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Review Article

Electrospun Fibers: Versatile Approaches for Controlled Release Applications

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Electrospinning has been one of the most attractive methods of fiber fabrication in the last century. A lot of studies have been conducted, especially in tissue engineering and drug delivery using electrospun fibers. Loading many different drugs and bioactive agents on or within these fibers potentiates the efficacy of such systems; however, there are still no commercial products with this technology available in the market. Various methods have been developed to improve the mechanical and physicochemical behavior of structures toward more controllable delivery systems in terms of time, place, or quantity of release. In this study, most frequent methods used for the fabrication of controlled release electrospun fibers have been reviewed. Although there are a lot of achievements in the fabrication of controlled release fibers, there are still many challenges to be solved to reach a qualified, reproducible system applicable in the pharmaceutical industry.

1. Introduction

A novel drug-delivery system (NDDS) is one the most interesting topics that can make the administration of drugs more efficacious, safe, and convenient [1]. In chronic situations, drugs should be administered periodically to have a constant level for therapeutic effect, which is preferred to be decreased in a more efficient way [2, 3]. On the other hand, in some diseases, drugs have some toxic effects in other organs that should be avoided to reach non-targeted sites. In addition, some drugs may need to be available at specific times with specific quantities to show the appropriate efficiency. Pulsatile release of hormones is a good example of this type of release [3–5].

For this purpose, there are many different delivery systems, as simple as enteric-coated or extended release tablets to more complicated ones such as liposomes, nanoparticles (NPs), and polymeric systems, which are developing very fast [6]. In all these systems, structure and function should be optimized to achieve a certain desired effect.

Studies on polymeric-based systems have demonstrated that fibers are potential to be utilized as a new generation of drug-delivery system (DDS). The solid structure of fibers with a wide range of diameters from micro- to nanoscale and large surface area make fibers a good option for drug incorporation. Based on the application, drugs can be encapsulated in or immobilized on fibers [7]. Among various methods available for fiber fabrication, electrospinning provides a promising solution especially applied for tissue engineering [8–17], wound healing [18–22], and drug delivery [23–31]. In all these applications, a wide range of drug release kinetics, such as immediate release [32], sustained release [33, 34], biphasic release [36], pulsatile release [25], or even targeted release [37], would be expected by changing the parameters and methods used in electrospinning.

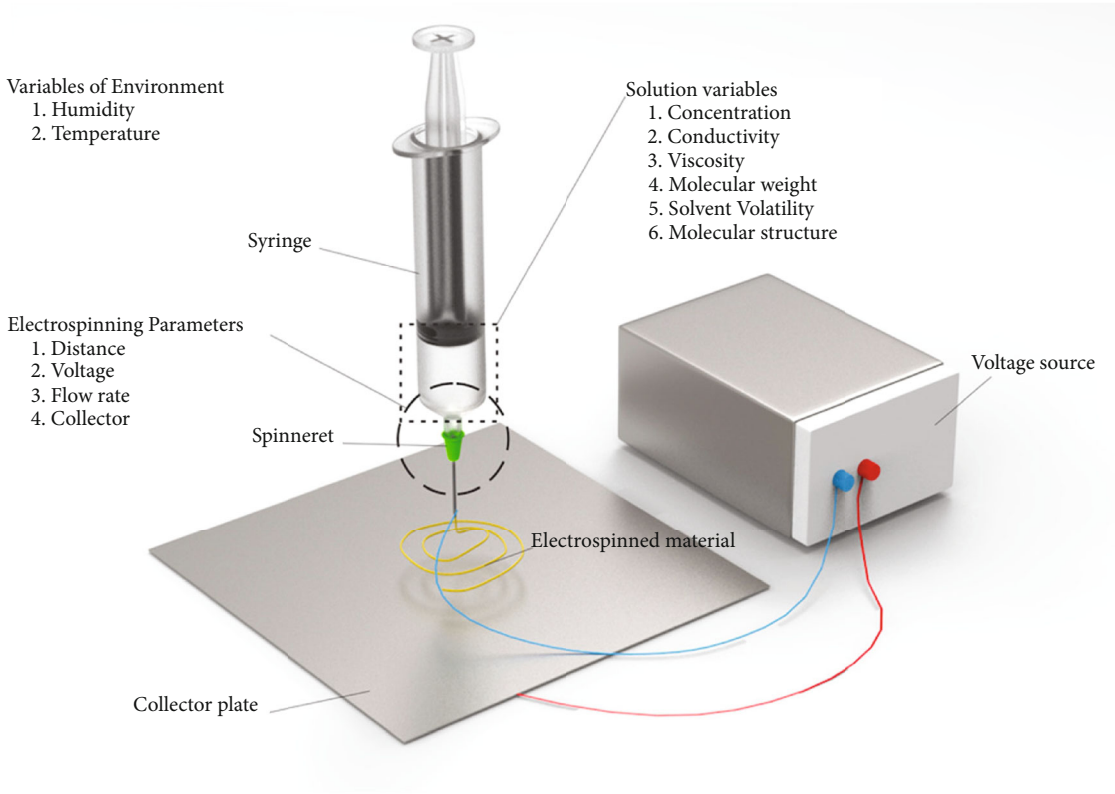

Figure 1: Schematic of the electrospinning principle and controlling parameters.

In this study, an overview is given on recent advances made in the development and application of controlled release electrospun fibers.

2. Electrospinning

Electrospinning has been derived from the electrospray method, which was first reported in 1882. The ejection of continuous liquid phase as a fiber under an electrical field was then explained in a patent in 1902 [15, 16]. At the beginning, researchers focused on instruments and parameters related to the process. The application of electrospinning in many fields, such as electronics, energy, environment, and medicine, has been widely studied [8, 15, 17]. As electrospun fibers are very similar to extracellular matrices (ECM), they have the potential to be utilized for repairing many organs. The skin [38–40], bone [12, 41, 42], cardiovascular system [43–46], nerve [47, 48], and liver [49, 50] are examples in which electrospinning has been evaluated for regeneration. To achieve the best results, loading drugs and bioactive molecules would potentially increase the efficiency of such scaffolds. A schematic of the electrospinning principle and controlling parameters is shown in Figure 1.

3. Electrospinning Methods

As there are several parameters in electrospinning, it can be categorized into different types based on these variables. Some are based on working fluid, some are instrumental dependent (based on spinneret or even collection type), and some are based on the electrohydrodynamic process [51, 52]. In the following, we tried to focus on the most studied and new methods. Some differences between these methods are summarized in Table 1.

3.1. Blend Electrospinning. Blend electrospinning is the first attempt for drug delivery by electrospinning. In this method, both spinnable material and therapeutic loaded agent were dissolved in one solvent simultaneously (Figure 2(a)). According to the theory of "like dissolve like," more similarity between the polymer and the loading agent results in more homogeneity and uniform release. The presence of a therapeutic agent also affected the viscosity and conductivity of the polymeric solution, which can also alter fiber diameter and porosity and consequently the release pattern [27].

With non-biodegradable polymers, drugs would be released by the diffusion mechanism while it could be erosion or combination of diffusion/erosion with biodegradable polymers [1].

Many antibiotics, anti-inflammatory agents, and some other small molecules have been incorporated in electrospun fibers [6, 53–55]. Electrospinning of hydrophilic polymers leads to quick dissolution and burst release of the total incorporated drugs. On the other hand, hydrophobic polymers would be more resistant in aqueous conditions, causing slower release behavior [6]. Macromolecules, such as proteins and growth factors are not good candidates for this type of encapsulation because of the harsh environment and the possibility of degradation. Most polymers used for electrospinning are hydrophobic dissolved in organic

Table 1: Summarized information about different types of electrospinning.

Electrospinning type	Suggested molecules for delivery	Advantages	Limitations
Blend electrospinning	Small molecules	The simplest method of electrospinning	Harsh process for sensitive molecules
Sequential electrospinning	Small molecules	Relatively simple method, multiphasic delivery	Harsh process for sensitive molecules independent non-protected layers
Coaxial/ multiaxial electrospinning	Wide range of drugs, such as small molecules, proteins, and RNA	Possibility to form core–shell nanofibers from miscible and immiscible polymers high loading capacity less harsh process multiphasic delivery with complex release profiles	Optimization of multineedle methods low production rate compatibility of core and shell fluids
Emulsion electrospinning	Wide range of drugs, such as small molecules, proteins, and RNA	Single nozzle formation of core–shell structure	Choosing polymers with sufficient interfacial tension needed care for preparation of emulsion
Side-by-side electrospinning	Small molecules	Relatively simple method, multiphasic delivery	Independent non-protected layers

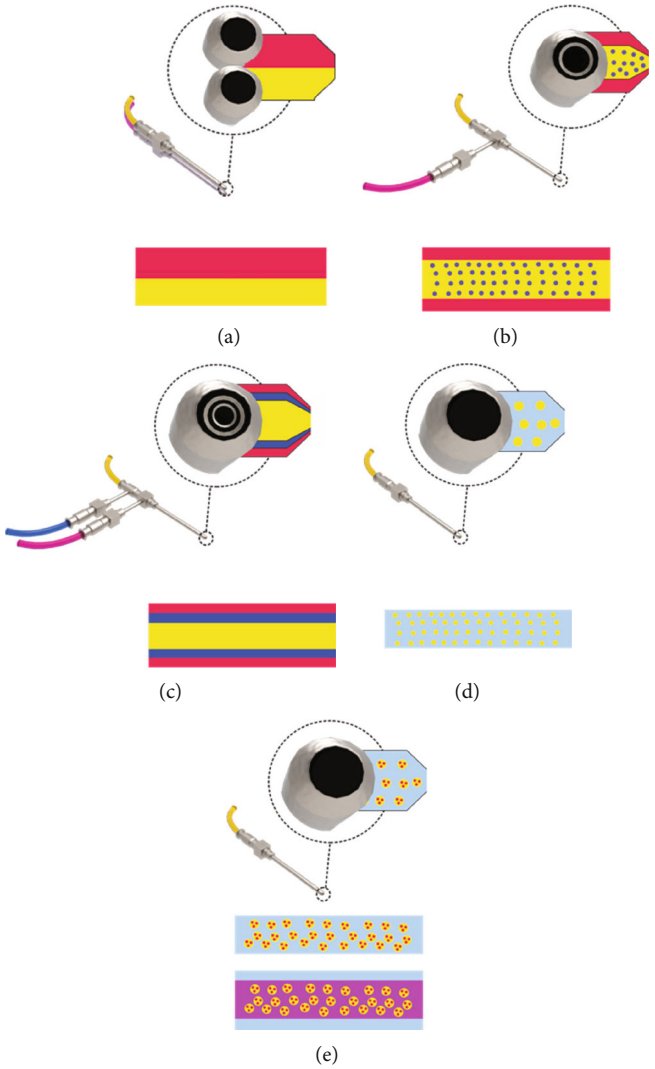

Figure 2: Schematic of some different types of electrospinning. (a) Side-by-Side side Electrospinningelectrospinning. (b) Coaxial Electrospinningelectrospinning. (c) Multiaxial Electrospinningelectrospinning. (d) Blending Electrospinningelectrospinning. (e) Emulsion Electrospinningelectrospinning.

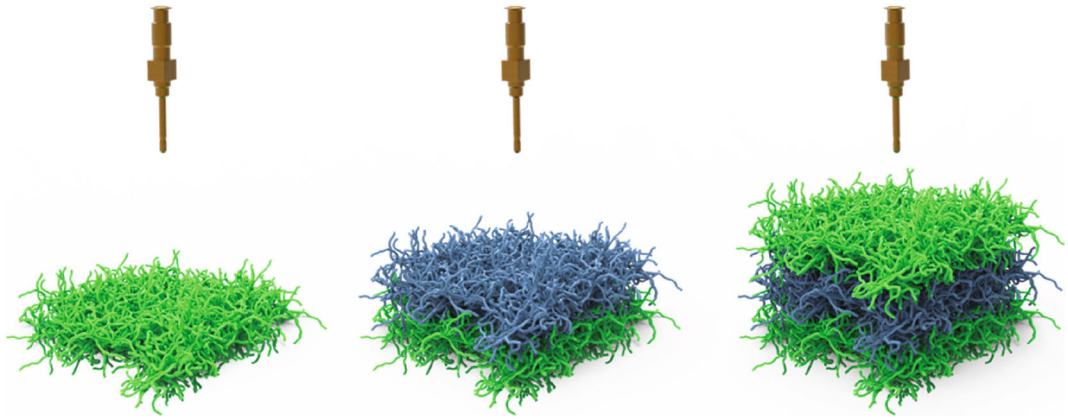

Figure 3: Schematic representation of the sequential electrospinning (from left to right, a new layer is added onto the previous one).

solvents (chloroform, methanol, etc.), which could change the arrangement of chains in macromolecules, leading to inactivity. Using hydrophilic polymers with more friendly solvents could solve this problem although it could not provide a controlled release system [1, 26].

Uniform dispersion is also another challenge in blend electrospinning, tendency to the surface during fiber formation is very common for charged molecules. Therefore, it can change the release kinetics, especially in erosion mechanisms. Concentration gradients would be different in nonhomogenous matrices showing diffusion mechanisms. In both conditions, an initial burst release could be expected [26]. Therefore, physicochemical properties of both polymer and loaded agents and interaction of these materials determine release patterns based on uniformity and drug distribution.

Drug–polymer miscibility plays an important role in uniformity and consequently the release behavior. Yuan et al. synthesized poly lactic acid (PLA) electrospun fibers with both hydrophilic doxorubicin hydrochloride (Dox-HCl) and hydrophobic free doxorubicin (Dox-base). Compatibility of Dox-base with PLA leads to homogeneous structure and slower release compared to Dox-HCl accumulated near the surface, promoting rapid release. Addition of co-solvents as dimethyl sulfoxide increased the miscibility of the drug and the polymer and obtained uniform drug distribution in the polymer matrix resulted in a slow-release profile [54].

Mechanical properties of scaffolds and stability of active agents within blended fibers are challenging issues leading to the development of newer electrospinning methods.

3.2. Sequential Electrospinning. Multi-layer scaffolds, shown in Figure 3, prepared by sequential electrospinning can also be another approach for controlling the release profile. In this type of electrospinning, each layer can be different from the other layer. The type of polymer, drug-to-polymer ratio, and thickness of each layer are the effective parameters in this type of electrospinning. While it seems to be simple, there are not many studies such as sequential layer-by-layer (LBL) electrospinning for drug delivery.

In one study reported by Huang et al., a tri-layer scaffold was fabricated [4]. Poly vinyl pyrrolidone (PVP) and ethyl cellulose (EC) were used in different layers to achieve the biphasic release profile for ketoprofen (PVP/EC/PVP) hydrophilicity of PVP led to fast dissolving (bulk erosion) of polymeric chains in aqueous medium and initial burst release of ketoprofen, while the EC layer decreased the rate of release due to hydrophobicity of the polymer. So, a sustained release behavior was observed in the second phase, which was described by Korsmeyer–Peppas equation (Equation (1)). Based on calculations, n was below 0.43, showing the diffusion mechanism for release from EC layer.

$$M_t/M_\infty = k_t n. \quad (1)$$

It was also concluded that the duration of each phase and the total amount of release could be regulated by the thickness of different layers.

Lee et al. also reported a sequential multilayered scaffold fabricated by Zein and PVP. They fabricated tri-layered Zein/PVP/Zein loaded with ketoprofen in all layers. Graphene oxide was added to the middle layer to increase the mechanical strength and the functionality of PVP. Release tests for each layer showed a sustained release profile for Zein layers and fast dissolution for PVP nanofibers. Using tri-layered matrix exhibited a combined release behavior, which could be more acceptable compared to burst release, especially for chronic pain. Therefore, biphasic release behavior of multilayered electrospun fibers could be potentially a good approach as time-regulated delivery systems.

In blending and sequential electrospinning, there are some obstacles for controlling the release of drugs from polymeric matrices. Poor compatibility of drugs with organic solvents used in electrospinning of polymers and burst release of most drugs from blended matrix because of surface tendency are some of the examples of difficulties in fabricating controllable scaffolds.

3.3. Coaxial Electrospinning. To overcome challenges in blending electrospinning, a coaxial method has been developed. Generally, coating is a simple way to tailor the stability and release behavior of active agents covered in the core in all drug-delivery systems. It can be supposed that coating is the basic principle of the coaxial process, which is based

on the simultaneous flow of two liquids with a concentric spinneret (Figure 2). Spinning liquids could be a polymeric solution, drug solution, free solvent(s), or drug–polymer solution. Thus, different structures and release kinetics would be expected [27, 38, 56–59].

Firstly, it was supposed that the polymer used as a shell layer should be spinnable, while it was not necessary for the core. Now, there are some other reports demonstrating that it is not important which solution is spinnable, as optimum conductivity in each one can lead to elongation of polymer and fiber formation [34, 35, 60].

Zhang et al. studied coaxial electrospinning of bovine serum albumin (BSA; labeled by fluorescein isothiocyanate [FITC]) loaded in polyethylene glycol (PEG, non-spinnable) as the core layer while polycaprolactone (PCL) was used as the shell [56]. Fibers showed more retardation in release compared to homogeneous blended fibers. A similar study was reported by Jiang et al., which used dextran as a carrier of BSA in the core layer. They showed biphasic release, which could be tailored by addition of porogens as PEG or any other hydrophilic structures to the hydrophobic shell. In both studies, PCL in the outer layer as a barrier prevented diffusion of water through the fiber to dissolve the drug.

Contrary to the previous studies, Qian et al. prepared a coaxial electrospun mat with PVP (non-spinnable) and EC as outer and inner layers, respectively. The hydrophilic shell with a hydrophobic core provided a dual drug release for acetaminophen, which was loaded in both layers. Release could be more tunable by changing the concentration of the core solution and addition of co-solvents [57]. Here, the outer hydrophilic structure provided an initial burst, which is important for pain-relief agents, while sustained release of the hydrophobic layer made a continuous effect.

3.4. Multiaxial Electrospinning. After developing the coaxial process, using a similar method as multiaxial electrospinning has also been evaluated in many studies, loading drugs either in the sheath or in the core of the fibers [61–68]. Han et al. worked on a tri-axial model with PCL and PVP (PCL/PCL/PVP). Dyes loaded in the inner and outer layers showed an initial burst release from the sheath and a sustained release profile from the PVP layer. The intermediate layer prevented the quick release by its hygroscopic properties provided a barrier for the diffusion of embedded dye [63]. Therefore, it has been demonstrated that multiaxial scaffolds could provide a more controllable release profile for both short- and long-term treatments.

In another study, Han et al. have also reported antimicrobial effects of tri-axial nanofibers encapsulated in core and covered by PCL and cellulose acetate (CA) in intermediate and outer layers, respectively. This scaffold showed a >99.99% biocidal effect for 5 days and also a bacteriostatic activity for 2 more days, which is more compared with the coaxial nisin incorporated nanofibers with only >99% biocidal activity for 1 day [64].

Multiaxial and sequential electrospinning enable encapsulation of different drugs in each layer. It can also provide different release behaviors for each one.

It seems that the presence of liquids in intermediate and core layers has not been well evaluated. There are not enough reports about the solvents used in inner layers. The boiling point of solvents would be a critical parameter for the stabilization of fibers. Khalf et al. investigated the effect of type of solvent, solvent volatilities, and molecular weight (MW) of polymer on the stability of tri-axial fibers. CA, PVA, and PCL are used for both sheath and intermediate layers with different concentrations and solvents. Mineral oil is used as the core layer for the fabrication of hollow structures. It was observed that quick evaporation of the outer layer leads to the formation of stable jet, while the opposite is true for intermediate layers. Therefore, the addition of other solvents to the intermediate solution in order to increase the boiling point would be helpful. This report also showed better fiber formation when the inner core MW was smaller or equal to that of the outer layer [61].

Also using organic solvents in inner layers could be harmful for bioactive agents incorporated in the core, which is not evaluated yet.

One of the advantages in multiaxial electrospinning is spinning non-spinnable liquids. Liu et al. reported a modified tri-axial electrospinning in which the core was just individually spinnable. The concentration of spinnable inner fluid is a critical parameter as it guides the other two layers for fiber formation. The middle layer of CA worked as a coating and the outer layer was a mixture of organic solvents. Therefore, the final structure was a core–shell like coaxial electrospinning [66]. The CA coating prevented burst release and caused close-to-zero-order release profiles. A similar study was reported by Yang et al. on ibuprofen [68].

Huang et al. worked on another type of tri-axial electrospinning, which spun non-spinnable fluids in both outer and inner layers (ethanol/ketoprofen in EC/ketoprofen). Intermediate and inner layers were also prepared by ethanol. It was observed that the outer fluid prevented the possible clogging of spinneret and the disturbances from the environment. Thus, more homogenous structures with a sustained release profile have been obtained [62].

Therefore, using a modified coaxial electrospinning process can lead to a monolithic structure while by a modified multiaxial setup, core–shell structure will be obtained (Figure 2(b)). These can provide potential tools to achieve more adjustable release profiles.

3.5. Emulsion Electrospinning. Preparation of core–shell structure by just one needle is also possible, which recently has been worked as an emulsion electrospinning [69, 70]. Basically, it is a combination of both blending and coaxial electrospinning (Figure 2(c)). Electrospinning of two immiscible solutions leads to core–shell fibers. Evaporation of the continuous phase increases the viscosity, which leads to the migration of the dispersed phase to the center of the jet. As discussed previously, core–shell structure can increase the stability of macromolecules during the electrospinning process and application. Interfacial tension and viscoelasticity of the aqueous phase play a critical role in the uniformity of the core. Release in this type of fiber is mostly based on

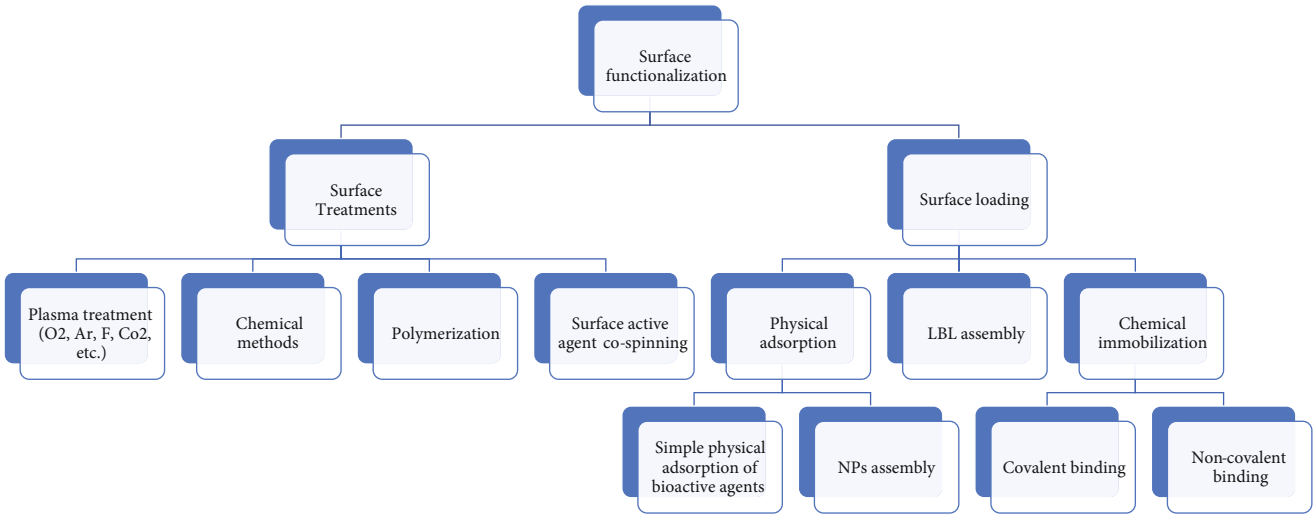

Figure 4: Different surface modification methods used on electrospun fibers.

diffusion through a barrier. Any variation in the erosion behavior of the outer layer or redistribution of the drug between two layers leads to a change in diffusivity of the drug.

Generally, water-in-oil emulsions (W/O) are used for emulsion electrospinning for the encapsulation of proteins and bioactive agents. Maretschek et al. studied the release profile of cytochrome C loaded in PLLA nanofibers by the emulsion electrospinning process [69]. A slow release profile was observed over 30 days, which increased in the presence of emulsifiers (more than CMC) and hydrophilic polymers due to more wetting of nanofibers. These changes are all dependent on the concentration of additional agents.

Viscosity and consequently morphology of the inner phase play a critical role in the release behavior of fibers fabricated by emulsion electrospinning. As in W/O emulsions, the rate of drug release is limited by water diffusion through the outer layer. If the core does not have a uniform and continuous structure, the bioavailability of the drug will be decreased. It will happen if the core does not have enough time for rearrangement in the center of the jet during solidification of the outer layer [1].

Oil-in-water emulsions (O/W) are also used for electrospinning, especially in food and cosmetic research for fish oil and fragrances, respectively [71, 72]. Multiphase emulsions (O/W/O and W/O/W) could be used for electrospinning needed more optimization to be stabilized.

3.6. Side-by-Side Electrospinning. Similar to coaxial electrospinning, another method uses for spinning two liquid simultaneously, called side-by-side electrospinning. In this method, two layers are adjacent to each other and there is no protection against the surrounding media for none of the layers. So, stability and rate of release are related to the composition of each layer independently [35, 36, 73], although the difference in the charge or rate of drying for each layer during spinning may lead to phase separation.

Mostly, this type of fiber provides a biphasic DDS. One side for fast release and the other for the extended release phase.

4. Surface Modification

Another approach that can be used for resolving burst release is surface modification of fibers. Postprocess functionalization can also be a good alternative for incorporation of many bioactive components, which are not compatible with organic solvents used in electrospinning [74, 75].

There are different surface modification methods used on electrospun fibers, which are summarized in Figure 4.

Physical adsorption is one of the simplest techniques for drug delivery by fibers. Most of the drugs show burst release by this method. However, release behavior can be slightly changed (from minutes to hours), depending on drugs and solvents' properties. Low MW, low hydrophobic interaction, and low affinity to functional groups of surfaces could increase rate of release, while the concentration and valence of ions in releasing the solution could also change the release behavior [76, 77].

As most of the polymers used for electrospinning have a passive surface with no functional groups, some treatments are needed to provide functional moieties for drug binding.

Chemical treatment (as hydrolysis) and surface oxidation can introduce amine, hydroxyl, and carboxylic acid functional groups on the surface of scaffolds, while plasma treatment can be used for providing both hydrophilic and hydrophobic properties based on the type of plasma with less degradation [76].

Im et al. reported a fluorination method to control drug release through a hydrophilic scaffold fabricated by PVA. Although PVA has many advantages as biocompatibility and non-toxicity, fast swelling of the polymer in aqueous media leads to rapid burst release of incorporated drugs. Thus, they modified electrospun fibers by fluorine gas in 3 different concentrations. Fluorinated scaffolds showed much

lower burst release and longer release period in comparison to non-treated mats especially in thin samples [77]. The kinetics of release might be unexpected in this kind of surface modification as a degree of hydrophobicity introducing on the mats is completely dependent on the thickness of scaffolds and pressure of the fluorine gas.

In some studies, chemical vapor deposition (CVD) polymerization was reported as a method for coating fibers to control the release behavior of scaffolds [78–80]. Zeng et al. studied the release and stability of BSA and luciferase embedded in PVA nanofibers fabricated by blending electrospinning. Nanofibers were coated by PPX (poly(*p*-xylylene)), a polymer with high hydrophobicity, applied mostly as a barrier for moisture. It was shown that the release of BSA retarded by PPX coating from 2 hours to 20 days. So, prolonged time release with long duration of activity of proteins and enzymes through polymeric systems can be obtained by controlling water solubility and permeability of the outer layer of scaffolds [79].

Some surface treatments can also be used for fabricating stimuli-responsive scaffolds. Jian et al. designed PCL nanofibers and immersed them in polydopamine solution after air plasma treatment, which induced polymerization and coated surface of the mat [81]. Doxorubicin was also loaded on nanofibers by immersion. In vitro release tests have shown more release in acidic medium (79.9% and 50.2% in pH values of 2.0 and 5.0) compared to pH values of 7.0 or 9.0 (less than 10%). This observation was due to selective permeability of polydopamine for charged molecules under different pH values.

Scaffolds would be more similar to ECM with biological ligands on the surface. Heparin and phosphatidylcholine are examples of ligands used to functionalize electrospun fibers.

LBL assembly of polyelectrolytes as one of the noncovalent immobilization techniques is another method, which is so versatile due to simplicity of the technique.

Fibers can also be coated by other delivery systems as NPs and liposomes. Many studies have reported such systems incorporated with drugs, proteins, and growth factors or some triggers for providing stimuli-responsive scaffolds as magnetic NPs located on fibers [82–84].

5. Co-Delivery by Electrospinning

One of the most attractive advantages of electrospinning, especially in tissue engineering, is the ability to incorporate two or more active agents for the synergic effect. They can be incorporated even in the same or different layers and act on the regeneration process via different ways. Based on the physicochemical properties of compounds, all methods discussed above can be used for co-delivery.

For example, in a mesoporous silicate nanoparticle (MSN)-based electrospun PCL/gelatin nanofibrous scaffold fabricated by Wang et al., alendronate (ALN) and silicate were used for bone remodeling by acting on different pathways [85]. ALN inhibited the bone-resorbing process while silicate promoted the bone-forming process, which leads to at least three times faster healing times in comparison to single drug scaffolds. Also sustained release of ALN from MSNs provides a non-toxic level of this molecule during its action.

Li et al. prepared another bone graft by a blend electrospun scaffold including bone morphogenetic protein-2 (BMP-2) and dexamethasone (DEX) [86]. To maintain the bioactivity of BMP-2, it is incorporated in BSA NPs before dispersion in polymeric solution. It is shown that sustained release of BMP-2 during 35 days in the presence of DEX accelerates bone repair.

It can be concluded that using NPs imbedded in the electrospun scaffold for some active agents has the beneficial of preserving stability and activity of the compounds while providing a multi-barrier system for a zero-order pattern of release.

Multi-layer methods are the most frequent techniques used for co-delivery to keep the release pattern independently. It is more important when the drugs have different physicochemical properties. For example, co-delivery of levonorgestrel (LNG) and tenofovir (TFV), which should be administered in high dose simultaneously for HIV prevention, is a challenge for researchers. According to Blakney et al.'s report, they fabricated 3 different scaffolds for co-delivery of these drugs. It was shown that release of TFV was reduced in blend scaffold due to saturation of surface layer by LNG [87]. So, using LBL or interwoven methods can be better alternative methods for co-delivery of high doses drugs.

6. Smart Systems

All discussed above are passive delivery systems that can potentially decrease rate of discharge while in some conditions we are looking for active delivery methods that respond to an environmental trigger to release drugs at the right time in the right place [58, 70]. For this purpose, smart systems that respond to either exogenous or endogenous stimuli get so much attention in drug-delivery research.

Stimuli-responsive DDSs (Table 2) can respond to any kind of physical, chemical, or biological changes, which leads to provision of drugs at the right time in target site [88–90]. These triggers are summarized in Figure 5. It is assumed that high porosity, submicron diameter, and high surface area of fibers could facilitate availability of stimulus to fibers and decrease dependency of response to diffusion process [88, 91].

Usually release of stimuli-responsive systems is based on diffusion with around 0.8 to 8×10^{-7} $cm^2\,s^{-1}$ diffusion coefficient. Therefore, it could limit the application of such systems. To overcome this problem, Cao et al. studied a hydrogel-based scaffold. They prepared crosslinked pH-responsive poly[styrene-co-(maleic sodium anhydride)] and cellulose (SMA-Na/cellulose) hydrogel nanofibers and evaluated swelling behavior in different pH values. Water swelling ratio of SMA-Na-DEG/cellulose composite nanofiber increased in high values of pH ($27.6\,g\,g^{-1}$ as the maximum value at pH = 9.1) due to dissociation of two protons in malic acid [91].

Table 2: Example of different types of stimuli-responsive fibers.

Type	Polymer(s)	Drug model	References
pH-responsive nanofibers	PLGA/chitosan/alginate	Ibuprofen	[113]
	PVA/PAA/bromobutyl blue (BTB)	Ciprofloxacin	[114]
	PLA	Resveratrol	[115]
	PVA/p(4VP-co-EGDMA)	Rose Bengal	[83]
	PVA/PCL	Doxorubicin	[92]
	PLGA/chitosan	Curcumin	[116]
Thermo-responsive nanofibers	PCL/poly-*N*-isopropylacrylamide (PNIPAM)	Doxycycline	[117]
	Poly (*N*-iso-propylacrylamide-*N*-methylolacrylamide-acrylamide) (PNIPAm-NMA-am)	Curcumin	[94]
	CO_2-derived poly (propylene carbonate) (PPC) electrospun fibers, covered with poly(3,4-ethylene dioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) and poly(*N*-isopropylacrylamide) (PNIPAM)	Cinnamon oil	[118]
	N-Isopropylacrylamide (NIPAAm)/*N*-hydroxymethylacrylamide (HMAAm)	FITC–dextran	[98]
	Poly(*N*-isopro-pylacrylamide-co-acrylamide-co-vinylpyrrolidone)P(NIPAAM AAm-VP)	Doxorubicin	[97]
Chemical-responsive nanofibers	Eudragit® RS100/poly(methyl methacrylate)	Rhodamine B	[25]
	Polydopamine coated PCL nanofibers	Metronidazole	[102]
Light-responsive nanofibers	PVA/PVP-FeOOH	Methylene blue	[105]
Magnetic-responsive nanofibers	Magnetic nanoparticle loaded PCL nanofibers	Rhodamine B, Nile red	[119]
	Magnetic gold coated poly(ε-caprolactonediol)-based polyurethane/poly(*N*-isopropylacrylamide)-grafted-chitosan core–shell nanofibers	Paclitaxel, 5-FU	[120]
Electro-responsive nanofibers	Poly(vinyl alcohol)/poly(acrylic acid)/multi-walled carbon nanotubes (MWCNTs) nanocomposites	Ketoprofen	[108]
	Chitosan–aniline oligomer/polyvinyl alcohol	Dexamethasone	[11]
Multi-responsive nanofibers	Bacterial cellulose nanofiber/sodium alginate (pH and electro-responsive)	Ibuprofen	[111]
	Poly(*N*-isopropylacrylamide)-co-poly(acrylic acid) (P(NIPAAm-co-AAc)) (Thermo- and pH-responsive)	Nifedipine	[99]
	Cellulose nanocrystal-zinc oxide (f-CNC-ZnO) nanohybrids based poly (3-hydroxybutyrate-co-3-hydroxy valerate) (PHBV) phase change nanofiber (PCF) (Thermo- and light-responsive)	Tetracycline hydrochloride	[121]

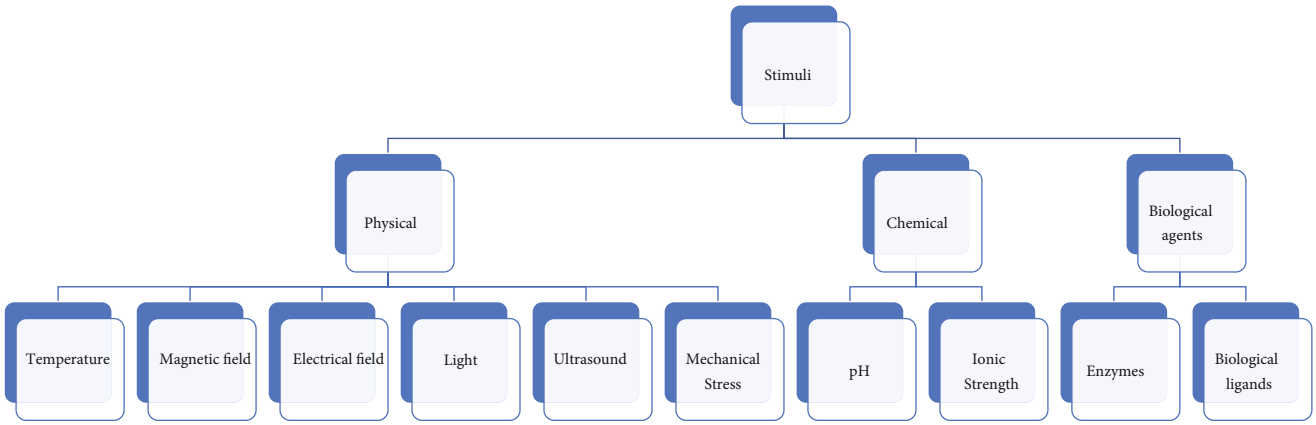

Figure 5: Triggers used in stimuli-responsive fibers.

6.1. pH-Responsive Fibers. Due to significant differences in pH of different organs and also change of pH in tissue upon infection, cancer or any other diseases, polymers with specific functional groups as amine or carboxyl might be used to control drug release in acidic or alkaline media, respectively [81, 92]. Therefore, release pattern of scaffold can be varied in different pH values.

Yan et al. reported a core–shell electrospun nanofiber composed of PVA (inner layer) and PCL (outer layer) as a simple pH-responsive DDS [92]. It was fabricated by coaxial electrospinning process with 3 different ratios of polymers and doxorubicin loaded in the core layer. Trend of release profiles in both neutral and acidic conditions were similar although drug was significantly released more in acidic medium (pH 4) which was due to higher degradation rate of PCL in lower values of pH compared to neutral condition (pH 7.4). It was also observed that rate of release was dependent on thickness of PCL layer as rate-limiting layer.

Demirci et al. studied on a pH-responsive nanofiber for ciprofloxacin used poly (4-vinylbenzoic acid co (arvinylbenzyl) trimethylammonium chloride)) [poly(VBA-co-VBTAC)] [93]. Release behavior was evaluated in 3 different pH media (acetate buffer solution, phosphate buffered saline, and tris-buffered saline) at 37°C. Because of similarity in hydrophobicity behavior in both drugs and polymers, burst release was relatively low from this fiber. In addition, electrostatic interaction between ciprofloxacin and cationic units of polymers (VBTAC) and presence of pH-responsive units (VBA) have shown reduction of release in basic solutions.

CVD was also used for preparation of pH-stimuli fibers. Sayin et al. deposited a thin layer of poly(4-vinylpyridine-co-ethylene glycol dimethacrylate) p(4VP-co-EGDMA) on the Rose Bengal loaded nanofibers (PVA-RB) [83]. The coating layer increased stability of nanofibers at neutral and basic pH values from 2 hours (in uncoated mats) to 72 hours. It was also shown that coated fibers released the drug in a controlled manner, which was higher at neutral and basic pH values, proportional to the pH of the solution and upon Fickian diffusion mechanism whereas uncoated nanofibers showed Peppas model because of dissolution of swelled polymer.

6.2. Thermo-Responsive Fibers. Another approach as an on-demand DDS is thermo-responsivity. Initial researches were carried out by thermo-responsive polymers, such as poly(*N*-alkyl) substituted acrylamides, poly(*N*-vinylalkylamides) and polyethers, which work by hydration-dehydration mechanism at the lower critical solution temperature (LCST) [94–96]. Release of loaded drugs could happen by changing shrunken structure of polymer to swollen in response to temperature elevation. Figure 6 shows the schematic of changes in the polymeric structure due to thermal stimuli.

As electrospun nanofibers of NIPAAm homopolymer are not stable in aqueous condition, copolymerization with desired co-monomers is required. Salehi et al. prepared doxorubicin-loaded nanofibers by poly(*N*-isopropylacrylamide-co-acrylamide-co-vinylpyrrolidone) P(NIPAAM-AAm-VP). Nearly zero-order kinetic of release was observed by these nanofibers for around 30 days, which has shown

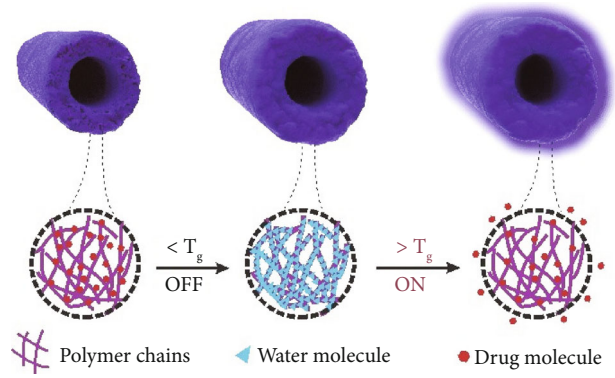

Figure 6: Schematic of changes in the thermo-responsive fibers.

good potential of such systems as implantable delivery over a long period [97].

In another study carried out by Kim et al., a new "on–off" controlled release system was prepared with the polysaccharide dextran [98]. Electrospinning was carried out using copolymers of NIPAAm and *N*-hydroxymethylacrylamide (HMAAm) subsequently crosslinked by thermal curing. Observed on–off switchable release of FITC–dextran was a result of volume changes in aqueous media in a fast and reversible response to cycles of temperature alternation. Amount of FITC–dextran released during cooling phases was negligible, which shows a successful on–off system.

As explained above, PNIPAAm as a well-known thermo-responsive polymer is water-soluble. It has a LCST of about 32°C in an aqueous medium, which is better to be changed to body temperature as DDS. For this purpose, the LCST of PNIPAAm could be adjusted by copolymerization with hydrophobic or hydrophilic monomers or also using other polymers as poly(acrylic acid) (PAA), with pH-sensitivity and bioadhesive properties [99]. These systems could be potentially utilized as dual stimuli-responsive DDS affected by both temperature and pH.

These thermo-responsive systems were not efficient enough as pulsatile DDS because of releasing most of the loaded-drugs in response to external stimulus [25]. To achieve a pulsatile profile, polymers with T_g near body temperature could be good alternatives. It was first reported by Amarjargal et al. They studied on a blended electrospun nanofiber composed of Eudragit® RS100 and bioinert poly (methyl methacrylate) (PMMA). It was shown that different ratios of the Eudragit to PMMA led to around 4 times decrease in the total amount of rhodamine B released in comparison to Eudragit® RS100/PMMA nanofiber with the ratio of 7 : 3. Due to restricted chains mobility below the T_g, premature release was prevented. On the other hand, increasing the chain mobility at the temperature above T_g, would be expected to promote a controlled release of the drug during the time.

Glassy state of polymers below wet T_g (here 37°C) leads to limited chain mobility and near zero release. Otherwise heating to above the wet T_g switches polymers to rubbery state results drug diffusion among chains. So, it was expected to provide an on-demand DDS by polymers with suitable T_g.

In the study above, they evaluated also this hypothesis and observed a sudden and sharp rise in the release rate during "ON" state (45°C), whereas a quenched release in the "OFF" state (37°C) over repeated temperature-driven cycles.

6.3. Chemical-Responsive Fibers. Most studies on chemical/biological sensitivity of electrospun fibers have been focused on sensing applications. High surface-to-volume ratio and using various materials with different conducting properties (electricity, ions, fluorescent, etc.) on or in electrospun fibers are attractive features for designing fast reactive biosensors. The large surface area of electrospun fibers leads to more loading of functional molecules in comparison to identical thin films and consequently higher detection signal [100].

Self-immolative polymers (SIPs), which have a head-to-tail depolymerization under triggering by external stimuli, have been studied in nanofiber membranes. As an example, electrospun fibers prepared by the mixture of SIP and polyacrylonitrile (PAN) provide ~25 times quicker and more responsive immolation than a cast film in the mixture of organic solvents as triggering condition. Depolymerization of SIP in the blended fibers results in increasing in the hygroscopicity of the membrane (−110° to ~0°). SIP/PAN in outer layer of coaxial fibers provides the minimal release of the encapsulated dye in non-triggering solution, while an instant release was shown in the triggering condition [101].

Accumulated macrophages in the infection site secrete cholesterol esterase (CE), which can hydrolyze ester bonds. The more severe the infection, the more the enzyme concentration is expected. In Shi et al.'s study, metronidazole (MNA) was grafted on PCL nanofibers, which were coated and functionalized by polydopamine and siloxane groups. The ester linkage of CE to the membrane can trigger the release of MNA from the nanofiber membranes [102]. A higher amount of MNA was released from the nanofiber mat by increasing the CE concentration, resulting in the enhancement of the antibacterial capability of the MNA-grafted nanofiber mat. This CE-responsive drug-delivery system seems to be an optimal choice for antibacterial guided tissue regeneration/guided bone regeneration membrane.

Despite high sensitivity of biologically responsive fibers, stability and bioactivity of enzyme's treated electrospun sensors are still a great challenge. Using enzyme-free scaffolds is a good alternative to overcome this problem. An electrospun fiber based on poly(vinylidene fluoride) and poly(aminophenylboronic acid) and containing boronic acid was prepared by Manesh et al. A complex of boronate groups with saccharides leads to the detection of glucose selectively using fibers containing the functional group 4-acryloyl-amidobenzo-15-crown 5. Sensors showed around 90% activity after 50 days, which shows good potential for long-term application [103].

6.4. Light-Responsive Fibers. Light is one of the environmental factors in both natural and artificial forms exposing human bodies. Although some short wavelengths (below 315 nm) are harmful to DNA, light can be a trigger of many smart delivery systems to control time and quantity of release [9].

The nanofibers fabricated by Li et al., through co-electrospinning of poly(*N*-isopropylacrylamide), silica-coated gold nanorods ($Au@SiO_2$), and polyhedral oligomeric silsesquioxanes, showed on-demand release of doxorubicin with NIR stimulation [104].

Goethite (–FeOOH) is a light stimulus used in some studies to provide a non-invasive way for prolonged release. In Sutka's study, methylene blue (MB) desorption was increased due to the dissociation of MB from geothite in the presence of mild visible light. Water-soluble drugs are good candidates to be used in such systems [105].

6.5. Magnetic-Responsive Fibers. One of the most interesting approaches for controlled and/or targeted drug delivery is magnetic-responsive systems. Using Fe_3O_4 NPs in fiber matrices makes specific magnetic and mechanical properties. In one study reported by Wang et al., the release behavior of hollow nanofibers loaded with iron oxide NPs and ketoconazole (Figure 7) was studied [106]. PCL and dimethyl silicone oil were used as the outer and inner layer of coaxial electrospinning, respectively. Faster drug release in the second phase was observed under an external magnetic field due to the increased movement of molecules and iron oxide NPs within drug-loaded fibers. It is hypothesized that Fe_3O_4 NPs movement under the magnetic field has a thermal effect, which can affect the integrity of fibers and release behavior as an accelerator parameter.

Spadaro et al. prepared a PEGylated-PLGA electrospun nanofibrous membrane loaded with silibinin [107]. The presence of iron oxide NPs in fibers provided remotely control and activation of release for at least 60 hours, without the burst effect. Although before applying the magnetic field, the samples were maintained at 37°C, a temperature of above 40°C was reached for both the solution and membrane. This observation confirms that drug release is because of heat inducing of the polymeric nanocomposites due to the delay in Neel relaxation of the magnetic moment.

6.6. Electro-Responsive Fibers. One of the key roles important in successful tissue engineering is similarity in conductivity between tissue and scaffolds. Conductive materials can potentiate cell growth, which is so interesting especially in muscle and nerve tissue engineering for maximum simulation to tissue behavior and increasing rate of regeneration [11].

Iontophoresis is an old application of electricity in drug delivery. However, limitation of transferrable molecules, skin irritation, and inflammation are some of the problems using this system. Metal NPs, carbon nanotubes, and electro-sensitive polymers can be used as good candidates in composite nanofibers that induce good conductivity in fibrous structures. Based on the voltage applied, drug release through nanofibers will change.

Yun et al. prepared electrospun poly(vinyl alcohol)/poly(-acrylic acid)/multi-walled carbon nanotubes (MWCNTs) nanocomposites modified by oxyfluorination to introduce the functional groups on the hydrophobic MWCNTs.

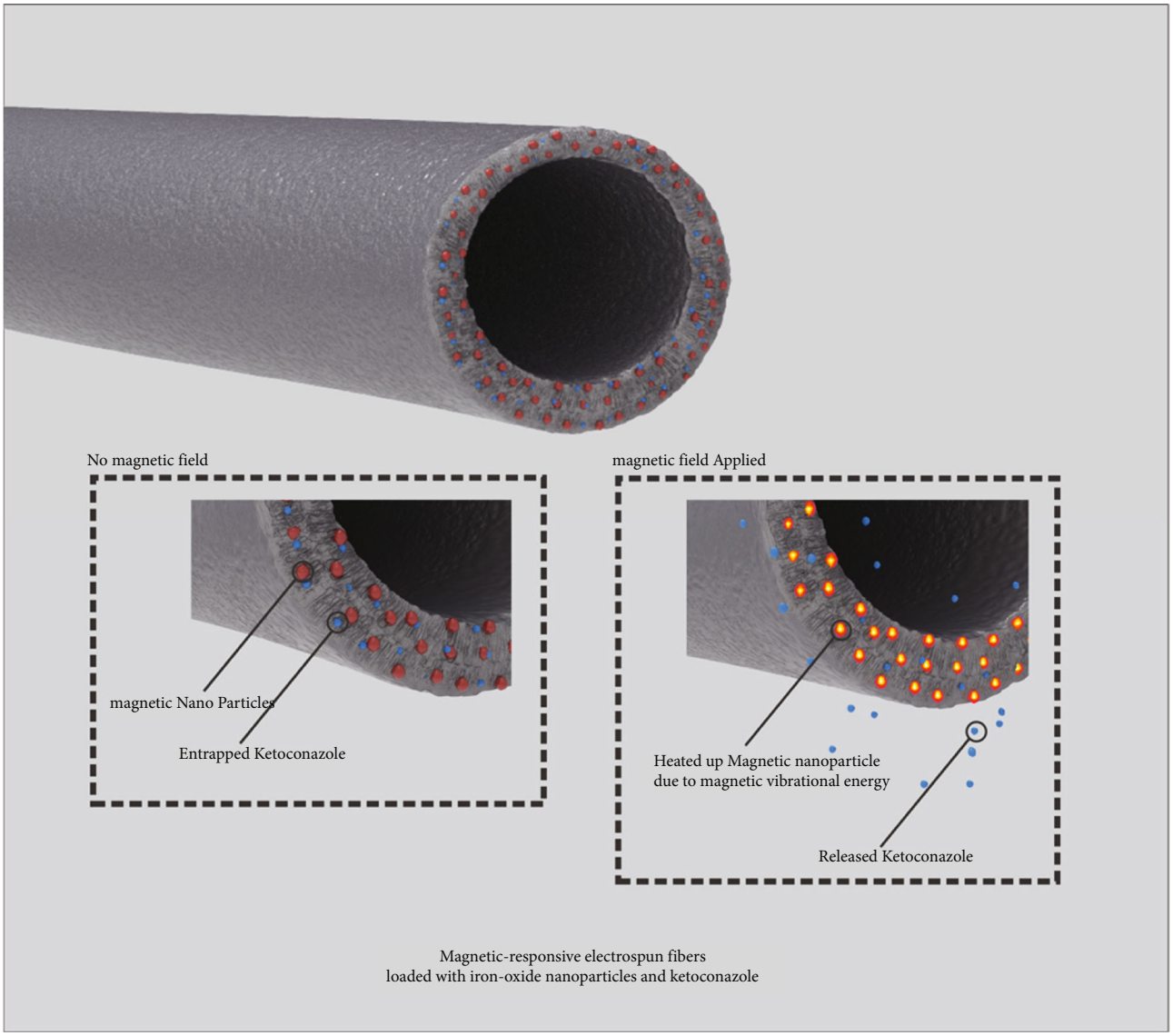

Figure 7: Release of ketoconazole from magnetic-responsive fibers [106].

Swelling behavior of nanofibers was dependent on the MWCNT content and oxyfluorination condition and drug release was also affected by these parameters. As shown in Figure 8, different external electric voltages applied on an electrospun structure lead to the variation of ionization of functional groups in the polymer matrices and consequently to a change in both swelling and drug release of nanofibers [108].

According to so many research studies on electro-responsive nanofibers in filtration, it seems separation techniques used in these studies can also be used in drug-delivery systems and electricity can be one of the triggers that can modulate time and amount of release for multi-drug systems [109].

In most studies, aniline was used as a conductive material in combination with other polymers, such as alginate, agarose, PCL, and carbon nanotubes. Bagheri et al. utilized chitosan–aniline oligomer/polyvinyl alcohol as blending electrospinning with conductivity value around $10{-}5\,S\,cm^{-1}$, which is suitable for tissue engineering. This property provided two features for scaffolds: one, as cell adhesion and activity enhancement by mimicking conductivity of the tissue and the other, potentiality of electro-responsive drug release as an on-demand release system [11].

Chen et al. also reported a core–shell electrospun microfiber fabricated by bacterial cellulose and poly (3,4)-ethylene dioxythiophene (PEDOT) as an electroactive scaffold. The release of diclofenac sodium, as a drug model, was dependent on external stimulation as there was no drug release below −0.3 V, while a pulsatile release observed under electrical stimulation around −0.6 to −0.9 V [110].

6.7. Multi-Responsive Systems. Improvement in polymer and biomaterial knowledge, using a mix of polymers with different characteristics and also bioactive agents, which have more than one trigger, is now an interesting subject for more

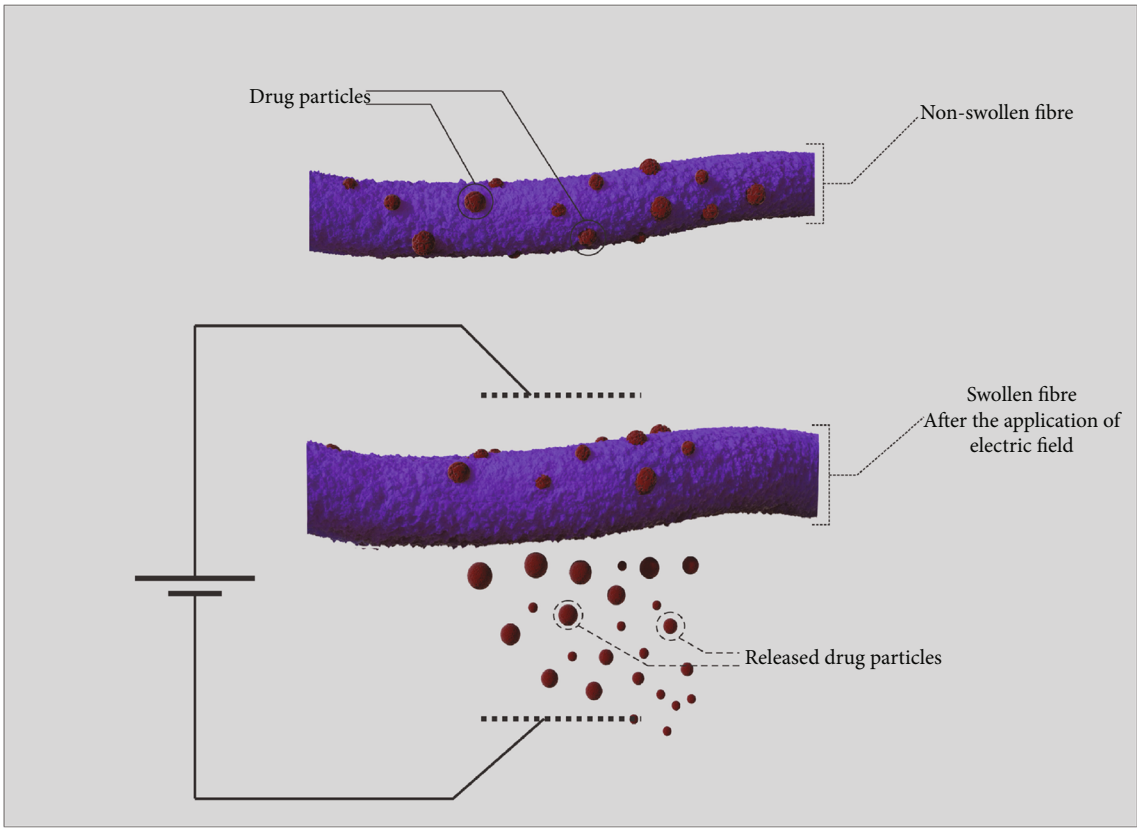

Figure 8: Release behavior from electro-responsive fibers.

adjustable and controllable electrospun systems for drug delivery. These can affect simultaneously or continuously.

As most of the electro-conductive polymers are also pH-sensitive, this kind of dual responsive structure can be a potentially good candidate for fabricating on-demand drug release systems [111]. Any changes in the pH and the electrical field that increase the swelling ratio of hydrogels lead to faster drug release and can be fitted with both Fickian diffusion and case-II transport based on Peppas' semi-empirical equation.

Embedding metal NPs, also called plasmonic NPs due to the surface plasma resonance phenomenon in the presence of light, within hydrogels is also another approach to provide a multi-responsive electrospun system. Based on the pulsatile irradiation of near infrared (NIR) laser, the matrix showed an on–off behavior. These NPs are sensitive to NIR light. Converting NIR to heat by NPs make the second stimuli that induce physical change in hydrogel. This photothermal effect has also benefits to fight against cancer cells [112].

Xiuling et al. prepared a composite nanofiber with synthesized thermo- and pH-sensitive copolymer of poly(*N*-isopropylacrylamide)-co-poly(acrylic acid) (P(NIPAAm-co-AAc)) and PCL-based polyurethane (PU) fabricated using the blend electrospinning technique and loaded with the water-insoluble drug nifedipine (NIF) [99]. The release amount of NIF from the nanofibers could be controlled effectively by adjusting even both the temperature or pH value of the aqueous medium and incorporating the hydrophobic PU. In higher temperatures, due to intramolecular hydrogen bonding between functional groups of PNIPAAm, polymeric chains do not swell and drug would be still embedded inside chains. On the other hand, AAc could change the behavior of the scaffold in different pH values. At low pH values, hydrogen bonding between the carboxyl group of PAA and the amide group of PNIPAAm was expected to be strong. Therefore, water solubility of matrix and drug release was reduced.

7. Conclusions, Challenges, and Future Perspectives

It seems that there is still a long way to solve challenges in the production of electrospun fibers in the pharmaceutical industry due to a lack of thermodynamic stability, not enough data about physicochemical parameters, drug loading, homogeneity of drug in fibers, and whole processing conditions [122, 123].

Although there are some electrospun grafts approved by FDA as medical devices, there is no DDS based on electrospun fibers until now. Only 174 patents are available for drug-incorporated electrospun fibers among more than 6,000 patents for electrospinning. As industrial aspect, Bioinicia has been established first Good Manufacturing Practice (GMP)-certified facility for fiber-based wound dressings. Most commercial products based on electrospun fibers have been developed in electronics and filtration systems and some in regenerative medicines as medical devices.

SURGICLOT® as a hemostatic dressing contains thrombin and fibrinogen proteins. This dextran based electrospun matrix can accelerate blood clotting at surgical or wound site. HealSmart™, Pathon, and Rivelin® patches are some examples that act as DDS but not as pharmaceutical products [122].

Different kinds of electrospun nanostructures exist for a wide variety of drug-controlled release profiles. The ways nanomaterials are made can be classified according to what determines the final structure of the material. Electrospinning is powerful in creating all types of nanostructures, such as core–shell, Janus, tri-layer core–shell, tri-section Janus, and other complicated ones [124–128]. These structures will be useful platforms to open new approaches for providing novel nanomaterials with the desired drug-controlled release profiles.

In conclusion, there are still a lot of studies needed for a reproducible, qualified DDS based on the electrospun fibers to be developed. It should be noticed that electrospinning fibers have also more applications besides controlling and targeting drug delivery. As the knowledge of polymers, spinnable materials and also new structures especially based on nanoscience are growing up, there would be much more options to use electrospun fibers. The most important challenge should be resolved is reproducibility of both fabrication and drug incorporation in large scale by development of new techniques or overcoming obstacles of present methods.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

S.K.A.: conceptualization, preparation of the manuscript, and rewriting the manuscript. M.A.: preparation of parts of the manuscript and all figures. F.A.D and H.A.J.: editing the manuscript. All authors discussed the writing concept and agreed to approve the manuscript. All authors have read and agreed to the published version of the manuscript.

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