Emerging frontiers in drug release control by core–shell nanofibers: a review

Mohammad Monfareda,b, Saeed Taghizadehc, Alireza Zare-Hoseinabadi, Seyyed Mojtaba Mousavi,a, Seyyed Ali Reza Hashemia, Saba Ranjbar d and Ali Mohammad Amani a

aDepartment of Medical Nanotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran; bStudent Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran; cDepartment of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran; dDepartment of Chemical Engineering and Materials Science, University of California, Irvine, CA, USA

ABSTRACT
In recent years, core–shell (CS) nanofiber has widely been used as a carrier for controlled drug release. This outstanding attention toward CS nanofiber is mainly due to its tremendous significance in controllable drug release in specific locations. The major advantage of CS nanofibers is forming a highly porous mesh, boosting its performance for many applications, due to its large surface-to-volume ratio. This inherently high ratio has prompted electrospun fibers to be considered one of the best drug-delivery-systems available, with the capacity to enhance properties such as cell attachment, drug loading, and mass transfer. Using electrospun fibers as CS nanofibers to incorporate different cargos such as antibiotics, anticancer agents, proteins, DNA, RNA, living cells, and diverse growth factors would considerably satisfy the need for a universal carrier in the field of nanotechnology. In addition to their high surface area, other benefit included in these nanofibers is the ability to trap drugs, easily controlled morphology, and their biomimetic characteristics. In this review, by taking the best advantages of the preparation and uses of CS nanofibers, a novel work in the domain of the controlled drug delivery by nanofiber-based scaffolds is presented.

ARTICLE HISTORY
Received 22 April 2019
Accepted 9 July 2019

KEYWORDS
Core–shell; electrospinning; nanofibers; controlled drug release

1. Introduction

In recent years, electrospun fibrous scaffolds-based drugs were widely studied to achieve controllable drug release and loading via practical production procedures (Nadri et al. 2017; Seon-Lutz et al. 2019; Xiang et al. 2019; Zargarian et al. 2019). Most recently, the controlled drug release by the electrospinning technology has broadened its application to load lipid-soluble (Li et al. 2015), water-soluble (Gu and Xu 2008; Kusamoto and Tajima 2008), and/or insoluble drugs (Lee and Kay Obendorf 2006) with other effective nanoparticles (Gorji et al. 2012). Of these, the most common type of drug delivery efforts is the water-solubilizing method due to their fantastic hydrophilicity and perfect absorption rate in vivo (Kowalczyk et al. 2008; Rojas and Pinto 2008). Due to their highly soluble nature, the human body can easily metabolize and absorb them through dissolution and diffusion processes.

Electrospinning is a newly established technique in drug delivery which can generate thin fibers with low diameters ranging from nanometers to micrometers. Moreover, the prosperous usage of electrostatic forces for fabrication of fibers dates back to 1930s (Anton 1934) when it was applied in various engineering areas such as filtration (Gopal et al. 2006; Aussawasathien et al. 2008; Nadri et al. 2017), development of masking and fabrics (Lee and Kay Obendorf 2006; Gu and Xu 2008; Kusamoto and Tajima 2008; Gorji et al. 2012), development of biosensors (Kowalczyk et al. 2008; Rojas and Pinto 2008), and energy-based applications (Dong et al. 2011). Electrospinning principles which manifest in fiber size distribution and processing, variables of solutions and structural and mechanical properties have been greatly pondered by researchers from all over the world (Subbiah et al. 2005; Pham et al. 2006; Hu et al. 2014).

Some novel reviews regarding in the scale-up processes of electrospinning and their usages in drug delivery and tissue engineering have written in order to update current understanding of scientific community about mentioned principles and information (Khil et al. 2003; Sill and von Recum 2008; Yoo et al. 2009;
To date, there have been many successes in applying this drug delivery approach. Descriptively, merits of applying electrospun fibers for drug delivery applications are due to several reasons: (a) the high ratio of drug loading (up to 60%) and encapsulation efficiency (up to 100%) (Ball and Woodrow 2014b; Blakney et al. 2014; Krogstad and Woodrow 2014), (b) the polymer diversity provided from different kinds of people or things to enhance the compatibility of physio-chemically distinct agents (Ball et al. 2012; Blakney et al. 2013), (c) the high performance for adjusting the drug release (Sundararaj et al. 2013; Falde et al. 2015), and (d) the simplicity of related process and their cost affordability (Ball and Woodrow 2014a).

1.1. Nanofibers produced via electrospinning

Although applying electrospinning as the primary technique to produce nanofibers dates back to the 1990s, Anton Formhals is known as the pioneer of the electrostatic force usage. He published his series of studies from 1934 to 1944, which focused on producing micrometer diameter fibers (Anton 1934). Shao et al. worked on the electrospinning process of polycrylonitrile (PAN) nanofibers which were used as substrates. Via the sol–gel technique, zinc oxide was deposited on top of the fiber membranes and a high-voltage power supply was needed to provide an electric-field for electrospinning. To continue the mechanism and flow the polymer solution or the polymer melt, single spinneret, or multi-spinnerets, was utilized. The desired fiber assemblies determined various designs of different collectors. Elaborately speaking, Figure 1 represents an electrospinning setup (Park et al. 2008). Electrospinning is one of the fastest methods for the production of fibers with diameters ranging from 1 to 2000 nm. Nevertheless, there would be a problem with the temperature since some widely used polymers like polyethylene (PE) and polypropylene (PP) are not able to undergo spinning at room temperature (Pavliková et al. 2003). Therefore, melting electrospinning is chosen. Flow rate optimization is a challenge to be tackled by anybody and everybody. This all depends upon polymer system variation. Moreover, undesired large diameters and bead formation are prone to be formed by the high voltage of electrospinning. Generally, the choice of polymer system used in nanofiber formation process is limited by electrospinning (Benavides et al. 2012).

1.2. Performance of electrospinning process

Overall, an electrospinning setup can be considered simple and includes several key components. Among these are the spinneret, the collector, and a high voltage power supply. However, the spinning mechanism can be somehow complicated owing to the complexity of electro-fluid mechanical issue. The controllable and constant flow rate of polymeric suspension is obtained by electrospinning in the presence of a 1–30 kV voltage.

Figure 2 shows the electrified solution which has been allowed to fall through the spinneret’s nozzle and the induced charges were evenly distributed throughout the device. By electrostatic interactions, the outcome is changed into the form of a conic object which is called ‘Taylor cone’ (Frenot and Chronakis 2003; Huang et al. 2003). Logically, there is a threshold value, which indicates that if the overall electrostatic force that exists between the Taylor cone’s surface charges and the external electric field violate this value, the surface tension of the polymeric suspension is wiped out by the electrostatic force; thus, the final suspension is ejected continuously from the nozzle in the form of a liquid jet. Then, the grounded collectors situated beneath the spinneret attract the electrified jet and as the solvent is evaporated, the surface of the collectors is covered with the deposited solid-polymeric fibers which are the nonwoven mat.

Concerning the formation of the ultrathin fibers, there is a hypothesis asserting that the surface charges repel each other and it could make the electrified jet into the splay, which can lead to the creation of thin fibers with roughly similar diameter and equal charge. Based on this hypothesis, the number of created splays determines the final size and diameter of the electrospun fibers (Reneker and Chun 1996).

Experimentally speaking, a single and rapidly whipping jet which appears to splay, plays the role of the thinning and electrified jet (Shin et al. 2001). At high

![Figure 1. Scheme of electrospinning process.](image-url)
field’s strength, the jet becomes unstable after traveling a short distance and starts whiplashing fast and repeatedly, while encountering bowing and stretching. A bulk of applied studies are now manifesting rather than splaying, and the electrospinning mechanism encompasses a whipping jet (Hohman et al. 2001). It has been demonstrated that the electrospinning instability is due to the interaction between the external electric field and the jet’s surface charges. Meanwhile, electrospinning fibers’ diameter is based on the fluid filament stretching, traveling speed, and then the solidification or deposition of them on the collector respectively.

1.3. Performance of electrospinning in controlling drug release

Electrospinning has platform versatility; therefore, many attentions are paid to the role of electrospin materials in filling clinical gaps associated with bacterial and viral infections treatment and prevention. The major goal of performing these studies is to develop long-acting drug formulations to overcome problems of adherence and emerging drug resistance. Nevertheless, in order to enhance the performance of medicines, high and frequent dosing is needed which due to their low inherent drug loading potential. This is due to their low intrinsic potency and short half-lives, especially when manipulated in vivo (Owens and Shorr 2009). To clarify this point, common antibiotics that are prescribed to wipe out bacterial infections can be exemplified. Indeed, they are dosed at a minimum of hundreds of milligrams per day for several weeks. Similar dosing regimens of market available antiretroviral drugs are prescribed to treat or prevent HIV as well (Spreen et al. 2013). In this study, the authors’ aim is elaborately manifesting current strategies in which electrospun fibers are utilized for sustaining drug release. These kinds of applications, with high drug dosages, are essential and beneficial for clinical efficacy. In other words, small molecule drugs that are hydrophilic in nature could be loaded on the surface of fibers in order to meet the demand of medical society for essential treatments.

2. Core–shell nanofibers

Multicomponent nanofibers have priority over conventional single component nanofibers since they are prone to bear novel properties derived from a combination of various components. Consequently, they have recently been under study. Core–shell (CS) nanofibers, as an example of multicomponent nanofibers, let non-fabricated or non-easily spinnable materials spin with a spinnable sheath surrounding them. Among CS mechanical and electrical structure priorities, functional improvements can be mentioned when comparing single component fibers. CS nanofibers are produced by coaxial dual nozzle and emulsion electrospinning methods. Descriptively, the coaxial electrospinning technology is
labeled by CS fibers electrospinning (Ziabicki 1976) and CS glass fibers fabrication (Yarin 1995).

2.1. Core–shell nanofibers morphology and alignment definitions

The deposited nanofibers typically assume a completely isotropic orientation provided via electrospinning. Notwithstanding, it is acceptable to control the alignment of the fibers for many applications since aligned nanofibers are able to improve cell attachment and proliferation. To introduce alignment into the deposited nanofibers, the fibers must be collected on a rotating drum with proper rotation speed for the extremely high-speed whipping motion which occurred due to bending instability. The alignment degree attained by performing this method is limited though (Zhang and Chang 2008). Moreover, this technique can lead to the development of fabric containing highly oriented nanofibers in different directions (Li et al. 2003; Li, Wang, et al. 2004; Li et al. 2005; Wang et al. 2010). Besides, the effect of rotating rate of motion on aligned nanofibers was studied in a work by Mathew et al. (2006). Unwoven deposited fibers on the collector’s surface will remain unchanged when the collector’s rotation speed is low. However, aligned nanofibers are rapidly forming due to the increase in the rotation speed and one of the ideal rotation speeds is defined around 4000 rpm. Aligned nanofibers which are similar to extracellular matrix (ECM), smooth muscle units, neurons, etc., have some nano-topographical cues. For example, nerve growth pipes as electric wires (NGC) which were fabricated by Wang et al. have shown fantastic performance as highly aligned middle part, heart wall, and outer structure nanofibers in mending damaged nerves (Wang et al. 2012). In fact, fabrication of highly oriented middle part, heart wall, and outer structure nanofibers have provided the mend possibility of damaged nerves and thus their growth around aligned nanofibers. Similarly, aligned middle part, heart wall, and outer structure provide fantastic possibilities for nerve regeneration. A view of this process can be seen in Figure 3.

Figure 3. (a) The aligned core–shell nanofibers (SEM) and TEM images. (b) The rats nerve regeneration is achieved by Surgical implantation of the aligned core–shell fibers as 13-mm nerve Defect Bridge. (c) The nerve contour after 12 weeks. (d) Regenerated nerve without any aligned core–shell fibers. (Reprinted under the permission of Li et al. (2006) Copyright (2012) Taylor & Francis).
In another work by Liao et al., they have developed CS nanofibers which polycaprolactone (PCL) was used as the shell, while platelet-derived growth factor (PDFG) or bovine serum albumin (BSA) was used as the core (Liao et al. 2006). Besides, nanofibers have been produced with a high overall drug loading rate and perfect sustain release of bioactive PDFG. In order to form porous electrospun threads, there are some different methods like applying low boiling point (39.6°C) and dichloromethane dissolved polymers such as poly(L-lactide) (PLLA) (Bognitzki et al. 2001; Asli et al. 2012). Porous threads formation is in part owing to quick evaporation of solvent and then solidification of polymer (Megelski et al. 2002). A highly porous core–sheath thread network is made by Gulfam et al. with co-electrospinning method in increased humidity and immersed water (Figure 2) (Gulfam et al. 2011). In fact, the phase separation could form breathing-holes and serve as a frame structure. Co-electrospinning which can get hollow, unbroken stretched, and nanoscale threads, as a template-directed view, is just applicatory for short length threads. Concerning co-electrospinning, hollow nanofibers were first made by Li and Xia (2004) with a mineral oil liquid and Ti(OiPr)4/PVP in ethanol serving as the core and the sheath solution, respectively. The mineral oil has been obtained by putting the threads in octane for some hours. Additionally, by calcining the fibers at 500°C air, the uniform hollow threads were obtained. Hollow nanofibers were traceable by TEM images. This could make researchers able to produce many ceramic hollow nanofibers just by replacing Ti(OiPr)4 with other precursors. The work done by Gu et al. who could make hollow LiNi0.8Co0.1O2-MgO CS threads is an example of this production (Gu and Jian 2008). In some drug-encapsulated CS fibers, which a water-soluble medical substance is used as the core, complete release has been observed and so a hollow structure is formed by solid CS nanofiber (Man et al. 2014). Though, in these fiber-based structures biomedical applications are rare (Chen et al. 2010; Bonino et al. 2012). CS electrospun nanofibers are produced by the techniques such as, the co-electrospinning (Loscertales et al. 2002; Sun et al. 2003), emulsion electrospinning (Xu et al. 2006; Yang et al. 2011), deposition method (Peng et al. 2007; Kayaci et al. 2012), electrostatic force induction method (Li et al. 2006), phase separation method (Li et al. 2007; Pant et al. 2013), etc.

2.2. Fabrication process of core–shell nanofiber

For fabrication of CS nanofibers, two practical techniques including co-axial electrospinning and emulsion electrospinning have been widely used. In this case, a brief explanation of the aforementioned methods can be seen in the following sections.

2.2.1. Co-axial core-shell nanofibers

Co-axial CS nanofiber formation is almost the same as usual formation of CS fibers but the smaller inner capillary is concentrically inserted in the bigger outer capillary in the spinneret (Figure 3). The sheath solution is in the outer needle, which is attached to the reservoir, and so the core solution is held by the inner needle. Figures 4 and 5 are showing the horizontal and vertical arrangement, respectively:

Either metering pumps or air pressures can be used to control the solutions feeding rates (Sun et al. 2003; Yu et al. 2004). In the vertical arrangement, exposing the sheath solution to the atmospheric pressure and allowing gravity-based flow is used in other studies (Huang et al. 2005; Elahi et al. 2013). Although the
currently used setups are simple and straightforward, a slightly different set up has been used by Wang et al. who precludes the required insertion of one capillary into the other (Wang, Jing, et al. 2006). Two different sized capillaries’ with separate syringes are used in this setup though the smaller capillary is introduced into the Taylor cone from outside which is formed at the output of the bigger capillary (Figure 6). The single jet electrospinning is considered similar to the co-axial electrospinning. By utilizing high voltage, the polymer solutions are charged such that the charge mainly accumulates on the sheath liquid surface that comes out from the outer co-axial capillary (Greiner et al. 2006). A conical shape is formed by elongating and stretching the sheath solution droplet after the charge-charge repulsion. This forming continues till a fine jet emerges from the cone. Sheath solution’s stress can cause the core solution sheared by generating viscous dragging and contact friction (Li and Xia 2004). Therefore, the conical shape is formed as a deforming reaction of the core liquid and a combined co-axial jet grows at the tip of the cones as depicted in Figure 7.

If the compound cone is stable, the core is uniformly incorporated into the sheath for core–sheath fiber formation. During the single fluid electrospinning, the bending unstableness made the jet have a whipping trajectory; consequently, the CS nanofibers are formed by evaporating both solvents of polymers’ solutions in egressed jet (Sun et al. 2003). It is noted that in the co-axial electrospinning, the core material is surrounded by the sheath solution which acts as a guide. There is a tension between the solutions brought on by viscous stress of the core and sheath’s interfacial surface which lets the compound Taylor cone and the jet form (Diaz et al. 2006). Yu et al. argues that the sheath prevents the jet break-up of the core fluid in two ways: the work hardening of the sheath and the core polymers; and the lesser forces between core and shell, which is able to be higher if the core contact was with the air or if the core fluid was electrospun inherently (Yu et al. 2004). Despite what was mentioned if the core viscosity was too low (He et al. 2006), the core jet break-up was still observed. However, it must be taken into account that the core fluid needs to have a particular minimum viscosity in case that the jet does not split up. In the following figure, conventional single fluid electrospinning is depicted and also the solution concentration enhancement is shown. The fiber diameter is increased when more material exists in the jet. Zhang et al. observed the same effect in co-axial electrospinning while experimenting with the core solution concentration by considering the fact that the more the core diameter increases, the more the thickness of the sheath should decrease (Zhang et al. 2004). This equation is satisfied as a logical result of the sheath with the same mass distributed over a larger core (Figure 8).

Figure 6. The co-axial electrospinning alternative set-up, (A) represents bigger capillary which carries sheath solution, (B) sheath solution’s Taylor cone, (C) depicts smaller capillary which holds core solution, (D) core solution’s Taylor cone formed co-axially inside the sheath’s Taylor cone, (E) Co-axial jet (From an open-access article distributed under the terms of the Creative Commons Attribution License. Copyright: © 2013 Elahi et al. (2013)).

Figure 7. Compound Taylor cone formation: (A) shows surface charges on the sheath solution, (B) shows deformed sheath droplet which exert the viscous drag, (C) represents Sheath–core compound Taylor cone made by continuous viscous drag (From an open-access article distributed under the terms of the Creative Commons Attribution License. Copyright: © 2013 Elahi et al. (2013)).
first, when the solutions meet at the tip of the capillary, the solvent existing in solutions must not precipitate the polymer from the other solution. Second, the sheath and the core interfacial tension must be kept as low as possible to form the stabilized compound Taylor cone. Besides, regarding the solvent vapor pressure, it is essential to know that the morphology of the core—sheath structure is greatly affected by the solvent type of the core solution. This is illustrated by a work done by Li, Babel, et al. (2004) in which it was observed that the high vapor pressure solvent used in the core solution, was immediately evaporated (e.g. acetone, chloroform, etc.), forming a thin layer at the sheath and the core interface. After turning into a solidified structure, the mentioned layer created a vacuum that, under the atmospheric pressure, made the core structure collapsed from a round to ribbon-like configuration. If the core solution components include chloroform dissolved conjugated polymer, the sheath can be removed and ribbon-shaped fibers are obtained. Besides, the same result made the pillars of the present paper researchers’ finding concerning this point that by using chloroform as a solvent for the core polymer, a collapsed structure is formed (Figure 11) (Moghe et al. 2005).

![Figure 8. The sheath thickness schematic affected by the core diameter: (A) represents smaller core diameter and larger sheath thickness whereas (B) depicts the larger core diameter and smaller sheath thickness.](image)

![Figure 9. FIB images of PP/PLA core–shell fibers: (A) PLA core/PP shell with PLA: PP mass ratio of 50:50. PP core/PLA shell with PP: PLA mass ratios of (B) 15:85, (C) 50:50 and (D) 90:10. Fibers at an aspirator pressure of 25 psi.](image)
Descriptively, the used sheath solution was water dissolved poly (vinyl alcohol) with the core of chloroform dissolved poly (ethylene oxide). Sometimes there is a possibility that high vapor pressure solvents were put aside in using sheath solution. The reason justifying this is that they may produce unstable Taylor cones and lead to multiple jets due to a fast evaporation (Larsen et al. 2004). But why has this happened? The reason is clear, because the co-axial electrospinning requires a stable compound Taylor cone with an initial jet to operate.

Moreover, it is highly paramount to know that it is the conductivity of the solution that determines the quality of electrospun fibers. Indeed, highly conductive solutions characterized by high surface charges density, owing to the self-repulsion of the excess charges under a given electrical field, the charges density makes the elongation force increase on the jet. Such effort is aimed to have fibers with smaller diameters by enhancing the whipping action (Fong et al. 1999; Hohman et al. 2001).

Regarding the notion of applied voltage on the co-axial electrospinning, literature bears Li and Xia (2004) who suggested liquids with low electrical conductivities are liable to be stretched and form thin filaments by co-electrospinning with another spinnable solution. Traditionally, these liquids were put aside to be used in electrospinning. However, this study showed that materials can undergo electrospinning and form long, uniform nanofibers with solid or hollow interiors. In the study conducted by Moghe et al. it is argued that a stable compound Taylor cone was formed by a polymeric solution while a small range of voltage was applied (Moghe et al. 2005) (Figure 10 (right)). Voltage below the critical range has negative side effects like making solutions drip followed by an intermittent jet from the sheath (Figure 10 (left)) with an occasional incorporation of the core. On the other hand, voltages higher than the critical range make the electric field strong enough to pass. In this situation, Taylor cones and jets showed different behaviors such that the former is prone to retreat and the latter is prone to emerge as the inner part of the capillaries, which are the cause of separate jets forming at the nozzle’s tip (Figures 12(C) and 13) without forming the core–sheath fibers. Actually, the result of such a process is a high variability structure called fiber diameters (Figure 14) indicating differing fiber configuration. More data have proved this fact in literature like, Dietzel et al. who noted that in a single fluid spinning, the Taylor cone receded inside the capillary (Deitzel et al. 2001).
Furthermore, the increase in the core liquid Taylor cone depends on the high core flow rate. In case that this rate is too high, Taylor cone size increases and makes the viscous drag applied by the sheath solution inadequate in restricting the core solution within the cone such that the inner cone loses its outer liquid layer, the sheath cannot enclose the core uniformly while it is moving fast so it makes the overall process unstable (Zhang 2003; Wang, Jing, et al. 2006; Wang, Yu, et al. 2006). To get rid of these problems, generally the core and the sheath flow rate ought to be commensurate.

2.2.2. Emulsion core–shell fibers

In comparison with the normal solution electrospinning, emulsion electrospinning is just the solution being replaced by an emulsion in the former and it generates jets which stretch into ultrafine fibers. Noticeable, the core of the electrospun fibers is made of the dispersed drop in the emulsion and the shell is formed by the continuous matrix. Another form of emulsion electrospinning is the water-in-oil (W/O) one which is exclusively utilized to make encapsulating hydrophilic drugs or bioactive molecules. These bioactive molecules are housed inside the electrospun CS fibers core and their function is to avoid the burst release and prolong the release time (Chew et al. 2005; Xu et al. 2005; Xu et al. 2006; Li et al. 2008; Xu et al. 2008; Yang, Li, Cui, et al. 2008; Yang, Li, Qi, et al. 2008; Li et al. 2009; Xu et al. 2009; Yan et al. 2009). Concerning the water-soluble polymer such as PEO and an amphiphilic polymer such as polyethylene glycol-poly (L-lactic acid) (PEG-PLA) diblock copolymer, Xu et al. concluded that they are incorporated into the W/O emulsion. Besides, they inferred that to get a low surface tension, proper emulsifying agent as a surfactant was usually applied (Xu et al. 2005; Xu et al. 2006). The reason justifies that the speed of evaporating the organic solvent was relatively faster than the distilled water; consequently, the viscosity of the droplets was enhanced less than the viscosity of organic matrix and the fiber’s core solidified less rapidly. Different viscosity made drops move inwardly and follow their mergence. Consequently, in the process of the emulsion electrospinning, the water-soluble polymer played the role of a core and the shell of the CS fibers held by the hydrophobic or amphiphilic polymer. Xu et al. observations indicated that instead of forming the continuous core, smaller droplets were made from emulsion drops during electrospinning. Consequently, after evaporating the organic solvent and after increasing the drop phase viscosity, the electrospun fiber has some detectable encapsulated liquid and solid particles in itself. At this time, the matrix viscosity was less than the matrix and drops did not further deform by standing still. Besides, different fields like scaffolds in tissue engineering, drug delivery systems, wound dressings, etc., take the best advantages of ultrafine CS fibers represented as nonwoven membranes produced by coaxial or emulsion techniques.

3. Core–shell nanofibers role in drug delivery

Usually, drug delivery systems are controlled during the treatment at a rate needed by the site of action’s
physiological environment. Therefore, these systems are highly important and are affected by adjusting the scaffold’s morphology, porosity, and composition. These scaffolds can be used as carriers for diverse types of drugs, genes, and growth factors that have been used for a decade. These systems are ranging from polymer micelles, liposomes, gels, complexes, to CS nanofibers (Tiwari et al. 2012). Among these systems, CS nanofibers are known as the most successful method, bearing some undeniable merits which can be mentioned as the highly flexible platforms and drug delivery systems selection, elevated efficacy of encapsulation, biocompatibility, low cost, ease of operation, and sustained control of drug release. Some frequent applications of nano fibrous drug-delivery systems are discussed in the following sections.

3.1. Drug delivery materials

The drug delivery materials are expected to be biocompatible either biodegradable or non-biodegradable, that is they must have no or minor toxicity and immune responses. Despite the previous sections which studied commercially natural or synthetic polymers, in the present section, the supporting matrix of CS fibers is discussed. The popularity of biodegradable materials is their ability to remove the implanted fibers without a procedure (Zhao et al. 2007). Some biodegradable polymers are named here: PCL, PEG, Poly-L(or D or DL)-lactide (PLA, PLLA, PDLA, PDLA), poly(vinyl alcohol) (PVOH, PVA, or PVAI), poly(lactic-co-glycolic acid) (PLGA), poly(L-lactide-co-caprolactone) (PLCL), etc. On the other hand, there are natural polymers which are named as polysaccharides such as chitosan, cellulose, alginate, chitin, and proteins such as collagen, gelatin, zein, and silk fibroin (SF). Sridhar et al. asserted that these natural materials can be used to produce biomedical electrospun nanofibers which are briefly mentioned in (Sridhar et al. 2015). Furthermore, the polysaccharides based electrospun fibers were studied by Lee et al. in which it was made clear that the degradation rate is highly paramount in choosing material (Lee et al. 2009). In applying non-biodegradable material-based drugs, by slow diffusion, drugs are released; though in biodegradable material-based drugs the release behavior is somehow cumbersome though a controlled and gradual release is considered ideal. In these systems, some undesired situations may occur such as drug release occurring fast or increased in its local concentration, which could make it toxic. Noticeably, there is a method to control the degradation rate known as changing the composition and crystallinity of a polymer blend or copolymer. Actually, the PLA’s methyl group makes it more hydrophobic than PGA. The result is that PLA degrades slower. Makadia and Siegel (2011) are devoted to a comprehensive review of PLGA. In a work done by Li et al. (2010) proteinase K which is a fungal serine protease is encapsulated in PEG matrix as a core. In this study, a shell was PLA that its hydrolysis is accelerated by the mentioned proteinase K. It is apt to mention that a hybrid blend of natural and synthetic polymer is always preferable.

3.2. How are drugs released?

In the case that a matrix is non-biodegradable polymer, diffusion is the underlying mechanism of the release. The release pattern in the water-soluble drugs is like the following process. The drugs dissolve in water while
the water molecules were diffused inside the polymer network, and then the drugs move out of the polymer matrix (Fredenberg et al. 2011). However, the release pattern in biodegradable CS fibers includes three principal factors; diffusion, degradation, and shell thickness that are shown in Figure 15. It is apt to mention that the core phase is situated with the highest drug concentration. Diffusion through the polymer matrix is responsible for the sustained release. As drug releases, the polymer is degraded.

In the study that was conducted by Tian et al. vascular endothelial growth factor (VEGF) was dissolved in the BSA by substituting the water phase with the oil phase (PLCL in chloroform). The release scenario had two steps known as the burst (first 24 h) and the sustained step (later 648 h). When dextran substituted the BSA as a protective agent, the burst release reduced about 8.6%. More VEGF on the surface PLCL–BSA was imaged by x-ray photoelectron spectroscopy (XPS). Finally, 28 d later, smaller fiber average diameter was observed than the fibers before the release (Tian et al. 2012). Other similar biphasic drug release patterns were reported by Wang et al. (2010) and Yang Y et al. (2011). Noticeably, by setting the sheath solution’s flow rate it is possible to control the drug release. Yu et al. assessed the effect of the sheath solution flow rate by selecting two different sheath solution flow rates (0.5 and 0.8 mL/h). In their study, PVP was chosen as a sheath and ketoprofen (KET) in ethyl cellulose as a core. The initial burst was reported as 30.7% for 0.5 and 41.2% for 0.8 mL/h (Yu et al. 2013). Usually, in binary release CS fiber system, two drugs are dissolved singly. For instance, in the Choi et al.’s (2011) study, the core phase encapsulated basic fibroblast growth factor (bFGF) and immobilized epidermal growth factor (EGF) on the shell surfaces in order to fabricate a dual release CS fiber as shown in Figure 16. Indeed, through a reaction of EGF surface carboxyl and amine groups, the mentioned immobilization could occur. Growth factors’ release profiles exhibited a clear binary release. Concerning the physically loaded bFGF administration, in the first 24 h, a high initial burst release happened; however, during the first 7 d, a negligible release was observed by the chemically loaded EGF.

Choi and Yoo (2010) are concerned with a similar study based on the core phase, in which multiple drugs can also be inserted together. Zupancić et al. demonstrated two possibilities of solving the problem of incorporation of hydrophilic drug into nanofibers and the following long-term controlled release (Zupancić et al. 2016). First, they considered the variation of flow rate ratios between monolithic core and shell during coaxial electrospinning. CS nanofibers with lower amount of PVA in the core (csPVA 1:5) generated by the CS flow ratio 1:5 could condemn the burst release and make the drug release during a 4-week period. Second, CIP release was controlled for more than 25 d with a 2 d lag time. In this scenario, the phase-separated blend (PVA: PMMA = 70:30) was the core and PMMA was the shell of the CS nanofibers. This scenario can be further studied by altering the PVA and PMMA ratios in the core. The whole set up can be seen in Figure 17.

3.2.1. Proteins
Noticeably in co-electrospinning, the sheath phase protects the core phase from direct harsh environment exposure. This quality cannot be seen in conventional methods. In the blend-electrospinning method, bioactivity of molecules is thoroughly or partially lost. Therefore, keeping the bioactive characteristic of drugs is highly paramount. Concerning proteins, fibrinogen (factor I) which is a glycoprotein was studied. Fibrinogens help form blood clots in the body. In an outstanding study, poly(glycerol sebacate)fibrinogen (PGS@fibrinogen) CS fibers were made by Ravichandran et al. (2013) who observed that the elastomeric PGS core phase is responsible for native-like tissue mechanical properties and also the fibrinogen shell phase is in charge of enhancing cell–fibers interactions. Regarding proteins, in other studies Wang et al. (2015) and Jiang
et al. (2006) encapsulated BSA and lysozyme water-soluble proteins in the core. By observing the release behavior, it was concluded that the more the molecular weight of the polymer, the higher the release rate reported and by altering the core solution’s feed rate, Jiang was able to control the release rate. The model protein was loaded more when a higher feed rate was injected. High loading consequently accelerated the BSA release. In this case, the relative activity of lysozyme was dependent on turbidity change computed in a Micrococcus lysodeikticus bacterial cell solution at 450 nm. As reported, after running the electrospinning
process and observing the release process, lysozyme remained bioactive since there was no decrease.

Actually, the released lysozyme kept its structure and bio activity (Jiang et al. 2005). In this study, the release behavior of proteins was investigated by adding small PEG molecules to the PCL shell. Results showed that as the flow rate of the inner solution was boosted, the loading efficiency and an accelerated release rate were enhanced as well (Jiang H et al. 2006).

Emulsion electrospinning is a useful technique that can load multi-drugs in ultrafine fibers through encapsulating of dispersed micro- or nanoparticles. Enjoying emulsion electrospinning, Jo et al. electrospun a PCL solution containing poly (N-isopropyl acrylamide) microgel particles or PMMA colloids and adjusted the physicochemical properties of the colloids (Jo et al. 2009). The recombinant human bone morphogenetic protein-2 (BMP-2) was loaded into PLGA fibers by means of hydroxypatite (Hap) nanoparticles for bone tissue regeneration in Nie et al. research. Results demonstrated that by enhancing the Hap amount which is used to enhance the attachment of bone marrow-derived mesenchymal stem cells; the BMP-2 sustained release was accelerated (Nie et al. 2008).

### 3.2.2. Growth factors

Growth factors, which can construct specific cellular responses and are considered special types of proteins, are influential in drug delivery and tissue regeneration. These mentioned responses or cell actions can cause cell growth, proliferation, migration, healing, and cellular differentiation. When cells bind to specific transmembrane receptors on target cells, the connection and therefore instruction of new cells become possible. For the sake of illustration in work, the bone tissue production was simulated in a typical case called protein 2 (BMP-2) (Lee et al. 2011). Moreover, BMP-2 and DEX were successfully incorporated into the poly(l-lactide-co-e-caprolactone) (PLCL)/collagen CS fibers by Su et al. (2012). Meanwhile, they could control the collagen CS fibers release profile which was highly similar to the BMP-2 and DEX in that their values were reported 73.7 and 60.5%, respectively, after 504 h. In the other work, the scaffold showed a sustained release when the PCL/polyethylene oxide (PEO) fibers were applied as a carrier for BMP-2, Srouji et al. (2011). Thus, it can be concluded that CS electrospun nanofibers are highly capable of bone tissue regeneration. Moreover, by taking the best advantages of the emulsion electrospinning Yang et al. were successful in embedding bFGF into CS fibers (Yang et al. 2011). Although a low (approximately 14.0–2.2%) bFGF initial burst release was reported, sustained release within the time span of the following 4 weeks was also observed. Regarding proteins, PDGF was chosen to be encapsulated in aligned core–sheath nanofibers by Liao et al. (2006). Observations showed that the release profile of PDGF with preserved bioactivity was completed after 35 d with near zero-order kinetics. Some other proteins were studied like encapsulation of VEGF in PLCL/dextran and PLCL/BSA by Tian et al. (2012) and an investigation into bFGF and EGF binary release system by Choi et al. (2011).

### 3.2.3. Anti-cancers

Anti-cancers are used to treat malignancies or cancerous growth. As seen in Figure 18, Quercetin is a powerful natural antioxidant with antitumor application. However, its therapeutic application is highly affected by its short half-life in body fluids. Vashisth et al. studied the quercetin-encapsulated PLGA-PCL nanofibers and the result was promising since they could handle its shortcomings (Vashisth et al. 2016). It was concluded that quercetin release rate was dependent on its encapsulated amount in the nanofibers. Following this study, in contrast with the native quercetin, the encapsulated one had an anti-proliferative and apoptotic effect against hepatocellular carcinomas.

In another study on determining the type I and type II CS PEO–PEI nanofibers drug dose therapeutic performance based on the curcumin and 5-FU drug delivery system were minutely investigated by Kumar et al. at two different times (Kumar et al. 2014). Based on the obtained results, both fibers were loaded equally in terms of drug values. However, there was a difference in the cell viability in 48 h, which was attributed to the drug release delay of type I nanofibers. Nevertheless, this difference vanished after 96 h as >90% in both type I and type II nanofibers since they were released prior to the mentioned time. Thus, considering this versatile PEO–PEI based nano-fibrous system, right amount of drug to the right place at right time (i.e. a characteristic controlled drug delivery system) can be modeled. Consequently, it was inferred that it is possible to

[Figure 18. Chemical structure of quercetin.]
defeat multiple drug resistance and decrease the chance of cancer recurrence by loading two different drugs, as seen in this work in which the CS PEO–PEI nanofibers were loaded with two different drugs (5-FU and curcumin) encompassed synergistic anti-cancer effects (Figure 19).

As mentioned, emulsion electrospinning has some applications one of which is hydrophilic drugs emulsion delivering. In literature of W/O emulsion electrospinning, a three-staged diffusion controlled mechanism concerning the release behavior of hydrophilic doxorubicin hydrochloride (DOX) from PEG-PLLA diblock copolymer fibers was first proposed by Xu et al. (2005, 2008). In another study, the release rate of hydrophobic paclitaxel (PTX) that was increased by hydrophilic DOX was manifested, considering loading them into ultrafine PEG-PLA fibers by running emulsion electrospinning (Xu et al. 2009). Additionally, Yang et al. (2014) could fabricate the nanoscale multi-agent delivery system (Cur-Ms/Dox-loaded nanofibers) by means of a simple electrospinning process (Figure 20).

Besides, the release time of Cur-Mss and Dox from the nanofibers to neoplastic cells indicated that the intracellular release of Cur was successful (Figure 21).

### 3.2.4. Antibiotics

Killing or inhibiting the bacteria growth is the task of antibiotics which are used largely as biocides. In healing wounds, CS fibers containing antibiotics can be extremely useful. In some works, some antibiotics were studied by Ignatova et al. who reviewed levofloxacin, tetracycline hydrochloride, ciprofloxacin, moxifloxacin, fusidic acid, and silver nanoparticles (AgNPs) encapsulated nanofibers (Ignatova et al. 2013). Gentamicin was studied by Giner et al. and encapsulations into PLA/collagen CS fibers were examined. Accordingly, results showed that pure and blended PLA fibers filled with gentamicin were able to be produced. However, in the blend type, the release value was (98%) within the first 50 h. Nonetheless, because of the hydrophobic nature of PLA, the release value was 33% in the first 50 h. There was no release between 250 and 500 h, and about 58% of the drug remained. In this case, there was no burst release because of the presence of the CS fibers which ensured that the sustained release could highly affect Staphylococcus epidermis, Pseudomonas aeruginosa, and Escherichia coli bacteria comprises a high capacity of cell proliferation. Thus, within the field of drug delivery systems, drug-encapsulated CS fibers are the ones that are highly effective. In another study,
another anti-bacteria known as ampicillin was incorpo-
ated into poly(methyl methacrylate) (PMMA)/nylon-6
CS fibers by Sohrabi et al. (2013). It is known that
the conductivity of the solution can be enhanced by adding
salt. It leads to a stronger electric force. Since ampicillin
sodium salt has an ionic nature; any enhancement of
the drug content can reduce the fiber diameter.
Regarding the kinetics of Fickian diffusion, the burst
release stage (Stage I) was not complying whereas
Stage II and III was conforming. It is proper to mention
that crystallization, which occurred as an outcome of
incubating in a potassium buffer solution for a long
time, made Stage III have a lower diffusion coefficient.
The highest antibacterial activity against Gram-positive
Listeria was the logical result of high drug concentrated
CS fibers (20%) (Figure 22).

In studying the tetracycline hydrochloride (TCH),
drug loaded CS nanofibrous mats had been prepared
by taking the best advantages of biodegradable polymers used as a shell (with and without drug) and antibiotic drug as a core (Maleki et al. 2013). In this study, the release behaviors and morphology were analyzed and a comparison was made between the obtained results and the release behaviors and morphology of monolithic blend fibers constructed with same polymers and mixed with similar drugs (Figure 23). Results indicated a change in the release behavior of the monolithic blend and various CS fiber delivery devices in which this behavior (total and burst release) was controllable by material and electrospinning variables. Therefore, either by adjusting the encapsulated drugs amount in the fibers or by making a distance among drug loaded portion and medium, it is possible to manipulate this behavior. Illustrating the above case, in chitosan-based CS fibers, it is a chitosan itself which acted as the antibacterial agent and handed in delivering the model drug (Nguyen et al. 2011).

In Sultanova et al. (2016), as one can see, blank PCL coated PCL nanofibers that are loaded with ampicillin (Figure 24) have been synthesized successfully with the

Figure 22. Ampicillin fibers antibacterial reaction by optical density measurement: The antibacterial effectiveness is gradually increased in: NF-AC1, NF-AC2, NF-AC3, NF-AC4, and NF-AC5 (corresponding to the concentration of 1, 2, 5, 15, and 20% ampicillin, respectively). (Reprinted under the authority of Yu et al. (2013), Copyright (2013) Elsevier).

Figure 23. The release altered behavior of the monolithic blend and different core–shell fiber delivery devices (Reprinted with permission from Wiley Online Library Copyright (2013)).

Figure 24. Core–shell scenarios ((a) Molecular structures of ampicillin, (b) PCL and (c) ATR-FTIR spectra of ampicillin, PCL and electrospun membranes (Reprinted under the authority of Zhang and Chang (2008), Copyright (2016) Elsevier).
altered coaxial electrospinning of the shell by employing diluted and partially electrospinnable PCL solution. The drug release profiles of CS 1, CS 2, and core membrane (CS1, CS2, and CR) during the first 4 h are shown in the following Figure 25. Describing this figure, it is evident that within the mentioned time, 85% of the ampicillin was released from CR. This release is called the burst release. However, during the same time CS1 and CS2 co-axial electrospinning membranes showed 16 and 7% release, respectively. CS1 and CS2 membranes release profiles were compared to single electrospinning membrane release profile. Interestingly among co-axial electrospinning, sample CS1 had a higher initial release than CS2 which had higher shell flow rate. This clarified that there is a relation between

Figure 25. The drug release profiles of CS1, CS2, and CR in the first 4 h (Reprinted under the authority of Zhang and Chang (2008), Copyright (2016) Elsevier).

Figure 26. Core–shell fibers SEM images (A and C) and emulsion coaxial fibers (B, D, E, and F). (E) shows a bigger dispersed-to-continuous phase ratio (1/5) in core (F) represents a smaller ratio (1/55). (Reprinted under the authority of Zhao et al. (2007) Copyright (2012) Royal Society of Chemistry).
the shell thickness and drug diffusion. On the other hand, the CR burst release was reasoned by the low ampicillin compatibility in PCL fibers, the ampicillin gathering on the fibers surfaces and a shell layer absence that can defer the release. In the case of CS2 which has a shell with greater flow rate, less drug release profile is observed than CS1. Thus, the shell thickness was responsible for the release in this case.

3.2.5. Other drugs

In electrospinning, other drugs such as, Levetiracetam (Lev, Keppra) which is an adult antiepileptic drug are employed (Lynch et al. 2004). Lev release in PLGA CS fibers was studied by Viry et al. who succeeded in combining the emulsion and co-electrospinning that its morphology is shown in Figure 26 (Viry et al. 2012). In the mentioned combinatory method, firstly the Lev holding the water phase of an emulsion with the PLGA as the oil phase. Then, the resultant material was co-electrospun with the pure PLGA solution. After evaporating, the core was made of micro cavities which served as drug reservoirs surrounded by fiber bulk. It is apt to mention that these cavities showed distinctive release kinetics from conventional CS fibers. It was concluded that if the core solution encompassed small dispersed-to-continuous phase ratio, small cavities could be shaped; consequently, long diffusive length was achieved. Nonetheless, a larger and shorter diffusive path was made in case that the ratio was bigger. Noticeably, the LEV released for over 21 d linearly and successively due to the presence of drug reservoirs. As mentioned, to treat epilepsy researchers have tried to implant PLGA-Lev nanofibers in the brain.

In a related case, through running the emulsion electrospinning, a CS nanofiber was prepared in which DEX was the core and SF-poly(ethylene oxide) was the sheath by Chen et al. The fibers are nontoxic if we use ‘Green electrospinning’ and non-organic solvents (Chen et al. 2015). As the term indicates in green electrospinning there is no toxicity. The released drug was able to decrease the lipopolysaccharide (LPS)-induced porcine hip artery endothelial cells (PIECs) without making inflammatory damage. This finding was supported by in vitro study. Additionally, in studying Lornoxicam which is an anti-inflammatory drug, Chen et al. concluded that the optimized nanofiber formulation (F15) is very similar to dissolution profiles (Chen et al. 2015). The stability of the optimized formulation (F15) was measured at 25°C as 60% RH and at 40°C as 75% RH for 3 months considering the dissolution rate in case that the formulation is assumed stable. In the (F15) optimized formulation, the inflammation inhibitory effect was enhanced. This conclusion was obtained when the mentioned effect was compared to the effect of pure drug against Carrageenan, which caused paw-edema in rats. Moreover, the release behavior of the (F15)-based drugs was considered effective since it was slow and extended during 8 h. Thus, the oral controlled release formulation is the best choice in fabricating these kinds of drugs. The other famous drug studied was dexamethasone. Chen et al. concluded that by running the emulsion electrospinning, Dex could be housed in the core and consequently CS structured SF/PEO nanofibers could form. In

![Figure 27. The process of Dex@SF/PEO nanofibers fabrication by emulsion electrospinning (Reprinted under the authority of Zhou et al. (2009), Copyright (2016) Elsevier).](image-url)
this study, ‘Green Electrospinning’ had occurred since the organic solvent had lost its toxicity. After running the emulsion and electrospinning, core of Dex@SF/PEO nanofibers released its DEX in a sustained and prolonged manner. In blood and skin tissue engineering, the SF/PEO nanofiber mat is considered as one of the drug carriers with the most potential (Figure 27).

Other beneficial studies have been conducted on the topic of nonsteroidal anti-inflammatory drug release profiles. These drugs can be named as Ketoprofen (Yu et al. 2013), Flurbiprofen axetil (Jiang et al. 2012), Ibuprofen (Nguyen et al. 2012), and Zein (Huang et al. 2013), etc.

4. Conclusion

Electrospun nanofibers with a unique CS morphology are developed and fabricated simply by coaxial and emulsion electrospinning. The mechanism behind electrospinning is based on the accessibility of the sheath phase modification and guidance that expands the material that is chosen. Pharmaceutically speaking, CS fibers holding various encapsulated drugs are made by selecting the materials with the optimal parameters accurately. The main characteristic of these, made bioactive drugs, is that they are able to be isolated while keeping their bioactive property after their release. In fact, a sustained release is the key characteristic of those drugs which are loaded with CS fibers. Co-electrospinning and emulsion electrospinning known as applicable valuable methods pave the way to control and manipulate the morphology, wettability, degradation, biocompatibility, and the mechanical features of synthesized fibers. Besides, they are able to change the biological response of the CS scaffold though they raise many challenges in their process of improvement. One of the most important challenges asserts that despite accessing robust physical theories concerning CS nanofibers formation, it is not likely to fulfill the entire theoretic expectation of the final morphology. One speculation indicates that in each system rheological and electric properties are different. It is apt to mention that, experimental trials with diverse parameters are required as well to handle these challenges. Besides, some specific requirements that are ignored in the conventional method should be met. The second challenge refers to the CS fibers dimensions which are bigger when compared with a single component fiber. So far, the fine CS fibers optimum diameter is measured as 60 nm whereas the diameter of single component fibers is computed as several nanometers. However, fabricating uniform and massive coaxial electrospun nanofibers has not been possible so far. In vivo includes most CS fibers studies of both drug delivery and tissue engineering though they are rare but increasing. Concerning coaxial fibers, there are other issues that must be handled like a precise control of the degradation rate and the drug release. To do so, a profound understanding of the interaction between CS fibers and cells, etc., must be obtained and further investigations and cooperation needs to be done between material scientists, physicists, biologists, biomedical scientists and chemists to find plausible answers to these challenges. Therefore, the progress of coaxial or emulsion electrospinning depends on the introduction of micro or nanoparticles.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was financially supported by School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran.

References

Anton F. 1934. Process and apparatus for preparing artificial threads. Google patents US1975504A.

Asli MM, Pourdeyhimi B, Loboa EG. 2012. Release profiles of tricalcium phosphate nanoparticles from poly(l-lactic acid) electrospun scaffolds with single component, core-sheath, or porous fiber morphologies: effects on hASC viability and osteogenic differentiation. Macromol Biosci. 12:893–900.

Aussawasathien D, Teerawattananon C, Vongchariya A. 2008. Separation of micron to sub-micron particles from water: electrospun nylon-6 nanofibrous membranes as pre-filters. J Membrane Sci. 315:11–19.

Ball C, Krogstad E, Chaowanachan T, Woodrow KA. 2012. Electrospun fibers for microbi-cide drug delivery. Drug delivery and development of anti-HIV microbicides. Boca Raton (FL): CRC Press; p. 459–507.

Ball C, Woodrow KA. 2014a. Electrospun fibers for microbicidal drug delivery. Drug delivery and development of anti-HIV microbicides. Boca Raton (FL): CRC Press; p. 459–507.

Ball C, Woodrow KA. 2014b. Electrospun solid dispersions of maraviroc for rapid intravaginal preexposure prophylaxis of HIV. Antimicrob Agents Chemother. 58:4855–4865.

Benavides RE, Jana SC, Reneker DH. 2012. Nanofibers from scalable gas jet process. ACS Macro Lett. 1:1032–1036.

Blakney AK, Ball C, Krogstad EA, Woodrow KA. 2013. Electrospun fibers for vaginal anti-HIV drug delivery. Antiviral Res. 100:59–516.

Blakney AK, Krogstad EA, Jiang YH, Woodrow KA. 2014. Delivery of multipurpose prevention drug combinations from electrospun nanofibers using composite microarchitectures. Int J Nanomedicine. 9:2967.
Bognitzki M, Czado W, Frese T, Schaper A, Hellwig M, Steinhart M, Greiner A, Wendoff JH. 2001. Nanostructured fibers via electrospinning. Adv Mater. 13:70–72.

Bonino CA, Efimenko K, Jeong SI, Krebs MD, Alsberg E, Khan SA. 2012. Three-dimensional electrospun alginate nanofiber mats via tailored charge repulsions. Small. 8: 1928–1936.

Chen W, Li D, Ahmed ES, El-Newehy M, El-Hamshary HA, Al-Deyab SS, He C, Mo X. 2015. Dexamethasone loaded core–shell SF/PEO nanofibers via green electrospinning reduced endothelial cells inflammatory damage. Colloids Surf B Interfaces. 126:561–568.

Chen H, Wang N, Di J, Zhao Y, Song Y, Jiang L. 2010. Nanowire-in-microwire structured core/shell fibers via multifluid coaxial electrospinning. Langmuir. 26: 11291–11296.

Chew SY, Wen J, Yim EK, Leong KW. 2005. Sustained release of proteins from electrospun biodegradable fibers. Biomacromolecules. 6:2017–2024.

Choi JS, Choi SH, Yoo HS. 2011. Coaxial electrospun nanofibers for treatment of diabetic ulcers with binary release of multiple growth factors. J Mater Chem. 21:5258–5267.

Deyab SS, He C, Mo X. 2015. Dexamethasone loaded core–shell PVA/PVP/zein nanofibers for biphasic drug release. Int J Pharm. 438:232–243.

Ehafi F, Lu W, Guoping G, Khan F. 2013. Core–shell fibers for biomedical applications—A review. Bioeng Biomed Sci J. 3:1–14.

Falde EJ, Freedman JD, Herrera VL, Yohe ST, Colson YL, Grinstaff MW. 2015. Layered superhydrophobic meshes for controlled drug release. J Control Release. 214:23–29.

Feng H, Chun I, Reneker D. 1999. Beaded nanofibers formed during electrospinning. Polymer. 40:4585–4592.

Frenot A, Chronakis IS. 2003. Polymer nanofibers assembled by electrospinning. Curr Opin Colloid Interface Sci. 8: 64–75.

Gopal R, Kaur S, Ma Z, Chan C, Ramakrishna S, Matsuura T. 2006. Electrospun nanofibrous filtration membrane. J Membrane Sci. 281:581–586.

Gorji M, Jeddri A, Ghereghahi A. 2012. Fabrication and characterization of polyurethane electrospun nanofiber membranes for protective clothing applications. J Appl Polym Sci. 125:4135–4141.

Greiner A, Wendorff J, Yarin A, Zussman E. 2006. Biohybrid nanosystems with polymer nanofibers and nanotubes. Appl Microbiol Biotechnol. 71:387–393.

Gu Y, Jian F. 2008. Hollow LiNi0.8Co0.1Mn0.1O2–MgO coaxial fibers: sol–gel method combined with co-electrospun preparation and electrochemical properties. J Phys Chem C. 112:20176–20180.

Gu Z, Xu Q. Inventors; CN101390814-A, Assignee. 2008. Cosmetic mask based on electrospinning nanometer fiber for skin, comprises electrospinning nanometer fiber non-woven fabric or nonwoven felt.

Hnummer MM, Shin M, Rutledge G, Brenner MP. 2001. Electrospinning and electrically forced jets. I. Stability theory. Phys Fluids. 13:2201–2220.

Hu X, Liu S, Zhou G, Huang Y, Xie Z, Jing X. 2014. Electrospinning of polymeric nanofibers for drug delivery applications. J Control Release. 185:12–21.

Huang ZM, He CL, Yang A, Zhang Y, Han XJ, Yin J, Wu Q. 2006. Encapsulating drugs in biodegradable ultrafine fibers through co-axial electrospinning. J Biomed Mater Res A. 77:169–179.

Huang ZM, Zhang YZ, Kotaki M, Ramakrishna S. 2003. A review on polymer nanofibers by electrospinning and their applications in nanocomposites. Compos Sci Technol. 63: 2223–2253.

Huang ZM, Zhang Y, Ramakrishna S. 2005. Double-layered composite nanofibers and their mechanical performance. J Polym Sci B Polym Phys. 43:2852–2861.

Huang W, Zou T, Li S, Jing J, Xia X, Liu X. 2013. Drug-loaded zein nanofibers prepared using a modified coaxial electrospinning process. Aaps PharmSciTech. 14:675–681.

Ignatova M, Rashkov I, Manolova N. 2013. Drug-loaded electrospun materials in wound-dressing applications and in local cancer treatment. Expert Opin Drug Deliv. 10: 469–483.

Jiang H, Hu Y, Li Y, Zhao P, Zhu K, Chen W. 2005. A facile technique to prepare biodegradable coaxial electrospun nanofibers for controlled release of bioactive agents. J Control Release. 108:237–243.

Jiang H, Hu Y, Zhao P, Li Y, Zhu K. 2006. Modulation of protein release from biodegradable core–shell structured fibers prepared by coaxial electrospinning. J Biomed Mater Res A. 79:50–57.

Jiang YN, Mo HY, Yu DG. 2012. Electrospun drug-loaded core–sheath PVP/zein nanofibers for biphasic drug release. Int J Pharm. 438:223–239.

Jo E, Lee S, Kim KT, Won YS, Kim HS, Cho EC, Jeong U. 2009. Core–sheath nanofibers containing colloidal arrays in the core for programmable multi-agent delivery. Adv Mater. 21:968–972.

Kayaci F, Ozgit-Akgun C, Donmez I, Biyikli N, Uyar T. 2012. Cosmetic mask based on electrospinning nanometer fiber nonwoven fabric or nonwoven felt.

Khalil MS, Cha DI, Kim HY, Kim IS, Bhattarai N. 2003. Electrospun nanofibrous polyurethane membrane as wound dressing. J Biomed Mater Res. 67:675–679.

Kowalczyk T, Nowicka A, Elbaum D, Kowalewski TA. 2008. Electrospinning of bovine serum albumin. Optimization
and the use for production of biosensors. Biomacromolecules. 9:2087–2090.

Kroegstad EA, Woodrow KA. 2014. Manufacturing scale-up of electrospun poly(vinyl alcohol) fibers containing tenofovir for vaginal drug delivery. Int J Pharm. 475:282–291.

Kumar SU, Matali I, Dubey P, Bhushan B, Sachdev A, Gopinath P. 2014. Differentially cross-linkable core–shell nanofibers for tunable delivery of anticancer drugs: synthesis, characterization and their anticancer efficacy. RSC Adv. 4:38263–38272.

Kusamoto N, Tajima T, Inventors. 2008. Fiber comprises an eggshell membrane component useful for producing a fiber assembly, which is used as a wound dressing or a cosmetic sheet.

Larsen G, Spretz R, Velarde-Ortiz R. 2004. Use of coaxial gas jackets to stabilize Taylor cones of volatile solutions and to induce particle-to-fiber transitions. Adv Mater. 16:166–169.

Lee K, Jeong L, Kang YO, Lee SJ, Park WH. 2009. Electrospinning of polysaccharides for regenerative medicine. Adv Drug Deliv Rev. 61:1020–1032.

Lee S, Kay Obendorf S. 2006. Developing protective textile materials as barriers to liquid penetration using melt-electrospinning. J Appl Polym Sci. 102:3430–3437.

Lee K, Silva EA, Mooney DJ. 2011. Growth factor delivery-based tissue engineering: general approaches and a review of recent developments. J R Soc Interface. 8:153–170.

Li D, Babel A, Jenekhe SA, Xia Y. 2004. Nanofibers of conjugated polymers prepared by electrospinning with a two-capillary spinneret. Adv Mater. 16:2062–2066.

Li Z, Huang H, Wang C. 2006. Electrostatic forces induce poly (vinyl alcohol)-protected copper nanoparticles to form copper/poly (vinyl alcohol) nanocables via electrospinning. Macromol Rapid Commun. 27:152–155.

Li W, Luo T, Yang Y, Tan X, Liu L. 2015. Formation of controllable hydrophilic/hydrophobic drug delivery systems by electrospinning of vesicles. Langmuir. 31:5141–5146.

Li D, Ouyang G, McCann JT, Xia Y. 2005. Collecting electrospun nanofibers with patterned electrodes. Nano Lett. 5:913–916.

Li XH, Shao CL, Liu YC. 2007. A simple method for controllable preparation of polymer nanotubes via a single capillary electrospinning. Langmuir. 23:10920–10923.

Li X, Su Y, Zhou X, Mo X. 2009. Distribution of sorbitan monooleate in poly (l-lactide-co-e-caprolactone) nanofibers from emulsion electrospinning. Colloid Surf B Biointerfaces. 69:221–224.

Li D, Wang Y, Xia Y. 2003. Electrospinning of polymeric and ceramic nanofibers as uniaxially aligned arrays. Nano Lett. 3:1167–1171.

Li D, Wang Y, Xia Y. 2004. Electrospinning nanofibers as uniaxially aligned arrays and layer-by-layer stacked films. Adv Mater. 16:361–366.

Li D, Xia Y. 2004. Direct fabrication of composite and ceramic hollow nanofibers by electrospinning. Nano Lett. 4:933–938.

Li X, Zhang H, Li H, Tang G, Zhao Y, Yuan X. 2008. Self-accelerated biodegradation of electrospun poly (ethylene glycol)–poly (l-lactide) membranes by loading proteinase K. Polym Degrad Stabil. 93:618–626.

Li X, Zhang H, Li H, Yuan X. 2010. Encapsulation of proteinase K in PELA ultrafine fibers by emulsion electrospinning: preparation and in vitro evaluation. Colloid Polym Sci. 288:1113–1119.

Liao I, Chew S, Leong K. 2006. Aligned core–shell nanofibers delivering bioactive proteins. Nanomedicine. 1:465–471.

Loscertales IG, Barrero A, Guerrero I, Cortijo R, Marquez M, Ganan-Calvo A. 2002. Micro/nano encapsulation via electrospayed coaxial liquid jets. Science. 295:1695–1698.

Luo C, Stoyanov SD, Stride E, Pelan E, Edirisinghe M. 2012. Electrospinning versus fibre production methods: from specifics to technological convergence. Chem Soc Rev. 41:4708–4735.

Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, Fubs B. 2004. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci USA. 101:9861–9866.

Makadia HK, Siegel SJ. 2011. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers (Basel). 3:1377–1397.

Maleki M, Latifi M, Amani-Tehran M, Mathur S. 2013. Electrospun core–shell nanofibers for drug encapsulation and sustained release. Polym Eng Sci. 53:1770–1779.

Man Z, Yin L, Shao Z, Zhang X, Hu X, Zhu J, Dai L, Huang H, Yuan L, Zhou C, et al. 2014. The effects of co-delivery of BMSC-affinity peptide and rhTGF-β1 from coaxial electrospun scaffolds on chondrogenic differentiation. Biomaterials. 35:5250–5260.

Mathew G, Hong J, Rhee J, Leo D, Nah C. 2006. Preparation and anisotropic mechanical behavior of highly-oriented electrospun poly (butylene terephthalate) fibers. J Appl Polym Sci. 101:2017–2021.

Megelski S, Stephens JS, Chase DB, Rabolt JF. 2002. Micro- and nanostructured surface morphology on electrospun polymer fibers. Macromolecules. 35:8456–8466.

Moghe A, Gluck J, Gupta B, King M. 2005. Electrospun bicomponent fibers for soft tissue engineering: book of abstracts. Newark (NJ): SN.

Nadri S, Nasehi F, Barati G. 2017. Effect of parameters on the quality of core-shell fibrous scaffold for retinal differentiation of conjunctiva mesenchymal stem cells. J Biomed Mater Res A. 105:189–197.

Nguyen TTT, Chung OH, Park JS. 2011. Coaxial electrospun poly (lactic acid)/chitosan (core/shell) composite nanofibers and their antibacterial activity. Carbohydr Polym. 86:1799–1806.

Nguyen TTT, Ghosh C, Hwang SG, Chanunpanich N, Park JS. 2012. Porous core/sheath composite nanofibers fabricated by coaxial electrospinning as a potential mat for drug release system. Int J Pharm. 439:296–306.

Nie H, Soh BW, Fu YC, Wang CH. 2008. Three-dimensional fibrous PLGA/HAp composite scaffold for BMP-2 delivery. Biotechnol Bioeng. 99:223–234.

Owens RC, Shorr AF. 2009. Rational dosing of antimicrobial agents: pharmacokinetic and pharmacodynamic strategies. Am J Health Syst Pharm. 66:S23–S30.

Pant HR, Risal P, Park CH, Tijing LD, Jeong YJ, Kim CS. 2013. Core–shell structured electrospun biomimetic composite nanofibers of calcium lactate/nylon-6 for tissue engineering. Chem Eng J. 221:90–98.

Park JY, Lee IH, Bea GN. 2008. Optimization of the electrospinning conditions for preparation of nanofibers from
polyvinylacetate (PVAc) in ethanol solvent. J Ind Eng Chem. 14:707–713.
Pavlikova S, Thomann R, Reichert P, Mülhaupt R, Marcinčin A, Borsig E. 2003. Fiber spinning from poly (propylene)-organoclays. J Appl Polym Sci. 89:604–611.
Peng Q, Sun XY, Spagnola JC, Hyde GK, Spontak RJ, Parsons GN. 2007. Atomic layer deposition on electrospun polymer fibers as a direct route to Al2O3 microtubes with precise wall thickness control. Nano Lett. 7:719–722.
Persano L, Camposeo A, Tekmen C, Pisignano D. 2013. Industrial upscaling of electrospinning and applications of polymer nanofibers: a review. Macromol Mater Eng. 298:504–520.
Pham QP, Sharma U, Mikos AG. 2006. Electrospinning of polymeric nanofibers for tissue engineering applications: a review. Tissue Eng. 12:1197–1211.
Pillay V, Dott C, Choonara YE, Tyagi C, Tomar L, Kumar P, Dutto LC, Ndesendo VM. 2013. A review of the effect of processing variables on the fabrication of electrospun nanofibers for drug delivery applications. J Nanomater. 2013:1.
Qu, H, Wei, S, Guo, Z. 2013. Coaxial electrospun nanostructures and their applications. J Mater Chem A. 1(38):11513–11528.
Ravichandran R, Venugopal JR, Sundararajan S, Mukherjee S, Sridhar R, Ramakrishna S. 2013. Expression of cardiac proteins in neonatal cardiomyocytes on PGS/fibrinogen core/shell substrate for Cardiac tissue engineering. Int J Cardiol. 167:1461–1468.
Reneker DH, Chun I. 1996. Nanometre diameter fibres of polymer, produced by electrospinning. Nanotechnology. 7:216.
Rieger KA, Birch NP, Schifman JD. 2013. Designing electrospun nanofiber mats to promote wound healing—a review. J Mater Chem B. 1:4531–4541.
Rojas R, Pinto NJ. 2008. Using electrospinning for the fabrication of rapid response gas sensors based on conducting polymer nanowires. IEEE Sensors J. 8:951–953.
Seon-Lutz M, Couffin AC, Vignoud S, Schlatter G, Hébraud A. 2019. Electrospinning in water and in situ crosslinking of highly soluble low molecular weight drugs. J Mater Chem. 19:4541.
Shin Y, Hohman M, Brenner MP, Rutledge G. 2001. Electrospinning: a whipping fluid jet generates submicron polymer fibers. Appl Phys Lett. 78:1149–1151.
Sill TJ, von Recum HA. 2008. Electrospinning: applications in drug delivery and tissue engineering. Biomaterials. 29:1989–2006.
Sohrabi A, Shaibani P, Etyash H, Kaur K, Thundat T. 2013. Sustained drug release and antibacterial activity of ampicillin incorporated poly (methyl methacrylate)–nylon 6 core/shell nanofibers. Polymer. 54:2699–2705.
Spreen WR, Margolis DA, Pottage JC. 2013. Long-acting injectable antiretrovirals for HIV treatment and prevention. Curr Opin HIV AIDS. 8:565.
Sridhar R, Lakshminarayanan R, Madhaiyan K, Barathi VA, Lim KHC, Ramakrishna S. 2015. Electrospayed nanoparticles and electrospun nanofibers based on natural materials: applications in tissue regeneration, drug delivery and pharmaceuticals. Chem Soc Rev. 44:790–814.
Srouji S, Ben-David D, Lotan R, Livne E, Avrahami R, Zussman E. 2011. Slow-release human recombinant bone morphogenetic protein-2 embedded within electrospun scaffolds for regeneration of bone defect: in vitro and in vivo evaluation. Tissue Eng A. 17:269–277.
Su Y, Su Q, Liu W, Lim M, Venugopal JR, Mo X, Ramakrishna S, Al-Deyab SS, El-Newehy M. 2012. Controlled release of bone morphogenetic protein 2 and dexamethasone loaded in core–shell PLLA–collagen fibers for use in bone tissue engineering. Acta Biomater. 8:763–771.
Subbiah T, Bhat G, Tock R, Parameswaran S, Ramkumar S. 2005. Electrospinning of nanofibers. J Appl Polym Sci. 96:557–569.
Sultanova Z, Kaleli G, Kabay G, Mutlu M. 2016. Controlled release of a hydrophilic drug from coaxially electrospun polycaprolactone nanofibers. Int J Pharm. 505:133–138.
Sun Z, Zussman E, Yarin AL, Wendorff JH, Greiner A. 2003. Compound core–shell polymer nanofibers by co-electrospinning. Adv Mater. 15:1929–1932.
Sundararaj SC, Thomas MV, Peyyala R, Dziubla TD, Puleo DA. 2013. Design of a multiple drug delivery system directed at periodontitis. Biomaterials. 34:8835–8842.
Tian L, Prabhakaran MP, Ding X, Kai D, Ramakrishna S. 2012. Emulsion electrospun vascular endothelial growth factor encapsulated poly (lactic acid-co-caprolactone) nanofibers for sustained release in cardiac tissue engineering. J Mater Sci. 47:3272–3281.
Tiwari G, Tiwari R, Sriswastawa B, Bhati L, Pandey S, Pandey P, Bannerjee SK. 2012. Drug delivery systems: an updated review. Int J Pharm Invest. 2:2.
Vashisth P, Singh RP, Pruthi V. 2016. A controlled release system for quercetin from biodegradable poly (lactide-co-glycolide)–polycaprolactone nanofibers and its in vitro antitumor activity. J Bioact Compat Polym. 31:260–272.
Viry L, Moulton SE, Romeo T, Suhr C, Mawad D, Cook M, Wallace GG. 2012. Emulsion-coaxial electrospinning: designing novel architectures for sustained release of highly soluble low molecular weight drugs. J Mater Chem. 22:11347–11353.
Wang M, Jing N, Su CB, Kameoka J, Chou CK, Hung MC, Chang KA. 2006. Electrospinning of silica nanochannels for single molecule detection. Appl Phys Lett. 88:033106.
Wang CY, Liu JJ, Fan CY, Mo XM, Ruan HJ, Li FF. 2012. The effect of aligned core–shell nanofibers delivering NGF on the promotion of sciatic nerve regeneration. J Biomater Sci Polym Ed. 23:167–184.
Wang C, Yan KW, Lin YD, Hsieh PC. 2010. Biodegradable core/shell fibers by coaxial electrospinning: processing, fiber characterization, and its application in sustained drug release. Macromolecules. 43:6389–6397.
Wang M, Yu JH, Kaplan DL, Rutledge GC. 2006. Production of submicron diameter silk fibers under benign processing conditions by two-fluid electrospinning. Macromolecules. 39:1102–1107.
Wang X, Yuan Y, Huang X, Yue T. 2015. Controlled release of protein from core–shell nanofibers prepared by emulsion electrospinning based on green chemical. J Appl Polym Sci. 132:41811.
Xiang Y, Liang J, Liu L, Wang F, Deng L, Cui WJ, Am, interfaces. 2019b. Self-Nanoemulsifying Electrospun Fiber Enhancing Drug Permeation. Appl. Mater. Interfaces. 11(8):7836–7849.
Xu X, Chen X, Ma P, Wang X, Jing X. 2008. The release behavior of doxorubicin hydrochloride from medicated fibers prepared by emulsion-electrospinning. Eur J Pharm Biopharm. 70:165–170.

Xu X, Chen X, Wang Z, Jing X. 2009. Ultrafine PEG-PLA fibers loaded with both paclitaxel and doxorubicin hydrochloride and their in vitro cytotoxicity. Eur J Pharm Biopharm. 72:18–25.

Xu X, Yang L, Xu X, Wang X, Chen X, Liang Q, Zeng J, Jing X. 2005. Ultrafine medicated fibers electrospun from W/O emulsions. J Control Release. 108:33–42.

Xu X, Zhuang X, Chen X, Wang X, Yang L, Jing X. 2006. Preparation of core-sheath composite nanofibers by emulsion electrospinning. Macromol Rapid Commun. 27:1637–1642.

Yan S, Xiaoqiang L, Shuiping L, Xiumei M, Ramakrishna S. 2009. Controlled release of dual drugs from emulsion electrospun nanofibrous mats. Colloids Surf B Biointerfaces. 73:376–381.

Yang Y, Li X, Cui W, Zhou S, Tan R, Wang C. 2008. Structural stability and release profiles of proteins from core-shell poly (DL-lactide) ultrafine fibers prepared by emulsion electrospinning. J Biomed Mater Res A. 86:374–385.

Yang Y, Li X, Qi M, Zhou S, Weng J. 2008. 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. 69:106–116.

Yang G, Wang J, Li L, Ding S, Zhou S. 2014. Electrospun micelles/drug-loaded nanofibers for time-programmed multi-agent release. Macromol Biosci. 14:965–976.

Yang Y, Xia T, Zhi W, Wei L, Weng J, Zhang C, Li X. 2011. Promotion of skin regeneration in diabetic rats by electrospun core-sheath fibers loaded with basic fibroblast growth factor. Biomaterials. 32:4243–4254.

Yarin A. 1995. Surface-tension-driven flows at low Reynolds number arising in optoelectronic technology. J Fluid Mech. 286:173–200.

Yoo HS, Kim TG, Park TG. 2009. Surface-functionalized electrospun nanofibers for tissue engineering and drug delivery. Adv Drug Deliv Rev. 61:1033–1042.

Yu JH, Fridrikh SV, Rutledge GC. 2004. Production of submicrometer diameter fibers by two-fluid electrospinning. Adv Mater. 16:1562–1566.

Yu D, Wang X, Li X, Chian W, Li Y, Liao Y. 2013. Electrospun biphasic drug release polyvinylpyrrolidone/ethyl cellulose core/sheath nanofibers. Acta Biomater. 9:5665–5672.

Zahedi P, Rezaeian I, Ranaei-Siadat SO, Jafari SH, Supaphol P. 2010. A review on wound dressings with an emphasis on electrospun nanofibrous polymeric bandages. Polym Adv Technol. 21:77–95.

Zargarian SS, Haddadi-Asl V, Kafrashian Z, Azarnia M, Mirhosseini MM, Seyedjafari E. 2019. Surfactant-assisted water-exposed versus surfactant-aqueous-solution-exposed electrospinning of novel super hydrophilic polycaprolactone based fibers: analysis of drug release behavior. J Biomed Mater Res A. 107:597–609.

Zhang S. 2003. Fabrication of novel biomaterials through molecular self-assembly. Nat Biotechnol. 21:1171.

Zhang D, Chang J. 2008. Electrospinning of three-dimensional nanofibrous tubes with controllable architectures. Nano Lett. 8:3283–3287.

Zhang Y, Huang ZM, Xu X, Lim CT, Ramakrishna S. 2004. Preparation of core–shell structured PCL-r-gelatin bi-component nanofibers by coaxial electrospinning. Chem Mater. 16:3406–3409.

Zhao P, Jiang H, Pan H, Zhu K, Chen W. 2007. Biodegradable fibrous scaffolds composed of gelatin coated poly(epsilon-caprolactone) prepared by coaxial electrospinning. J Biomed Mater Res A. 83:372–382.

Zhou FL, Gong RH, Porat I. 2009. Mass production of nanofibre assemblies by electrostatic spinning. Polym Int. 58:331–342.

Ziabicki A. 1976. Fundamentals of fibre formation: the science of fibre spinning and drawing. Hoboken (NJ): John Wiley & Sons, Ltd.

Zupanciç S, Sinha-Ray S, Sinha-Ray S, Kristl J, Yarin AL. 2016. Controlled release of ciprofloxacin from core-shell nanofibers with monolithic or blended core. Mol Pharm. 13:1393–1404.