release the desired amount of therapeutic doses at the target site.*Yohe et. al.* have recently reported that the local delivery device, where air was used as a degrading component to control the drug release. In the experiment, poly(ε-caprolactone) (PCL) with the hydrophobic polymer dopant poly(glycerol monostearate-co-ε-caprolactone) (PGC-C18) was electrospun for developing mechanically stable nanofibrous meshes to control the release of two anticancer drugs (CPT-11 and SN-38). As the mesh became hydrophobic with the addition of PGC-C18, drug release was slowed downboth by the traditional means of drug diffusion, as well as by increasing the stability of the entrapped air layer. Authors also claimed that resultant superhydrophobic meshes were suitable for surgical buttressing of the anastomosis according to mechanical test measurements. Release chemotherapy over a prolonged period of time (>90 days) showed significant tumor cytotoxicity against a human colorectal cell line (HT-29) [38].

Nanofibers with porous structure are also highly influent on the release profile of the nanofibrous meshes. *Huang et. al.*fabricated luminescent Eu3+/Tb3+ added mesoporous bioactive glass nanofibers (MBGNFs), with average diameter of 100–120 nm, by blend electrospinning method. In order to obtain nanofibers with porous structure, Pluronic P123 and N-cetyltrimethylammonium bromide (CTAB) were used as co-

surfactants.These luminescent nanofibers showed sustained release properties for ibuprofen (IBU) in vitro. Release profile of the nanofibrous meshes was easily tracked and monitored by photoluminescence measurements [39].

For improving the dissolution profile of poorly water –soluble drugs, blend electrospinning technique was used effectively. Feruloyl-oleyl-glycerol (FOG) as a model drug and polyvinylpyrrolidone (PVP) K90 as a polymer were blended in a mixed solvent of chloroform/ethanol. Fourier-transform infrared spectroscopy proved that a satisfactory compatibility between FOG and PVP was occurred and a good distribution of FOG within the fibers was observed. Wetting time assays approved fast-dissolving manner of the FOG-loaded PVP fiber membranes [40].

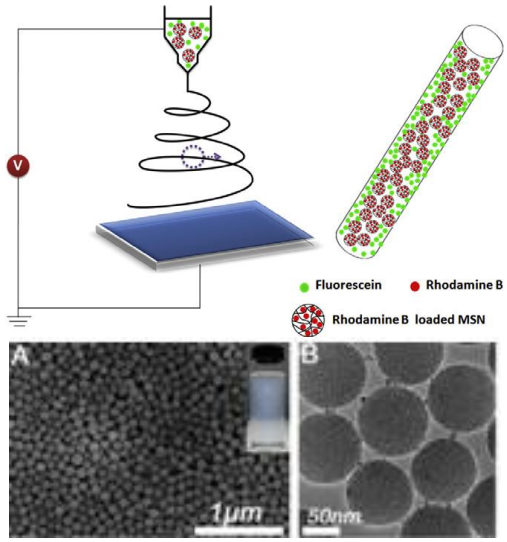
Fast-dissolving drug delivery systems have become attractive to develop new strategies for drug delivery applications because of their remarkable advantages, such as raising drug solubility level, onset of action and bioavailability. *Li et.al.*prepared fast-dissolving drug delivery systems by using blend electrospinning method. In their study, Polyvinyl alcohol (PVA) was chosen as a carrier polymer, and caffeine and riboflavin were used as the model drugs. SEM analysis showed that uniform nanofibers withan average diameter in the range of 260–370 nm were obtained.Pharmacotechnical tests presented that the dissolution time was about 1.5 s and wetting time was about 4.5 s which were similar for PVA/caffeine and PVA/riboflavin nanofibrous mats. The release measurements indicated that drugs were tended to release in a burst manner from the PVA nanofibrous matrices [41].

Drug release mechanisms of the electrospun nanofibers can also be modified according to pH changes of the biologic media. Eudragit® L 100-55 nanofibers loaded with diclofenac sodium (DS) were successfully fabricated by blend electrospinning process.Solvent mixture of 5:1 (v/v) ethanol:DMAc was used for the preparation of drug loaded polymer solution before the electrospinning process. FTIR analysis of nanofibers confirmed the hydrogen bondings between drug and the polymer.In vitro dissolution tests indicated that all the drug-loaded Eudragit® L 100-55 nanofibers had pH-dependent drug release profiles. The release was limited and less than 3% when the pH value was 1.0, on the other hand, a sustained and complete release was observed at pH 6.8 [42].

Most studies related to blend electrospinning technique concentrated on single drug delivery systems, which may not satisfy the requirements in clinical therapies all the time. Through blend electrospinning method, it is possible to functionalize nanofibers by using more than one drug. In this way, therapeutic efficacy could be enhanced. *Xu et.al.*developed novel electrospun fiber mats including hydrophobic and hydrophilic drugs. Poly(L-lactic acid) (PLLA) was chosen as the carrier polymer for the experiment. Bovine serum albumin (BSA, used as a hydrophilic model drug) was firstly enveloped into chitosan microspheres by spray drying method. Benzoin (used as a hydrophobic model drug) was directly dissolved in PLLA solution and then the chitosan microspheres were suspended into the PLLA solution. Polyvinylpyrrolidone (PVP) was also added into the PLLA solution to adjust the drug release behaviors.Then electrospinning process was realized to fabricate drug loaded nanofibrous mats. Test measurements indicated that the chitosan microspheres were uniformly distributed in the fibers.BSA exhibited a short-term release while benzoin showed a longterm and sustained release, and the release of both hydrophobic and hydrophilic drugs could be controlled by changing the ratio of PVP/PLLA [43].

There are also different techniques to include more than one drug into same nanofibrous matrices. Recently, Okuda et al. [44] fabricated multilayered electrospun polymer

matrices with two drugs (in the first and third layers) where the two drugs had different release kinetics. However, delivery of the drugs in the surrounding medium was not proper that might decline the efficiency of multi-drug combination teraphy. In order to bring a solution to this limitation, a novel drug releasing mechanism was developed by incorporating mesoporous silica nanoparticles (MSNs) into electrospun fibers to facilitate dual controlled release. One of the drugs[Fluorescein (FLU)] loaded in electrospun poly(lactic-co-glycolic acid) (PLGA)fibers which delivered one drug in a faster manner, and the other [Rhodamine B (RHB)] in mesoporous silica nanoparticles which delivered another drug in a more sustained manner (Fig. 3) [45].



(a) (b)

Fig. 3 Schematic illustration of the process of fabrication of dual drug-loaded electrospun composite fiber and the position of the two model drugs located in the fiber (a) SEM and (b) TEM images of MSNs [46]

One of the ways for getting benefit from rapid onset of drug action is sublingual administration of active pharmaceutical substances. For example, treatment of migraines can be realized efficiently by sublingual usage of the drugs. *Vrbata et.al.*used two frequently used drugs, sumatriptan succinate and naproxen, to prepare nanofibrous membranes through blend electrospinning to develop a novel material for the treatment of migraines. The efficiencies of drug solutions and drug loaded membranes were compared *in vitro*. Results depicted that the permeation rates of drugs, released from nanofibrous membranes, through sublingual mucosa were several times higher than the drug solution itself [46].

The phenomenon of Transdermal Delivery System (TDS) has recently become attractive topic for drug administration. TDS enables drugs to penetrate readily through the skin and get into the body. The system offers many reasonable benefits such as improved patient compliance, avoidance of gastric irritation and first-pass effect, and controlled therapeutic responses. On the other hand, TDS has some limitations like extremely low drug release rate due to the low drug permeability through the skin. Hence, precise control over the release amount and the release rate should be taken into account to offer optimum conditions for the teraphy. *Yun et. al.* developed the electro-responsive transdermal drug delivery system by blend electrospinning of poly(vinyl

alcohol)/poly(acrylic acid)/multi-walled carbon nanotubes (MWCNTs).The surface of MWCNTs was modified with oxyfluorination to introduce the functional groups which enhanced the compatibility between MWCNTs and the polymer matrices.The MWCNT content and oxyfluorination condition were crucial parameters for the swelling properties and drug release characteristics of nanofibers. It was found that the conductivity of nanofibers increased by increasing the content of MWCNTs. At the end of experiments, promising electrospun nanofibrous structures with electro-responsive swelling properties and controllable drug releasing behaviors were obtained [47].

The idea behind the development of nanofibrous scaffold structures is to create ideal biocompatible materials that can replace the natural extra cellular matrix until the host cells can grow, migrate and synthesize a new natural cellular matrix. Today, the number of studies related to design and synthesis of inorganic fillers embedded polymer matrices used in tissue engineering and drug delivery applications have been increasing. *Choi et.al.*prepared drug and ceramic particles added polyurethane (PU) basedcomposite nanofibers by blend electrospinning. Two different approaches were defined to fabricate PU composite nanofibers. Firstly, PU/drug composite nanofibers were obtained from the 10 wt% PU solution containing ciprofloxacin HCl (CipHCl). In the second approach, PU solution including ciprofloxacin HCl drug and ceramic hydroxyapatite (HA) particles was electrospun. SEM analysis indicated that smooth, bead-free, and continuous nanofibers were formed through the electrospinning process.The diameter of the nanofibers was in the range of 150–250 nm. It was reported that drug loaded PU composite nanofibers exhibited excellent inhibitory action against S.aureus and E.coli bacterial strains. Experimental results revealed that PU/Drug/HA composite nanofibers were potential candidates to be used in tissue engineering and drug delivery field [48].

Blend electrospinning, on the other hand, has certain critical drawbacks that some specific proteins and cytokins may denature and lose their bio-properties when blending with solvents. In order to overcome this problem, water soluble polymers such as Polyvinyl alcohol (PVA), Polyethylene oxide (PEO) etc. have been used with sensitive biomolecules [49,50].

Another vital matter have to be considered about the blend electrospinning is that most bioactive molecules are highly charged substances and they migrate toward the jet surface as a result of charge repulsion during electrospinning. This may influence the uniformity of the biomolecules dispersion within the fiber. Sun et. al. [51] used PEGylated proteins to be immobilized on the fiber surface and they observed that rather than a uniform distribution of the molecules in fibers, surface enrichment was occurred during the electrospinning process.

Location of drug particles on fiber surface during blend electrospinning causes another problem called 'burst release' at the initial stage. To overcome this problem, post-processing methods such as chemical vapor deposition [52] or fluorination [53] could be applied. Furthermore, by encapsulating drugs or proteins into the electrospun fibers by co-axial electrospinning or emulsion electrospinning would be effective alternative techniques to resolve the problems derived from initial burst release phenomenon.

2.3. Co-axial Electrospinning

Co-axial electrospinning is another useful technique for fiber functionalization. In the mechanism of co-axial electrospinning, there are two concentrically arranged nozzles system in where two different solutions are pumped through. In this technique, two polymer solutions are kept separate until the moment they leave the nozzles, and

eventually core-shell fiber formation is obtained (Fig. 1). It has been claimed that interaction between core and shell phases plays a crucial role in determining the electrospinnability of the solutions. Satisfactory results have been gained when the common solvent was used. Also, Chakraborty et al. stated that the ratio of the flow rates of the sheath and core solutions should be taken into account because of the possibility of jet break-up and uneven fiber deposition [53].

Co-axial electrospinning has become highly reputative among researchers to fabricate variety of novel bioactive products as well as drug delivery materials. *Ortega et. al.* [54] have investigated the best conditions for co-axial electrospinning of cellulose acetate (CA)/poly(vinyl pyrrolidone) (PVP), containing amoxicillin (Amoxi), core-shell fibers. According to test results, fibers were produced successfully and the tensile strength of the fibrous composite was not affected by the existence of amoxicillin, however, rigidity decreased by around 45%. It was noticeable that the amount of released amoxicillin was greater at higher pH values (Fig. 4).

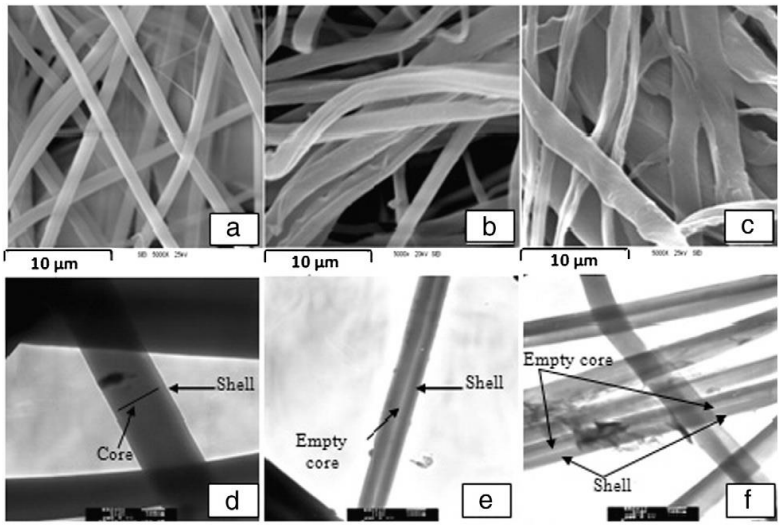


Fig. 4 (a) SEM micrographs for the fibrous membrane CA/PVP-Amoxi/CA before amoxicillin release, (b) after amoxicillin release at pH 7.2, (c) after amoxicillin release at pH 3.0, (d) TEM micrographs for the fibrous membrane CA/PVP-Amoxi/CA before amoxicillin release (e) after amoxicillin release at pH 7.2 (f) after amoxicillin release at pH 3.0 [55]

Nguyen et. al focused on fabrication and characterization of porous core/sheath structured composite nanofibers by co-axial electrospinning technique. For sheath layer, poly(lactic acid) (PLA) was chosen, whereas, the core part was consisted of blended salicylic acid (SA) and poly(ethylene glycol) (PEG). Results indicated that the feed rates of the core and sheath polymer solutions strongly affected the stability of core/sheath structure and porous density of the composite nanofibers. This also influenced the release characteristics of SA. At lower ratios of feeding rates, better stable core/sheath structures of nanofibers (with higher porous density) were gained with a sustained release of SA over 5 days [55].

Yu et. al. studied the core/sheath nanofibers prepared by co-axial electrospinning to concentrate on adjustable biphasic drug release. Ketoprofen was used as the model drug,

polyvinylpyrrolidone as the sheath polymer, and ethyl cellulose as the core matrix. Co-axial electrospinning process was carried out smoothly and continuously without any spinneret clogging. *In vitro* dissolution tests showed that the core/sheath nanofibers were able to provide typical biphasic drug release profiles consisting of an immediate and sustained release [56].

An authentic approach was demonstrated by *Jiang et. al.* which focused on developing nanofibrous meshes through co-axial electrospinning of biodegradable core-shell nanofibers with PCL as shell and protein-containing PEG as core. Two model proteins, BSA and lysozyme, were embedded in the nanofibers. Authors claimed that this was the first time to demonstrate the capabilities of this technique for incorporation of water-soluble bioactive agents into biodegradable non-woven polymer meshes; and their subsequent controlled release. Moreover, the technique offered high loading effeciency/capacity and relatively steady release action. It was found out that the released lysozyme maintained its structure and bioactivity. It was also perceived that the thickness of the core and shell could be adjusted by the feed rate of the inner dope, which in turn affected the release profiles of the incorporated proteins [57].

In controlled release drug therapy, a predetermined concentration of a drug is delivered to a particular target site over a determined duration. The main aim of this process is to enhance the effectiveness of the drug by localizing the delivery, minimizing the side effects, decreasing the number of the administrations. In vitro drug release mechanism of core/shell nanofibers of poly(methyl methacrylate)(PMMA)/nylon6 fabricated through co-axial electrospinning including various amounts of ampicillin was explored. The system showed sustained drug release through three steps. During step I, the release occurred according to non-Fickian diffusion. A significant decline in the diffusion coefficient from step II to step III was noticed, which was considered to be the result of crystallization of fibers because of long-term incubation in an aqueous solution. Optical density (OD) measurements proved the antibacterial activity of the designed drug delivery system against Gram-positive L. innocua [58].

Recently, research on biodegradable and biocompatible scaffolds incorporated with multiple wound healing mediators has increased. Through controlled delivery, this type of scaffolds can minimize the toxicity effects and enhance the clinical efficiency. *Jin et.al.*carried out electrospinning process according to two different approaches; blend electrospinning and core-shell spinning. Gelatin and poly(L-lactic acid)-co-poly-(e-caprolactone) (PLLCL) solutions containing multiple epidermal induction factors (EIF) such as epidermal growth factor (EGF), insulin, hydrocortisone, and retinoic acid were prepared and electrospun. No burst release was observed from EIF loaded core–shell nanofibers, whereas, an initial burst release (44.9%) was recorded from EIF blended nanofibers over a period of 15 days. Adipose-derived stem cells (ADSCs) were used to explore the impact of EIF-containing nanofibrous scaffolds on cell proliferation. After 15 days, it was noted that cell growth and differentiation were higher on EIF containing core-shell nanofibers compared to scaffolds obtained by blend electrospinning. This was explained by the sustained release of EIF from the core-shell nanofibers. It was claimed that EIF loaded core-shell nanofibers could be a promising material for skin regeneration [59].

Nowadays, the clinical benefit of bacteriophage therapy has become an attractive topic and suggested as an alternative to chemical antibiotics. Bacteriophage therapy can also offer a potential use for food preservation and storage. *Korehei et.al.*developed a food packaging material from electrospun biobased nanofibers. T4 bacteriophage (T4 phage) was embedded into core/shell electrospun fibers obtained from poly(ethylene oxide)

(PEO), cellulose diacetate (CDA), and their blends. Depending on the PEO/CDA ratio, the post-release electrospun fiber morphologies varied from discontinuous fibers to minimally swollen fibers. Fibers prepared using PEO as the shell polymer showed an immediate burst release of T4 phage. Increasing the PEO molecular weight also increased the electrospun fiber diameter and the viscosity of the releasing medium, which resulted in a relatively slower T4 phage release. It was noticed that no T4 phage release detected from the solely CDA fibers [60].

Controlled release of hydrophilic substances, such as peptides, proteins and even pDNA, is difficult to accomplish with conventional methods. *Tiwari et.al.*introduced a novel approach for partition controlled release of such substances by using co-axial electrospinning. The electrospun fibers were consisted of two layers. Outer layer was the polymer sleeve covering the inner part, where the drug was encapsulated. PCL, PLLA and PLGA (80/20) polymers were used for the system. Experimental results revealed that altering physical and chemical properties of the core and shell solutions could adjust the release rate of the hydrophilic drug (metoclopramide hydrochloride) [61].

There are common biological substances (plasmids, nerve growth factor, bovine serum albumin) that have been encapsulated and subsequently release from electrospun nanofibers. The large surface area of nanofibers enables the high quantities of enzyme to be encapsulated, and meanwhile, preserves the efficiency of its catalytic function. Furthermore, the surface of the nanofibers can be modified to gain several porosity degrees, so that nanofibers behave as enzymatic nanoreactors. The b-galactosidase, lysozyme and luciferase are some examples of enzymes successfully released from polymeric nanofibers [62-66]. *Moreno et. al.* reported that sustained release of lactate dehydrogenase (LDH, EC 1.1.1.27) from electrospun poly (vinyl alcohol) (PVA) nanofibers was successfully realized by using co-axial electrospinning technique. Findings exhibited that most of the encapsulated LDH enzyme was released in a sustained manner from the PVA nanofibers within a period of 1 month [67].

Sustaining biological agents over a period of days rather than direct delivery decreases the drawbacks of limited bioactivity associated with short half-lives of most biological factors. By the improved delivery strategies, it is possible to cope with the requirement of high doses for specific biomedical applications. *Saraf et.al.*used co-axial electrospinning technique to fabricate scaffolds act as reservoirs for the biological molecules.Poly(ε-caprolactone) was chosen as the sheath polymer and poly(ethylene glycol) was the core polymer. Several fiber mesh scaffolds comprising plasmid DNA (pDNA) within the core and the non-viral gene delivery vector poly(ethylenimine)-hyaluronic acid (PEI-HA) within the sheath of coaxial fibers were prepared. The release kinetics of PEI-HA from the fibers was influenced by the loading concentration of pDNA. Two-dimensional cell culture experiments with model fibroblast-like cells presented that complexes of pDNA with PEI-HA released from nanofibrous scaffolds were successful to transfect cells and impulse the expression of enhanced green fluorescent protein (EGFP). What is more, fibroblastlike cells seeded onto coaxial fiber mesh scaffolds having PEI-HA and pDNA exhibited EGFP expression over 60 days, which was significantly higher than the EGFP expression noticed with scaffolds containing pDNA alone [68].

Limited supply of traditional bone graft tissue and high risk of immune reactions to auto- and allografts are critical matters for clinical applications. Abilities of electrospun nanofibers regarding mimicking the native extracellular matrix of bone tissue have generated remarkable interest among researchers. *Su et.al.*used co-axial electrospinning method to prepare poly(L-lactide-co-caprolactone) (PLLACL), PLLACL/collagen nanofibers loaded with bone morphogenetic protein 2 (BMP2) and dexamethasone (DEX)

to develop controlled release action during bone tissue regeneration. Release performance of the scaffolds was explored by measuring viability of human mesenchymal stromal cells (hMSC) on the nanofibrous mats. The experimental results demonstrated thatcontrolled release of BMP2 and DEX can induce hMSC to differentiate into osteogenic cells which are crucial for bone tissue regeneration [69].

Nerve tissue repair is one of the hot topics in research field, because, it is directly related to the quality of human life. One of the influential methods for nerve tissue engineering is the fabrication of three dimensional nanofibrous scaffolds with nerve cells and encapsulated bioactive proteins (Nerve Growth Factor). *Yan et.al.*investigated the electrospun poly(L-lactide-co-3-caprolactone) [PLLACL] nanofibers for nerve tissue regeneration. Bovine Serum Albumin (BSA) or/and Nerve Growth Factor was the two main substances that were released in a sustained manner. Satisfactory results have been gained from the experiments carried out with rat pheochromocytoma cells (PC12) [70].

A modified process based on coaxial electrospinning has recently been unveiled. In this specific system, only unspinnable organic solvents were used as sheath fluids [71,72]. Although nanofibers prepared by the modified coaxial process have no remarkably different structural characteristic compared with the ones obtained from traditional co-axial electrospinning, unspinnable organic solvents and small-molecule solutions can now be used as sheath fluids. Unspinnable dilute polymer solutions may also be used as sheath fluids in this system to produce core/sheath nanofibers.

Yang et. al. [73] have recently explored the composite fibers fabricated by a modified co-axial electrospinning. Unspinnable acetic acid was determined as sheath liquid and an electrospinnable co-dissolving solution of zein and ferulic acid (FA) as core liquid. Zein consists of various types of proteins and has excellent properties such as; biodegradability, biocompatibility, low hydrophility, good elasticity, film-forming capability etc.Ferulic acid (FA, 4-hydroxy-3-methoxycinnamic acid) is an antioxidant capable of scavenging free radicals and can reduce blood glucose level, therefore, it could be used for the treatment of diabetes.

Yu et. al.[74] explored a novel type of drug-delivery membrane prepared by a modified coaxial electrospinning process. Unspinnable zein solution was preferred as sheath fluid. The process has been successfully carried out and ketoprofen (KET)-loaded zein nanofibers coated with a thin layer of blank zein were prepared. *In vitro* dissolution tests exhibited that the nanofibers coated with blank zein did not possess any initial burst release effect, and could enable linear drug release over a period of 16h via a diffusion mechanism.

Above studies reveal that coaxial electrospinning is a robust technique that offers one step encapsulation of sensitive bioactive agents, and generates controlled release mechanism by preventing the quick release of core content [75].

2.4. Emulsion Electrospinning

Emulsion electrospinning is another specific application to functionalize nanofibers. As it has been explained in the previous section, co-axial electrospinning is a dynamic process and influenced by many factors such as flow rate of the inner and outer solutions, interfacial tension and viscoelasticity of two polymer solutions. These factors are extremely effective on the final fiber morphology. What is more, co-axial electrospinning process requires a special apparatus to obtain the desired core-shell fiber formation [74].

Recently, producing core-shell type fibers by emulsion electrospinning has gained great popularity [76,77]. In emulsion electrospinning processes, mainly water-in-oil types of emulsions are used. In oil phase, polymers are dissolved into organic solvent, however, in water phase, micron or sub-micron sized emulsion spheres are the substances used in which drugs or proteins are dissolved. During the process, under the electrostatic forces, emulsion containing oil phase of polymer solution and water based spheres are elongated and formed as core-shell type fibers (Fig. 1). It is noticeable that unlike co-axial electrospinning which requires a special apparatus, emulsion electrospinning technique only needs a single needle [78].

Xu et al. [79] have given additional explanation regarding the process that the oil phase rapidly evaporates during electrospinning. The water phase spheres thus migrate to the center of the jet because of the viscosity gradient. The water and oil phase spheres are merged in the presence of the electric field because of the mutual dielectrophoresis, which creates column-like structures that finally shape the core-shell fiber morphology. There is also possibility that the inner column may be divided into smaller droplets due to Rayleigh instability [80,81].

Maretschek et. al. [82] fabricated nanofibrous mats, composed of poly(L-lactide) solution and an aqueous protein solution, by emulsion electrospinning. Cytochrome C was chosen as a hydrophilic model protein for encapsulation. It was presented that the amount of protein release was strongly related with the surface tension of the release medium. Another factor that affected the release of macromolecules was the hydrophobicity of the nanofibrous mats, thus, in order to rise up the level of protein release, hydrophilic polymers such as poly(ethylene imine) (PEI) and poly(L-lysine) (PLL) were blended with PLLA. At the end, it was uderstood that the release profiles of nanofibrous mats could be adjusted by altering the amount of added hydrophilic polymers.

Yang et. al. [78] prepared core-shell structured composite fibers (lyz-MC/PDLLA). Lysozyme was the model protein that was encapsulated into the poly (DL-lactic acid) (PDLLA) fibers along with methyl cellulose (MC). The reason for choosing Lysozyme as the model protein was its size similarity to most growth factors. SEM images showed that the obtained fibers through emulsion electrospinning were uniform and bead-free, and the fibrous mats were highly porous and consisted of randomly arrayed fibers. Authors claimed that this type of structure could alleviate the initial burst release and improve sustainability of fiber-based releasing devices.

Xu et. al. [7] fabricated Doxorubicin hydrochloride-Dox (water-soluble anticancer agent) loaded amphiphilic poly(ethylene glycol)–poly(L-lactic acid) (PEG–PLA) diblock copolymer nanofibers by emulsion-electrospinning.The average diameters of core-sheath nanofibers were around 570 nm. Analysis proved that surfaces of the fibers were very smooth and there were not drug crystals detected. The laser scanning confocal microscopic (LSCM) imagesindicated that Dox was molecularly distributed in the center of the fibers, forming a reservoir-type drug-loaded system (Fig. 5).Dox release interestingly decreased as the Dox content in the fibers increased. The release profile of Dox consisted of three sequential stages that were all diffusion controlled.

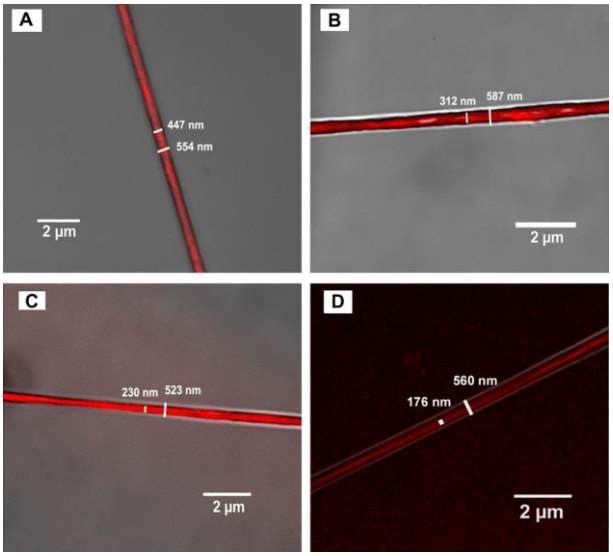


Fig. 5 LSCM images of Dox-loaded electrospun nanofibers. The contents of Dox in the composite fibers were (A) 0.5 wt%, (B) 1.0 wt%, (C) 2.0 wt% and (D) 3.0 wt%, respectively [7]

Both liphophilic (rifampin and paclitaxel) and hydrophilic drugs (tetracycline hydrochloride and doxorubicin hydrochloride) as well as biomacromolecules (protein and DNA) have been encapsulated into electrospun fibers. Loading strategy of such molecules into the electrospun nanofibers is very important in terms of modulating the loading capabilities and adjusting the control release mechanisms. *Lou et.al.* prepared core-sheath fibers by using emulsion electrospinning technique. Fibers were core-loaded with hydroxycamptothecin (HCPT), and their antitumor activities were evaluated both *in vitro* on cancer cell lines and *in vivo* on tumor bearing mice. Experimental results proved that emulsion electrospun fibers were potential drug carriers for local treatment of solid tumors [83].

In order to suppress the burst release, Zhang et.al. have recently developed core-shell nanofibers by emulsion-core (EC) coaxial electrospinning with using water-in-oil (W/O) emulsions as the core. Bovine serum albumin (BSA) as a model protein that was entrapped in the core part for controlled release.Copolymers of poly(llactide-co-glycolide) (PLGA) with different compositions were employed in the emulsion to adjust the release rate. A solution of methoxy polyethylene glycol-b-poly(l-lactide-co-ε-caprolactone) (PELCL) was also prepared as the shell. The release profiles of BSA from the EC electrospun membranes were explored and compared with the releasing activity of the coaxial electrospun membrane. The results demonstrated that EC coaxial electrospinning exhibited better performance than conventional coaxial electrospinning in the case of protein delivery [84].

Recently, there has been a growing number of studies to develop novel drug delivery systems. Enhancing the effectiveness of drug therapy, minimizing the toxic side effects of anticancer drugs and providing stable storage and selective targeting, establishing long blood circulation time and lower interactions with reticuloendothelial system (RES) are the main reasons to produce novel drug delivery systems. It is already known that various polymeric materials, either biodegradable or biocompatible ones, can be used as

delivery matrices. *Xu et.al.* fabricated ultrafine fibers containing water-soluble drugs by electrospinningfrom water-in-oil (W/O) emulsions. In the system,the aqueous phase contained the water-soluble anticancer drugs (doxorubicin hydrochloride, DOX) and the oily phase was a chloroform solution of amphiphilic poly (ethylene glycol)-poly (l-lactic acid) (PEG-PLLA) diblock copolymer. The diameters of the electropsun nanofibers recorded as 300 nm–1 μm, respectively. It was stated that the release mechanism of the drug from the fibers was determined by combined diffusion mechanism and enzymatic degradation mechanism. MTT test procedure was employed to evaluate the antitumor activity of the DOX incorporated PEG-PLLA fibers against mice glioma cells (C6 cell lines). Findings exhibited that DOX could be released from the fibers without losing cytotoxicity [85].

Paclitaxel (PTX) and doxorubicin hydrochloride (DOX) are described as the two most common anticancer drugs in clinical use because of their powerful anticancer activity against various solid tumors. *Xu et.al.* reported the solubility properties and distribution status of two drugs in the emulsion electrospun fibers. It was observed that DOX was easily diffused out from fibers because of hydrophilicity, and it was released quicker than the hydrophobic PTX. Furthermore, it was found that the release rate of PTX was accelerated by DOX's release from the same drug-loaded fibers. Also, *in vitro* cytotoxicity tests resulted that dual drug combination showed a greater inhibition and apoptosis against Glioma C6 cells than a single drug-loaded system [86].

The high price of purified biological substances and the risk of denaturation during storage or scaffold formulation are additional limitations for their application in inductive tissue engineering scaffolds. Hence, controlled release of such molecules from nanofibrous scaffolds is an important approach. *Yang et.al.* used emulsion electrospinning to fabricate core–sheath structured fibers with a core loading of pDNA or pDNA polyplexes and a sheath of poly(DL-lactide)–poly(ethylene glycol) (PELA). Also, poly(ethylene imine) (PEI) and poly(ethylene glycol) (PEG) were added to the system to tailor the release profiles and to set a balance between cytotoxicity and transfection efficiency. It was observed that core-sheath fibers increased the structural integrity and maintain the biological activity of pDNA during the electrospinning process. The inclusion of hydrophilic PEI into the fiber matrix speeded up the pDNA release, however, no further release of pDNA after an initial burst was noted when the pDNA polyplexes encapsulated within the fibers. On the other hand, increase in the transfection efficiency and sustained release of pDNA polyplexes have been achieved through PEG incorporation [87].

Studies overally proved that emulsion electrospinning is a kind of useful funtionalization technique. Multicomponent release by adding different substances into nanofibers is possible. It seems that emulsion electrospinning will enable researchers to develope novel drug release materials.

3. Conclusion

There are tremendous efforts are being spent on the development of controlled drug delivery systems by researchers. The main motivation behind these efforts is to provide many advantages compared with the conventional dosage forms such as improving therapeutic efficacy, reducing toxicity by delivering the drugs at a controlled rate. In the recent decade, electrospinning has gained increasing interest for the preparation of drug loaded nanofibrous matrices for biomedical applications. This is understandable because electrospun nanofibrous structures have unique properties such as high specific surface area, high degree of porosity with a very small pore size and their resemblance to

extracelluar matrix. Furthermore, electrospun nanofibrous structures enable site-specific delivery of drugs to the body. Encapsulating more than one drug directly into the fibers, high drug loading capacity, high encapsulation efficiency, ease of operation and cost effectiveness also make electrospinning technique very attractive for researchers dealing with drug delivery systems. Drug loading of electrospun matrices for developing novel drug delivery systems can be achieved by several techniques including post-spinning modifications, electrospinning of drug/polymer blends or polymer/nanoparticle blends, co-axial electrospinning and emulsion electrospinning. Each technique has advantages as well as limitations. According to area of utilization one of these methods can be chosen to functionalize the electrospun nanofibers.

References

1. Erdem R and Akalın M. Characteriazation and evaluation of antimicrobial properties of electrospun chitosan/polyethylene oxide based nanofibrous scaffolds (with/without nanosilver). J Ind Text, 2015; 44(4): 553 – 571.
2. Li D and Xia Y. Electrospinning of Nanofibers: Reinventing the Wheel. Adv Mater, 2004; 16(14): 1151 – 1170.
3. Ma Z, Kotaki M, InaiR, and Ramakrishna S. Potential of Nanofiber Matrix as Tissue-engineering Scaffolds. Tissue Eng, 2005; 11(1–2): 101 – 109.
4. Min BM, Lee G, Kim SH, Nam YS, Lee TS, and Park WH. Electrospinning of silk fibroin nanofibers and its effect on the adhesion and spreading of normal human keratinocytes and fibroblasts in vitro. Biomater, 2004; 25(7–8): 1289 – 1297.
5. Matthews JA, Simpson DG, Wnek GE, and Bowlin GL. Electrospinning of collagen nanofibers. Biomacromolecules, 2002; 3(2): 232 – 238.
6. Li WJ, Laurencin CT, Caterson EJ,Tuan RS, and Ko FK. Electrospun nanofibrous structure: a novel scaffold for tissue engineering. J Biomed Mater Res, 2002; 60(4): 613 – 621.
7. Xu X, Chen X, Ma P, Wang X, and Jing X. The release behavior of doxorubicin hydrochloride from medicated fibers prepared by emulsion-electrospinning. Eur J Pharm Biopharm, 2008; 70: 165 – 170.
8. Martins A, Araujo JV, Reis RL, and Neves NM. Electrospun nanostructured scaffolds for tissue engineering applications. Nanomed, 2007; 2(6): 929 – 942.
9. Kenawy ER, Bowlin GL, Mansfield K, Layman J, Simpson DG, et.al. Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend.J Controlled Release, 2002; 81(1–2): 57 – 64.
10. Zong X, Kim K, Fang D, Ran S, Hsiao BS, et.al. Structure and process relationship of electrospun bioabsorbable nanofiber membranes. Polym, 2002; 43(16): 4403 – 4412.
11. Zeng J, Xu X, Chen X, Liang Q, Bian X, et.al. Biodegradable electrospun fibers for drug delivery. J Controlled Release, 2003; 92(3): 227 – 231.
12. Jiang H, Fang D, Hsiao BS, Chu B, Chen W. Optimization and characterization of dextran membranes prepared by electrospinning. Biomacromolecules, 2004; 5(2): 326 – 333.
13. Kenawy E-R, Abdel-Hay FI, El-Newehy MH, and Wnek GE. Controlled release of ketoprofen from electrospun poly (vinyl alcohol) nanofibers. Mater Sci Eng A, 2007; 459(1–2): 390 – 396.
14. Yan S, Xiaoqiang L, Shuiping L, Xiumei M, and Ramakrishna S. Controlled release of dual drugs from emulsion electrospun nanofibrous mats. Colloids Surf B, 2009; 73: 376 – 381.

15. Szentivanyi A, Chakradeo T, Zernetsch H, and Glasmacher B. Electrospun cellular microenvironments: understanding controlled release and scaffold structure. Adv Drug Delivery Rev, 2011; 63: 209 – 220.
16. Yoo H, Kim T, and Park T. Surface-functionalized electrospun nanofibers for tissue engineering and drug delivery. Adv Drug Delivery Rev, 2009; 61: 1033 – 1042.
17. Baker SC, Atkin N, Gunning PA, Granville N, Wilson K, et.al. Characterization of electrospun polystyrene scaffolds for three-dimensional in vitro biological studies. Biomater, 2006; 27: 3136 – 3146.
18. Park H, Lee KY, Lee SJ, Park KE, and Park WH. Plasma-treated poly(lactic-coglycolic acid) nanofibers for tissue engineering. Macromol Res, 2007; 15: 238 – 243.
19. Ma ZW, He W, Yong T, and Ramakrishna S. Grafting of gelatin on electrospun poly(caprolactone) nanofibers to improve endothelial cell spreading and proliferation and to control cell orientation. Tissue Eng, 2005; 11: 1149 – 1158.
20. Croll TI, O'Connor AJ, Stevens GW, and Cooper-White JJ. Controllable surface modification of poly(lactic-co-glycolic acid) (PLGA) by hydrolysis or aminolysis i: physical, chemical, and theoretical aspects. Biomacromolecules, 2004; 5: 463 – 473.
21. Nam YS, Yoon JJ, Lee JG, and Park TG. Adhesion behaviors of hepatocytes cultured onto biodegradable polymer surface modified by alkali hydrolysis process. J Biomater Sci Polym Ed, 1999; 10: 1145 – 1158.
22. Yuan XY, Mak AFT, and Yao KD. Surface degradation of poly(l-lactic acid) fibres in a concentrated alkaline solution. Polym Degrad Stab, 2003; 79: 45 – 52.
23. Sun H and Onneby S. Facile polyester surface functionalization via hydrolysis and cell-recognizing peptide attachment. Polym Int, 2006; 55: 1336 – 1340.
24. Zhu YB, Gao, CY, Liu XY, and Shen JC. Surface modification of polycaprolactone membrane via aminolysis and biomacromolecule immobilization for promoting cytocompatibility of human endothelial cells. Biomacromolecules, 2002; 3: 1312 – 1319.
25. Zhu YB, Leong MF, Ong WF, Chan-Park MB, and Chian KS. esophageal epithelium regeneration on fibronectin grafted poly(l-lactide-co-caprolactone) (PLLC) nanofiber scaffold. Biomater, 2007; 28: 861 – 868.
26. Turmanova S, Minchev M, Vassilev K, and Danev G. Surface grafting polymerization of vinyl monomers on poly(tetrafluoroethylene) films by plasma treatment. J Polym Res, 2008; 15: 309 – 318.
27. Ma ZW, Kotaki M, Yong T, He W, and Ramakrishna S. Surface engineering of electrospun polyethylene terephthalate (PET) nanofibers towards development of a new material for blood vessel engineering. Biomater, 2005; 26: 2527 –2536.
28. Yao C, Li XS, Neoh KG, Shi, ZL, and Kang ET. Surface modification and antibacterial activity of electrospun polyurethane fibrous membranes with quaternary ammonium moieties. J Membr Sci, 2008; 320: 259 – 267.
29. Bolgen N, Vargel I, Korkusuz P, Menceloglu YZ, and Piskin E. In vivo performance of antibiotic embedded electrospun pcl membranes for prevention of abdominal adhesions. Journal of Biomedical Materials Research B Applied Biomaterials, 2007; 81: 530 – 543.
30. Meinel AJ, Germershaus O, Luhmann T, Merkle HP, and Meinel L. Electrospun matrices for localized drug delivery: current technologies and selected biomedical applications. Eur. J. Pharm Biopharm, 2012; 81: 1 – 13.
31. Zhang H, Lou S, Williams GR, Branford-White C, Nie H, et.al. A systematic study of captopril-loaded polyester fiber mats prepared by electrospinning. Int J Pharm, 2012; 439: 100 – 108.

32. Chen HM and Yu DG. An elevated temperature electrospinning process for preparing acyclovir-loaded PAN ultrafine fibers. J Mater Process Technol, 2010; 210: 1551 – 1555.
33. Toncheva A, Paneva D, Maximova V, Manolova N, Rashkov I.Antibacterial fluoroquinolone antibiotic-containing fibrous materials from poly(L-lactide-co-D,L-lactide) prepared by electrospinning. Eur J Pharm Sci, 2012; 47: 642 – 651.
34. Huang C, Soenen SJ, Gulck E, Vanham G, Rejman J, et.al. Electrospun cellulose acetate phthalate fibers for semen induced anti-HIV vaginal drug delivery, Biomater, 2012; 33: 962 – 969.
35. Kim K, Luu YK, Changa C, Fang D, Hsiao BS, et.al. Incorporation and controlled release of a hydrophilic antibiotic using poly(lactide-co- glycolide)-based electrospun nanofibrous scaffolds. J Controlled Release, 2004; 98: 47 – 56.
36. Karuppuswamy P, Venugopal J R, Navaneethan B, Laiva A L, and Ramakrishna S. Polycaprolactone nanofibers for the controlled release of tetracycline hydrochloride, Mater Lett 2015; 141: 180 – 186.
37. Luu YK, Kim K, Hsiao BS, Chu B, and Hadjiargyrou M. Development of a nanostructured DNA delivery scaffold via electrospinning of PLGA and PLA–PEG block copolymers. J Controlled Release, 2003; 89: 341 – 353.
38. Yohe ST, Herrera VLM, Colson YL, and Grinstaff MW. 3D superhydrophobic electrospun meshes as reinforcement materials for sustained local drug delivery against colorectal cancer cells. J Controlled Release, 2012; 162: 92 – 101.
39. Huang S, Kang X, Cheng Z, Ma P, Ye Jia Y, et.al. Electrospinning preparation and drug delivery properties of Eu3+/Tb3+ doped mesoporous bioactive glass nanofibers. J. Colloid Interface Sci, 2012; 387: 285 – 291.
40. Quan J, Yu Y, Branford-White C, Williams GR, Yu D-G, et.al. Preparation of ultrafine fast-dissolving feruloyl-oleyl-glycerol-loaded Polyvinylpyrrolidone fiber mats via electrospinning. Colloids Surf B, 2011; 88: 304 – 309.
41. Li X, Kanjwala MA, Lind L, and Chronakis IS. Electrospun Polyvinyl-alcohol nanofibers as oral fast-dissolving delivery system of caffeine and riboflavin. Colloids Surf B, 2013; 103: 182 – 188.
42. Shena X, Yu D, Zhu L, Branford-White C, White K, et.al. Electrospun diclofenac sodium loaded Eudragit® L 100-55 nanofibers for colon-targeted drug delivery. Int J Pharm, 2011; 408: 200 – 207.
43. Xu J, Jiao Y, Shao X, and Zhou C. Controlled dual release of hydrophobic and hydrophilic drugs from electrospun poly (l-lactic acid) fiber mats loaded with chitosan microspheres. Mater Lett, 2011; 65: 2800 – 2803.
44. Okuda T, Tominaga K, and Kidoaki S. Time-programmed dual release formulation by multilayered drug-loaded nanofiber meshes. J Controlled Release, 2010; 143: 258 – 264.
45. Song B, Wu B, and Chang J. Dual drug release from electrospun poly(lactic-co-glycolic acid)/mesoporous silica nanoparticles composite mats with distinct release profiles. Acta Biomater, 2012; 8: 1901 – 1907.
46. Vrbata P, Berka P, Stránská D, Doleˇzal P, Musilová M, et.al. Electrospun drug loaded membranes for sublingual administration of sumatriptan and naproxen. Int J Pharm, 2013; 457: 168 – 176.
47. Yun J, Im JS, Lee Y-S, and Kim HI. Electro-responsive transdermal drug delivery behavior of PVA/PAA/MWCNT nanofibers. Eur Polym J, 2011; 47: 1893 – 1902.
48. Choi Y, Nirmala R, Lee JY, Rahman M, Hong S-T, et.al. Antibacterial ciprofloxacin HCl incorporated polyurethane composite nanofibers via electrospinning for biomedical applications. Ceram Int, 2013; 39: 4937 – 4944.
49. Zeng J, Aigner A, Czubayko F, Kissel T, Wendorff JH, et.al. Poly(vinyl alcohol) nanofibers by electrospinning as a protein delivery system and the retardation

of enzyme release by additional polymer coatings. Biomacromolecules, 2005; 6: 1484 – 1488.
50. Szentivanyi A, Assmann U, Schuster R, and Glasmacher B. Production of biohybrid protein/PEO scaffolds by electrospinning. Materialwiss Werkstofftech, 2009; 40: 65 – 72.
51. Sun XY, Nobles LR, Borner HG, and Spontak RJ. Field-driven surface segregation of biofunctional species on electrospun PMMA/PEO microfibers. Macromol Rapid Commun, 2008; 29: 1455 – 1460.
52. Im JS, Yun J, Lim YM, Kim HI, and Lee YS. Fluorination of electrospun hydrogel fibers for a controlled release drug delivery system. Acta Biomater, 2010; 6: 102 – 109.
53. Chakraborty S, Liao I-C, Adler A, and Leong KW. Electrohydrodynamics: A Facile technique to fabricate drug delivery systems. Adv. Drug Delivery Rev, 2009; 61: 1043 – 1054.
54. Castillo-Ortega MM, Montaño-Figueroa AG, Rodríguez-Félix DE, Munive GT, and Herrera-Franco PJ. Amoxicillin embedded in cellulose acetate-poly (vinyl pyrrolidone) fibers prepared by coaxial electrospinning: preparation and characterization, Mater Lett, 2012; 76: 250 – 254.
55. Nguyen TTT, Chiranjit Ghosh C, Hwang SG, Chanunpanich N, and Park JS. Porous core/sheath composite nanofibers fabricated by coaxial electrospinning as a potential mat for drug release system. Int J Pharm, 2012; 439: 296 – 306.
56. Yu DG, Wang X, Li XY, Chian W, Li Y, and Liao YZ. Electrospun biphasic drug release polyvinylpyrrolidone/ethyl cellulose core/sheath nanofibers. Acta Biomater, 2013; 9: 5665 – 5672.
57. Jiang H, Hu Y, Li Y, Zhao P, Zhu K, and Chen W. A Facile Technique to Prepare Biodegradable Coaxial Electrospun Nanofibers for Controlled Release of Bioactive Agents. J Controlled Release, 2005; 108: 237 – 243.
58. Sohrabi A, Shaibani PM, Etayash H, Kaur K, Thundat T. Sustained drug release and antibacterial activity of ampicillin incorporated poly(methyl methacrylate)-nylon6 Core/shell nanofibers. Polym, 2013; 54: 2699 – 2705.
59. Jin G, Prabhakaran MP, Kai D, and Ramakrishna S. Controlled release of multiple epidermal induction factors through core–shell nanofibers for skin regeneration. Eur J Pharm Biopharm, 2013, In Press.
60. Korehei R and Kadla JF. Encapsulation of T4 bacteriophage in electrospun poly(ethylene oxide)/cellulose diacetate fibers. Carbohydrate Polymers, 2014; 100: 150 – 157.
61. Tiwari SK, Tzezan R, Zussman E, and Venkatraman SS. Optimizing partition-controlled drug release from electrospun core–shell fibers. Int J Pharm, 2010; 392: 209 – 217.
62. Nie H and Wang C-H. Fabrication and Characterization of PLGA/Hap composite scaffolds for delivery of BMP-2 plasmid DNA. J Controlled Release, 2007; 120: 111 – 121.
63. Valmikinathan CM, Defroda S, and Yu X. Polycaprolactone and bovine serum albumin based nanofibers for controlled release of nevre growth factor. Biomacromolecules, 2009; 10(5): 1084 – 1089.
64. Dror Y, Kuhn J, Avrahami R, and Zussman E. Encapsulation of enzymes in biodegradable tubular structure. Macromol, 2008; 41(12): 4187 – 4192.
65. Yang Y, Li X, Qi M, Zhou S, and Weng J.Release pattern and structural integrity of lysozyme encapsulated in core–sheath structured Poly (DL-lactide) ultrafine fibers prepared by emulsion electrospinning. Eur J Pharm Biopharm, 2008; 69: 106 – 116.

66. Jiang H, Hu Y, Li Y, Zhao P, Zhu K, et.al. A Facile technique to prepare biodegradable coaxial electrospun nanofibers for controlled release of bioactive agents. J Controlled Release, 2005; 108: 237 – 243.
67. Moreno I, González-González V, and Romero-García J. Control release of lactate dehydrogenase encapsulated in poly (vinyl alcohol) nanofibers via electrospinning. Eur Polym J, 2011; 47: 1264 – 1272.
68. Saraf A, Baggett LS, Raphael RM, Kasper FK, and Mikos AG. Regulated non-viral gene delivery from coaxial electrospun fiber mesh scaffolds. J Controlled Release, 2010; 143: 95 – 103.
69. Su Y, Su Q, Liu W, Lim M, Venugopal JR, et.al. Controlled release of bone morphogenetic protein 2 and dexamethasone loaded in core–shell PLLACL–collagen fibers for use in bone tissue engineering. Acta Biomater, 2012; 8: 763 – 771.
70. Yan S, Xiaoqiang Li, Lianjiang T, Chen H, and Xiumei M. Poly(L-lactide-co-3-caprolactone) electrospun nanofibers for encapsulating and sustained releasing proteins. Polym, 2009; 50: 4212 – 4219.
71. Yu DG, Chatterton NP, Yang JH, Wang X, and Liao YZ. Coaxial electrospinning with triton X-100 solutions as sheath fluids for preparing PAN nanofibers. Macromol Mater Eng, 2012; 297: 395 – 401.
72. Yu DG, Williams GR, Gao LD, Bligh SWA, Yang JH, et.al. coaxial electrospinning with sodium dodecylbenzene sulfonate solution for high quality Polyacrylonitrile nanofibers. Colloids Surf A, 2012; 396: 161 – 168.
73. Yang JM, Zha LS, Yu DG, and Liu J. Coaxial electrospinning with acetic acid for preparing ferulic acid/zein composite fibers with improved drug release profiles. Colloids and Surf B, 2013; 102: 737 – 743.
74. Yun D-G, Chian W, Wangn X, Li X-Y, Li Y, et.al. Linear drug release membrane prepared by a modified coaxial electrospinning process. J Membr Sci, 2013; 428: 150 – 156.
75. Jiang H, Wang L, and Zhu K. Coaxial electrospinning for encapsulation and controlled release of fragile water-soluble bioactive agents. J Control Release, 2014; 193: 296 – 303.
76. Xiaoqiang L, Yana S, Shuipinga L, Lianjianga T, Xiumei M, and Ramakrishna S. encapsulation of proteins in poly(l-lactide-co-caprolactone) fibers by emulsion electrospinning. Colloids Surf B, 2010; 75: 418 – 424.
77. Qi H, Hu P, Xu J, and Wang A. Encapsulation of Drug Reservoirs in Fibers by Emulsion Electrospinning: Morphology Characterization and Preliminary Release Assessment. Biomacromol, 2006; 7: 2327 – 2330.
78. Yang Y, Li X, Qi M, Zhou S, and Weng J. Release pattern and structural integrity of lysozyme encapsulated in core-sheath structured poly(DL-lactide) ultrafine fibers prepared by emulsion electrospinning. Eur J Pharm Biopharm, 2008; 69(1): 106 – 116.
79. Xu XL, Yang L, Xu XY, Wang X, Chen X, et.al. Ultrafine medicated fibers electrospun from w/o emulsions. J Controlled Release, 2005; 108: 33 – 42.
80. Sy JC, Klemm AS, and Shastri VP. Emulsion as a means of controlling electrospinning of polymers. Adv Mater, 2009; 21(8): 1814.
81. Venugopal G, Krause S, and Wnek GE. Morphological variations in polymer blends made in electric-fields. Chem Mater, 1992; 4: 1334 – 1343.
82. Maretschek S, Andreas Greiner A, and Kissel T. Electrospun biodegradable nanofiber nonwovens for controlled release of proteins. J Controlled Release, 2008; 127: 180 – 187.
83. Luo X, Xie C, Wang H, Liu C, Yan S, et.al. Antitumor activities of emulsion electrospun fibers with core loading of hydroxycamptothecin via intratumoral implantation. Int J Pharm, 2012; 425: 19 – 28.

84. Zhang H, Zhao Y, Han F, Wang M, and Yuan X. Controlled release of bovine serum albumin from electrospun fibrous membranes via an improved emulsion-core technique. J Controlled Release, 2011; 152: 133 – 191.
85. Xu X, Yang L, Xu X, Wang X, Chen X, et.al. Ultrafine medicated fibers electrospun from W/O emulsions. J Controlled Release, 2005; 108: 33 – 42.
86. Xu X, Chen X, Wang Z, and Jing X. Ultrafine PEG–PLA fibers loaded with paclitaxel and doxorubicin hydrochloride and their in vitro cytotoxicity. Eur J of Pharm and Biopharm, 2009; 72: 18 – 25.
87. Yang Y, Li X, Cheng L, He S, Zou J, et.al. Core– sheath structured fibers with pDNA Polyplex loadings for the optimal release profile and transfection efficiency as potential tissue engineering scaffolds. Acta Biomater, 2011; 7: 2533 – 2543.