



# Functional Nanofiber for Drug Delivery Applications

# 23

Rana Imani, Maryam Yousefzadeh, and Shirin Nour

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R. Imani (✉) · S. Nour  
Department of Biomedical Engineering, Amirkabir University of Technology (AUT), Tehran,  
Tehran, Iran  
e-mail: [r.imani@aut.ac.ir](mailto:r.imani@aut.ac.ir); [Shirin.nour@aut.ac.ir](mailto:Shirin.nour@aut.ac.ir)

M. Yousefzadeh  
Department of Textile Engineering, Amirkabir University of Technology (AUT), Tehran, Iran  
e-mail: [yousefzadeh@aut.ac.ir](mailto:yousefzadeh@aut.ac.ir)

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### Abstract

Electrospinning is an appropriate process to fabricate nanofibers for various applications. Regarding the intrinsically high surface-to-volume ratio of electrospun fibers, they are suitable candidates for drug loading with enhanced mass transfer properties. The diverse therapeutic agents, e.g., proteins, DNA, RNA, as well as chemical drugs, could be incorporated to the nanofibers. By controlling the nanofiber morphologies, its type, and drug incorporating methods, the preferred drug release and diffusion can be adjusted depending on the intended application. In this chapter, an attempt is made to cover the most usable methods to incorporate the therapeutic agents into the nanofibers and investigate the release mechanisms, factors, and methods to control the drug releasing rate. Most usable polymeric materials to fabricate fiber-based drug delivery formulations will also be introduced.

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### Keywords

Electrospinning · Nanofibers · Drug · Sustained release · Biomaterials

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## Introduction

Drug delivery systems (DDSs) have great importance for medical applications. Traditional DDSs are often imprecise, as they cannot provide a desirable therapeutic effect due to the delivery of an insufficient amount of drugs to the site of action as well as fast removal of drugs from the body, which needs repeating the dosage administration. Nowadays, more advanced DDSs are aimed at improving pharmacological properties of conventional dosage forms (e.g., tablet, capsules, topical creams, and injections). Most of the advanced DDSs are aimed at delivering a sufficient amount of drug for a desired period of time, avoiding the degradation of non-released drugs within the body and controlling the release rate to avoid undesired fluctuations of drug concentration in the bloodstream [1].

Over the past few decades, researchers have developed numerous carriers for drug delivery applications. Among them, micro- and nanofibers have become an attractive prospective as drug delivery carrier [2]. The local delivery and controllable release profiles make electrospun ultrafine fibers potentially implantable drug carriers and functional coatings of medical devices. Electrospinning seems to provide the simplest approach to produce nanofibers and is the most economically viable. It could provide a loading drug into the fiber matrix at room temperature processing conditions with simple situations. In addition, the morphology of the electrospun fibers as well as controllability of their properties, such as fiber

diameter, porosity, and surface properties, makes them ideal candidates for DDS application.

This chapter mainly aims at reviewing recent developments in employing the electrospun fibers for drug delivery applications. The different drug-loading techniques are introduced, and further considerations in designing fiber-based DDSs with controlled release rate are briefly discussed. Smart nanofiber systems with stimuli-responsive drug release behavior are pointed out as advanced fiber-based DDSs. The main applications of drug-incorporated fibrous structures are categorized and briefly reviewed.

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## Drug-Loading Mechanisms in Fiber-Based DDSs

The type of electrospinning process can greatly influence the properties of the resulting drug-loaded fibrous system. According to the characteristics and application of the drug-incorporated fibers, the loading approach is being chosen. In this section, the different electrospinning approaches for drug loading will be briefly reviewed.

### Direct Drug-Loading Approaches

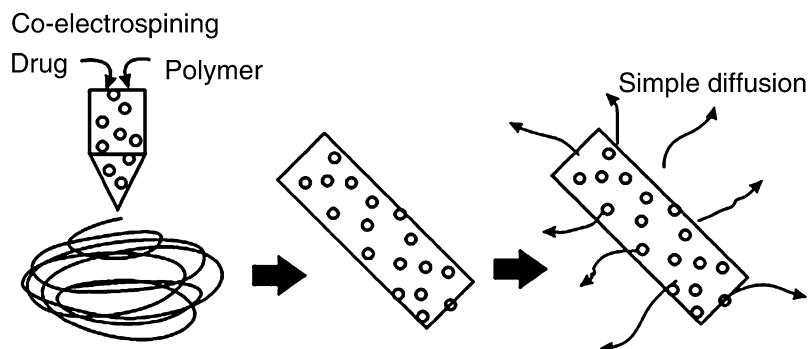
#### Simple Drug Loading

In this approach, drug molecules can be simply mixed with polymer solution before the electrospinning process. Subsequently, the homogenous drug/polymer/solvent solution forms the fiber structure through simple blending and electrospinning. In addition, the drug molecules can be physically immobilized on the preformed fibers via simple immersion of the electrospun mat into the drug solution or chemically conjugated onto the surface-activated fiber.

#### Electrospinning of Drugs and Polymer

The most predominant drug-loading method is dissolving or dispersing both the drug and polymer in the same solvent and electrospinning the mixture called co-electrospinning (Fig. 1). High drug-loading efficiency and ability to homogeneously disperse the drugs within the fibers are the main advantages of this technique.

It is also important to control the distribution of the drug molecules into the electrospun fibers as well as the morphology of the fibers because drug release behavior is dependent on them. In order to attain perfect encapsulation of drugs into electrospun fibers, the physicochemical properties of polymers and their interaction with drug molecules must be precisely considered. To prevent high attraction between the drug and polymer which limits the tendency of the drug molecules to migrate to the surface of the nanofibers and consequently release fast, it is necessary to determine optimized criteria [4]. According to the aforementioned reasons, one of



**Fig. 1** Schematic of drug loading via co-electrospinning method [3] (Copyright © 2013, The Pharmaceutical Society of Korea)

the main factors in co-electrospinning is the drug solubility in the polymer solution and homogeneity, which will be discussed later.

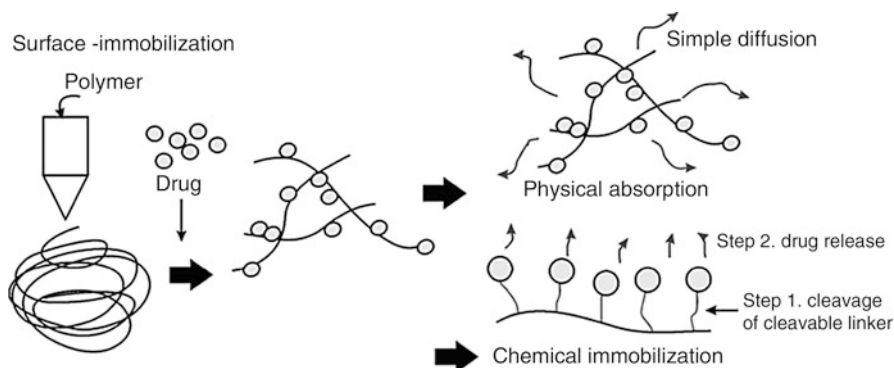
Natural polymers (such as gelatin, silk fibroin, collagen, alginate, and chitosan) have received much attention to incorporate hydrophilic drugs homogeneously as these polymers can completely dissolve in the aqueous phase. However, they have some limitations such as the collapse of nanofibers during posttreatment such as the cross-linking process and low viscosity of solution, which impede the electrospinning. To overcome these problems, additional hydrophilic synthetic polymers (like PEO) are required for increasing the solution viscosity.

Due to the negative effects of exposure to organic solvents and high voltage, co-electrospinning would not be a suitable method for sensitive drugs, particularly bioactive molecules. Moreover, simple blending of drug-loading methods exhibits a short time of release with an initial fast release, termed the “burst release effect.”

### Surface Immobilization on the Nanofibers

Other simple direct methods of drug loading are physical or chemical surface immobilization with target biomolecules (Fig. 2). In physical methods, secondary forces such as hydrogen bonding, electrostatic, hydrophobic, and *van der Waals* interactions are usually responsible for retaining the drugs on the nanofibers surface. In addition, the therapeutic agents can be directly immobilized on the fiber surface via chemical modification of the fiber surface with functional groups such as amine, carboxyl, hydroxyl, and thiol.

Compared to the co-electrospinning, one of the main advantages of physical and chemical surface immobilization of drugs on the fiber is that it can avoid drug denaturation caused by high voltage or organic solvents. Another advantage of the approach is the ability to control the amount of drugs immobilized by controlling drug feeding ratio. More importantly, this method exhibits slow drug release kinetics with reduced initial burst release, which can preserve the functionality of the surface-immobilized biomolecules for a longer period [3]. Hence, this approach is suggested



**Fig. 2** Schematic presentation of drug loading via surface immobilization method [3] (Copyright © 2013, The Pharmaceutical Society of Korea)

for gene or growth factor delivery, where a slow and prolonged release of the agent is required.

### Core/Shell Nanofibers

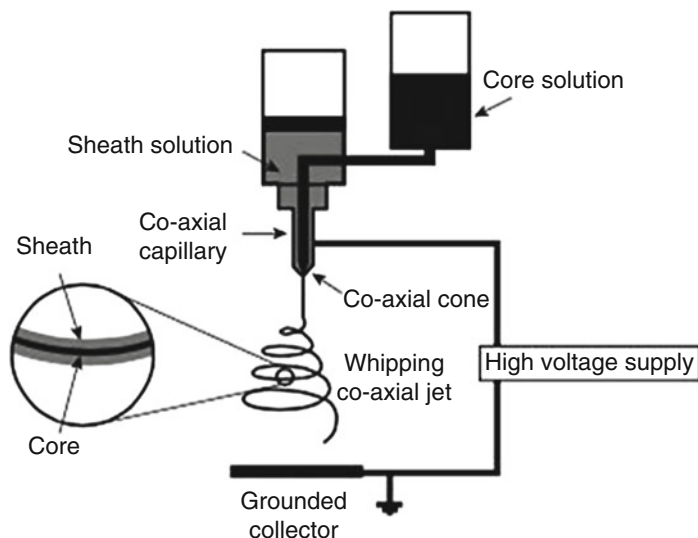
Despite being a simple approach, co-electrospinning has some limitations including problems with drug release kinetics and the immiscibility of drugs and polymers. The coaxial electrospinning technique has been developed for loading multiple drugs with different solubilities in polymers and controlling the release kinetics of each drug.

This method uses a coaxial spinneret needle that consists of an inner and outer nozzle arranged in a concentric geometry and attached to a double-compartment syringe of polymer supply, for spinning two separate solutions to produce core/sheath nanofibers, in which the biomolecule solution formed the inner jet and polymer solution formed the outer jet (Fig. 3). With the benefit of simultaneous electrospinning in this technique, electrospinning of two immiscible polymer solutions containing drugs in the core and sheath is possible [4, 5].

Feeding rates of the polymer solutions, applied voltage, compound concentrations, and molecular weights in the feeding fluids are controllable parameters for the formation of the core/shell with desired radius and thickness, respectively. Furthermore, the formation of a continuous fiber jet under the electric field in the coaxial electrospinning greatly depends on the solutions' conductivity and viscosity [6].

Most of the core/shell nanofibers used in drug delivery systems are loaded with hydrophilic polymers (such as PEG, PVP, PEO, or PVA) and drugs (e.g., proteins) in the core and hydrophobic moieties in the sheath. Furthermore, hollow nanofibers can be constructed by selective removal of the cores after the coaxial electrospinning procedure [8].

Although drug-loading efficiency is still in high amount in this method, sheaths of the nanofibers result in decreased initial burst release. Indeed, shell materials with hydrophobic properties (e.g., PCL) can play a barrier role against diffusion of the



**Fig. 3** A schematic of drug loading via coaxial electrospinning method [7] (Copyright © 2016 Wiley Periodicals, Inc)

drug molecules loaded in the core [7]. Since electric charges concentrate at the outer surface of the droplet, active agents incorporated in the core can be protected against electric charges. Apart from the mentioned advantages, there are some disadvantages including the complexity of the method and insufficient amount of released drugs, which may cause low local therapeutic concentration.

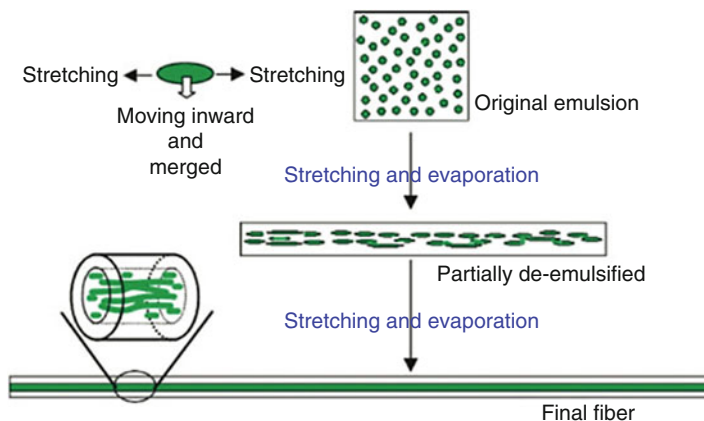
There is also an opportunity for surface bio-functionalization of the electrospun core/shell fibers by simply selecting natural bioactive compounds for the spinning of the shell layer or immobilization of functional groups on the fiber surface. Coaxially electrospun fibers can be employed for sustained, local, and efficient genes and growth factor delivery to the desired location within the body.

### Emulsion Electrospinning

In coaxial electrospinning, there are a lot of factors, which should be considered in the design step. Nevertheless, only a limited portion of the produced fibers can form the proper core/shell structure.

Emulsion electrospinning is a method whereby the drug or aqueous protein solution is emulsified within a hydrophobic polymer solution. At the end of electrospinning, the biomolecule-loaded phase can be distributed within the fibers (Fig. 4).

The ratio of hydrophilic to hydrophobic solution is one of the parameters that affect the distribution of the biomolecules within the fibers. This parameter plays a key role in regulation of the releasing profile, stability, and bioactivity of the encapsulated drug. In addition to the coaxial electrospinning, it is shown that by using ordinary single-nozzle electrospinning and the emulsion electrospinning method, it is possible to construct core/shell nanofibers [5].



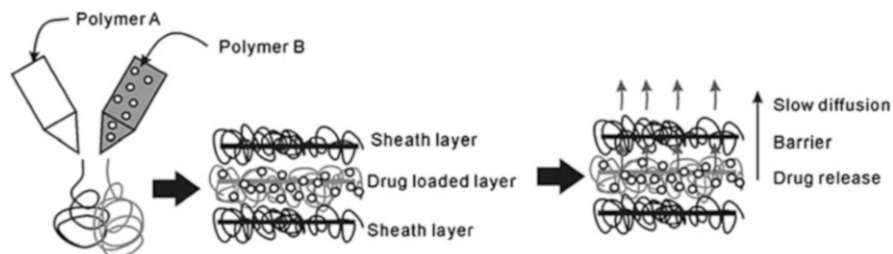
**Fig. 4** Mechanism of drug loading via emulsion electrospinning method [5] (Copyright © 2014 Taylor & Franc)

The main advantage of the emulsion electrospinning is that the drug and polymer can be dissolved in appropriate solvents. Consequently, numerous hydrophilic drugs and hydrophobic polymeric combinations can be used, while during this process the drug in contact with the organic solvent is minimal. However, there would still be a possibility to damage or degrade sensitive biomolecules like nucleic acids, mainly because of the shearing force and tension between the two phases of the emulsion. Therefore, further modifications like condensation of carrier gene in gene therapy might be useful for more protection [9]. During the emulsification or ultra-sonication procedures in emulsion electrospinning, the contact of core materials with the solvent is increased, which may cause probable damage to the drug contents.

### Layer-by-Layer (LBL) Nanofibers

One of the most practical methods used in the synthesis of different biomedical devices such as nano-/microparticles, micelles, films, and fibers, for tissue engineering and drug delivery applications, is LBL assembly. As depicted in Fig. 5, the LBL fibrous structure could be produced using two separate nozzles, which usually electrospin two different solutions simultaneously. The LBL structure can also be produced using sequential electrospinning of different drug-loaded polymer mixtures to fabricate a multilayered electrospun nanofiber mesh. The nozzle systems can be either coaxial or single [9]. Similar to the coaxial electrospinning, LBL systems provide reduced initial burst release because of the control drug release by sheet barriers. Commonly, polymer solutions without drugs were electrospun between the different drug-loaded solution electrospinning steps to reach the purpose of time-controlled drug release. Therefore, a sandwich-like structure will be created with different layers.

LBL systems can provide a great opportunity for construction of multilayered fibrous structure, where each layer could include specific drug. In such structures, the



**Fig. 5** Schematic illustration of drug loading via layer-by-layer electrospinning method [3] (Copyright © 2013, The Pharmaceutical Society of Korea)

drug release rate and timing could be affected by layer thickness and fiber size. In fact, multilayer-coated nanofibers can be produced through electrostatic or hydrogen bonding or even acid–base pairing in order to create polyelectrolyte multilayer structures that are suitable for drug delivery applications [10].

### Fiber–Hydrogel Hybrid Structure

Electrospun nanofibers can be hybridized with hydrogels for efficient drug delivery or raising the properties of the tissue-engineered scaffold. Hydrogels have attracted considerable attentions in drug delivery and tissue engineering applications due to their high capacity of water retention and drug loading, ability of dual drug delivery, extending to a variety of shapes, and resembling native tissue properties [11, 12]. A combination of the electrospun nanofibrous structure with the hydrogels can merge both their advantages. Studies have demonstrated that drug incorporation in nanofibers hybridized in the hydrogel dramatically reduced the initial burst release because of the hydrogel effect on delaying the drug diffusion rate after being released from the nanofiber (Fig. 6).

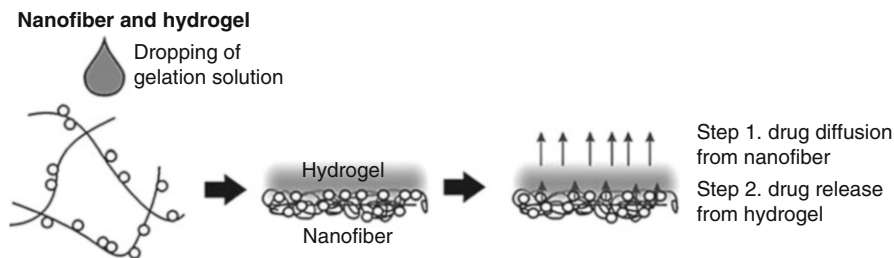
It is worth mentioning that in hydrogel–nanofiber hybrid systems, the electrospun polymer should maintain its fibrous structure in water with the hydrogel properties. Moreover, comprehensive swelling of hydrogel in body fluid environment can squeeze the incorporated nanofibers which may lead to fast release of loaded drugs. This phenomenon is almost a new approach in designing smart drug delivery systems [13].

### Beaded Nanofibers

It is important to point out that electrospinning process variables should be controlled in order to generate a flawless nanofiber and prevent beaded morphologies. Studies have shown that there is approximately a direct relation between both low and high flow rate of polymer solution and high applied voltage in increasing the beaded defect in fibers [14].

Despite being considered as an undesired phenomenon in electrospinning, the beaded nanofibers have interestingly acquired more attention in drug delivery applications nowadays. In fact, it is so challenging to encapsulate particle drugs (micron size level) into nanofibers. Employing the beaded nanofibers in the system





**Fig. 6** Schematic of drug loading via nanofiber–hydrogel method [3] (Copyright © 2013, The Pharmaceutical Society of Korea)

called bead-on-string nanofibers (in which beads are connected to each other with continuous nanofibers) can be an effective approach for micron-sized drug loading and their sustained release, because the beads are usually in the range of 1–2  $\mu\text{m}$  in diameter (Fig. 7) [15].

Investigation of the optimized condition to form the beaded nanofibers has illustrated that competition of surface tension and viscoelasticity as well as concentration of polymer solution are the key parameters in the formation of such beaded structures. In addition to electrospinning processing parameters and ambient conditions, the solution properties are the critical factors for adjusting the bead morphologies and diameters. The bead diameter is considered as an important parameter in evaluation of the encapsulation capacity of the electrospun bead-on-string nanofibers [16].

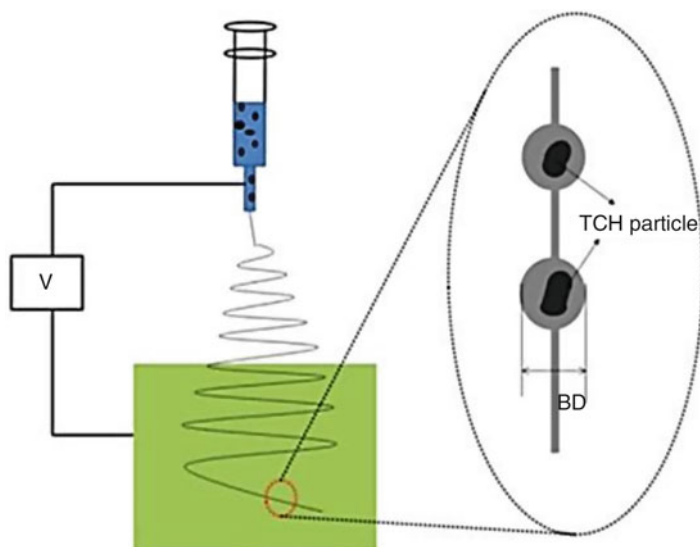
In order to synthesize the aforementioned structures, the microparticle drugs are initially dispersed in the same solvent of the electrospinning polymer solution to create a homogenous suspension. Then, the prepared suspension is gently added to the polymer solution and stirred. The final solution/suspension mixture is electrospun to produce the beaded nanofibers.

From the results reported in different studies, the beaded structures would be created only in a certain range of polymer concentration depending on the type of polymer and its critical entanglement concentration. Indeed, lowering the concentration of polymer in the electrospun solution will result in smaller diameter beads. Moreover, an increase in stretching force on the jet, which comes from the high conductivity of the solvent or adding charged particles into the solution, can hinder the formation of the beads.

Considering the release mechanism in bead-on-string nanofibers, the beads had bigger diameter representing reduced burst release than smaller ones, due to their thicker shell encapsulated in the drug particles [15].

## Nanocomposite-Embedded Fibers

During the past few decades, delivery of bioactive compounds, such as drugs, proteins, and genes, using nanoparticle (NP) encapsulation has been widely



**Fig. 7** Schematic illustration of beaded nanofibers encapsulating tetracycline hydrochloride (TCH) as particle drugs (*BD* bead diameter) [15] (Copyright © 2016 Elsevier B.V. All rights reserved)

investigated because NPs can be uptaken by cells and pass through cell membranes. Engineered NPs can provide an enhanced surface-to-volume ratio to load drugs on the surface or within particles and facilitate the delivery of payloads to the targeted cells [17].

Various nano-/micro-particulate drug delivery systems such as polymeric micro-/nano-formulations (e.g., polyerosoms, micelles), lipid-based particles (e.g., liposomes, niosomes, solid lipid nanoparticle), inorganic nanoparticles (e.g., porous silica, carbon nanotubes, graphene, clays), and metallic nanoparticles (iron oxide, Au nanoparticle) have gained huge interest as engineered drug delivery carriers [9].

Regarding electrospun fiber unique properties, the fibrous structure offers several desirable features suitable for DDSs. However, control of the burst drug release is one of the most important challenges for nanofiber-based drug carriers. Direct electrospinning of the drug/polymer mixed solution results in nanofibers with dispersed drugs in the polymer matrix, which usually display the burst drug release behaviors via the Fickian diffusion effect [18].

Recently, incorporating functional particles within the electrospun fiber matrix serves as emerging topics in electrospinning researches. NP-embedded electrospun fibers exhibit various potential applications in many different fields such as super-capacitors, batteries, solar cells, catalysts, sensors, and biomedicine, since the NP fiber composite properties can be tuned by the polymer and the NP properties as well as NP ratio [19]. The NP incorporation into the electrospun structure mainly aims at improving the fiber performance, e.g., increasing mechanical, thermal, and electrical properties or preserving the NPs from corrosion and/or oxidation.

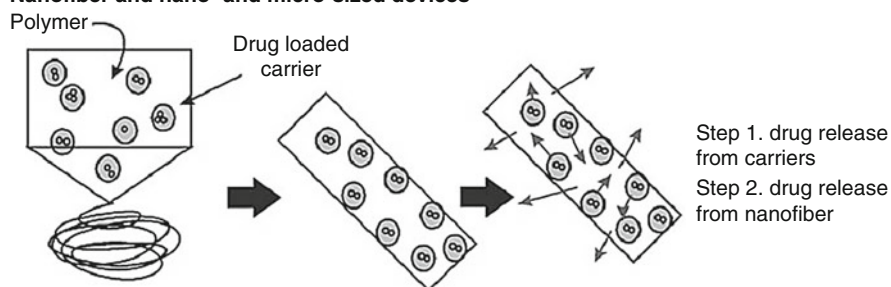
Combining the nano-/micro-particulate drug delivery carriers with electrospun fibers enables merging the advantages of both as well as introducing new capabilities to the combined structure (Fig. 8). Prolonged drug release from electrospun fibers can also be achieved by incorporating drug-loaded nano-/microparticles in the electrospun fibers [20].

Electrospun fiber hybridization with other types of particular drug carriers such as polymeric nanoparticles, nanotubes, micelles, microspheres, and liposomes could improve drug-loading efficiency, release pattern, and drug safety. Nano- and micro-particulate drug-embedded nanofibers almost resemble the core/shell nanofibers as they protect drug stability from organic solvents during the fiber forming and sustain the period of drug delivery [3]. Although the electrospinning process is convenient to incorporate therapeutic nano-/micro-carriers into the fibers, the parameter adjusting is important because adding the nano-/microparticles into polymer solution could change the viscosity of the solution. Regarding the size of the electrospun polymeric fiber, incorporation of the NPs seems more convenient than microparticles [19].

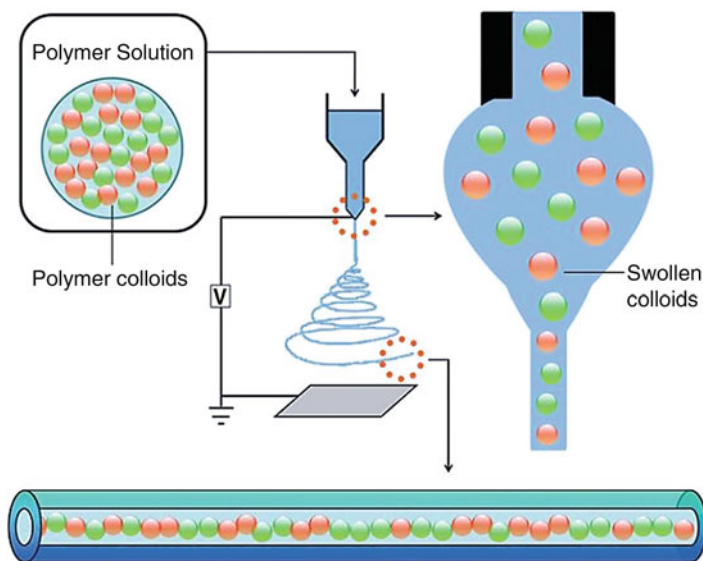
As mentioned before, studying the release behavior of embedding a single drug species into electrospun fibers demonstrated that most of the time, the release behavior is uncontrollable because considerable amounts of drugs are positioned on the surface of the nanofibers, which could release fast. Therefore, coaxial electrospinning was also proposed as a one-step process for producing core/shell nanofibers containing nano-/microparticles, which showed more prolonged release behavior for drugs embedded in the core part [21]. However, the single-nozzle electrospinning is more favorable, because it is a simple process with easier scale-up in production. For example, Jo et al. [22] developed a facile electrospinning method for producing the core/shell nanofibers composed of an array of different cross-linked polymeric particles loaded by different active agents (Fig. 9). The results demonstrated that by adjusting the physical properties of the colloids in the core, the process provides independent programmed control over the release of each agent.

The core/shell electrospun fibers have good potential to embed nanoparticle-based carriers in the core part. The shell could be employed as a barrier to render

#### Nanofiber and nano- and micro-sized devices



**Fig. 8** Schematic illustration of the nanofiber with nano- and micro-sized particles as DDS [3] (Copyright © 2013, The Pharmaceutical Society of Korea)



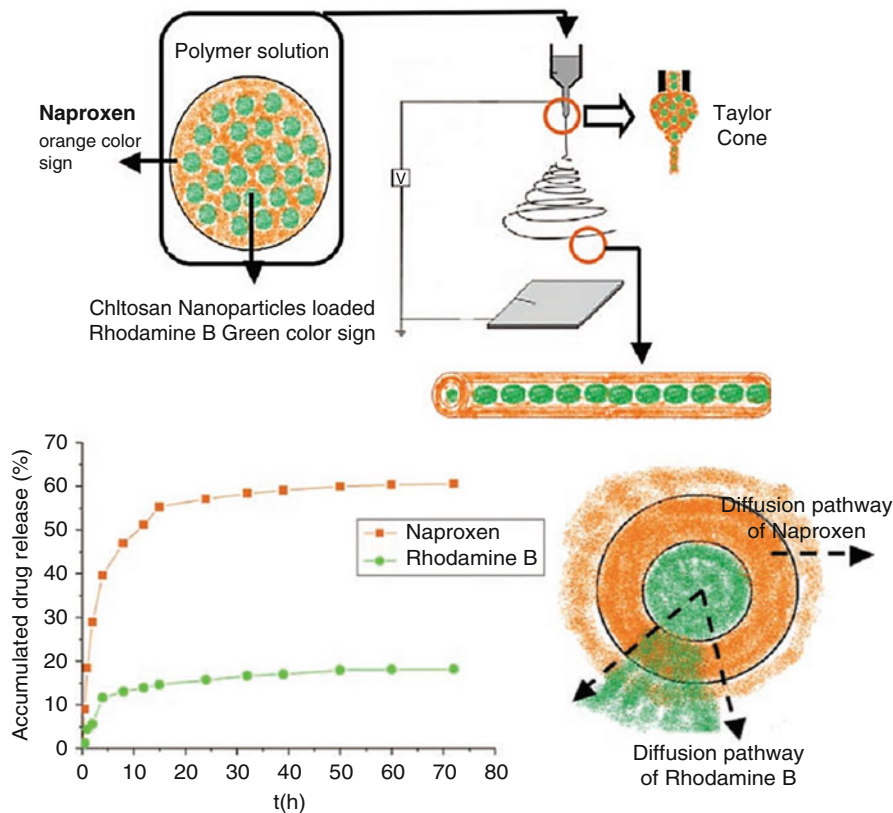
**Fig. 9** Schematic view of producing core–sheath nanofibers containing an array of colloids in the nanofiber core [22] (Copyright © 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

drug diffusion rate and potentially provide a more sustained-release rate. However, in the dual drug delivery approach, the shell could also be directly loaded with the other drug at the same time. Multiple agents loading in different sites of the core/shell nanofiber can provide independent control over the release of each agent. Wang and co-workers described the development of a novel controlled drug release system for Rhodamine B and naproxen, two model drugs, consisting of chitosan nanoparticles in PCL electrospun core/shell nanofibers [21]. They showed that the developed DDSs provided distinct release patterns for each drug (Fig. 10).

Two main methods could be employed to fabricate NPs/fiber composite structure including direct blending approach and surface immobilization approach. In the direct blending approach, the NPs could be incorporated into the fiber matrix during the fiber formation. The NPs could simply mix with the polymer solution before electrospinning. However, the stability of nanoparticles during the electrospinning process seems a challenging issue [19].

To achieve a uniform distribution of the nanoparticles within the fiber matrix, they should be completely wrapped by the polymer solution. Nonuniform distribution due to the nanoparticle aggregation may result in a wide distribution of fiber diameter [23, 24]. Also, aggregation or sedimentation of the NPs during the process may disturb the fiber formation due to clotting of the nozzle tip.

As mentioned, the hybridization of nano-/microparticles and the electrospun fibers can be utilized for multidrug delivery purposes, which is a very beneficial approach in combinatorial therapies [25]. The multiple drugs can be loaded into the NPs and the nanofibers separately using co-electrospinning, or two different drugs



**Fig. 10** Up: Schematic representation of preparing core/shell nanofibers containing chitosan nanoparticles encapsulating Rhodamine (as core) and naproxen (as shell). Down: Release behavior of two loaded drugs regarding their distinct diffusion pathways [21] (Copyright © 2010 Wiley-Liss, Inc. Published by Elsevier Inc. All rights reserved)

can be loaded into the nanoparticles embedded within the electrospun polymer solution [21, 22].

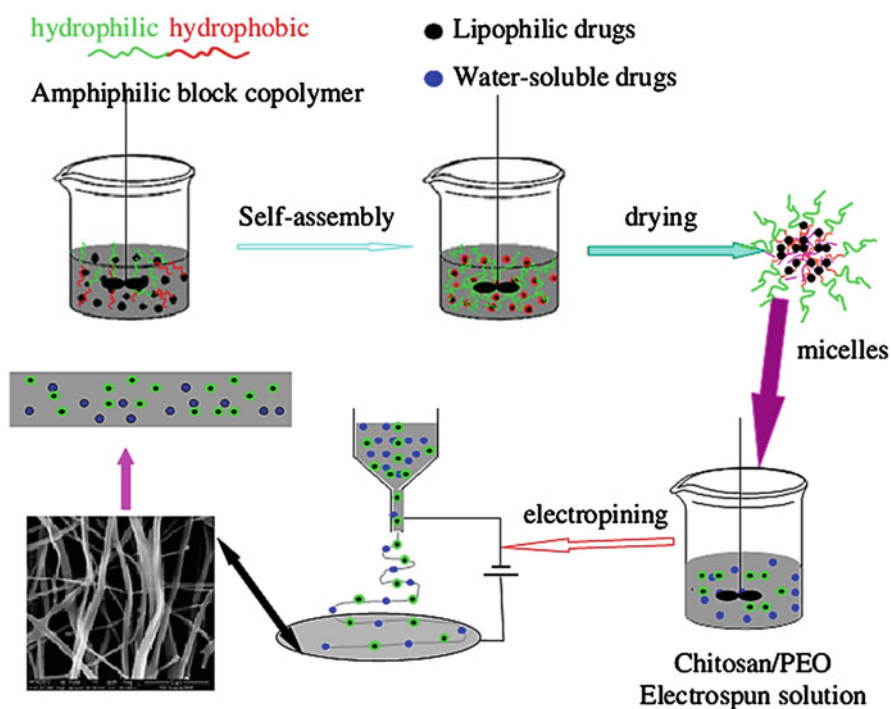
Apart from the direct blending of nano-/microparticles into the fiber, the drug-loaded particles could be immobilized on the surface of fibers. However, the drug delivery pattern of such systems shows faster release from the surface than bulk of the fiber. For example, Son and Yoo investigated the release rate of the micelle-incorporated drugs which were introduced on the surface of nanofibers by surface-immobilized polymer chains for antiproliferation studies of smooth muscle cells [26].

Among various nano-/microparticles introduced as drug delivery carriers, polymeric ones have been commonly utilized in combination with electrospinning fibers [19]. For example, polymeric nano-/micro-micelles, which are usually synthesized by self-assembling of amphiphilic polymers [27], could be simply incorporated into the fiber during electrospinning. Hu et al. combined the advantages of

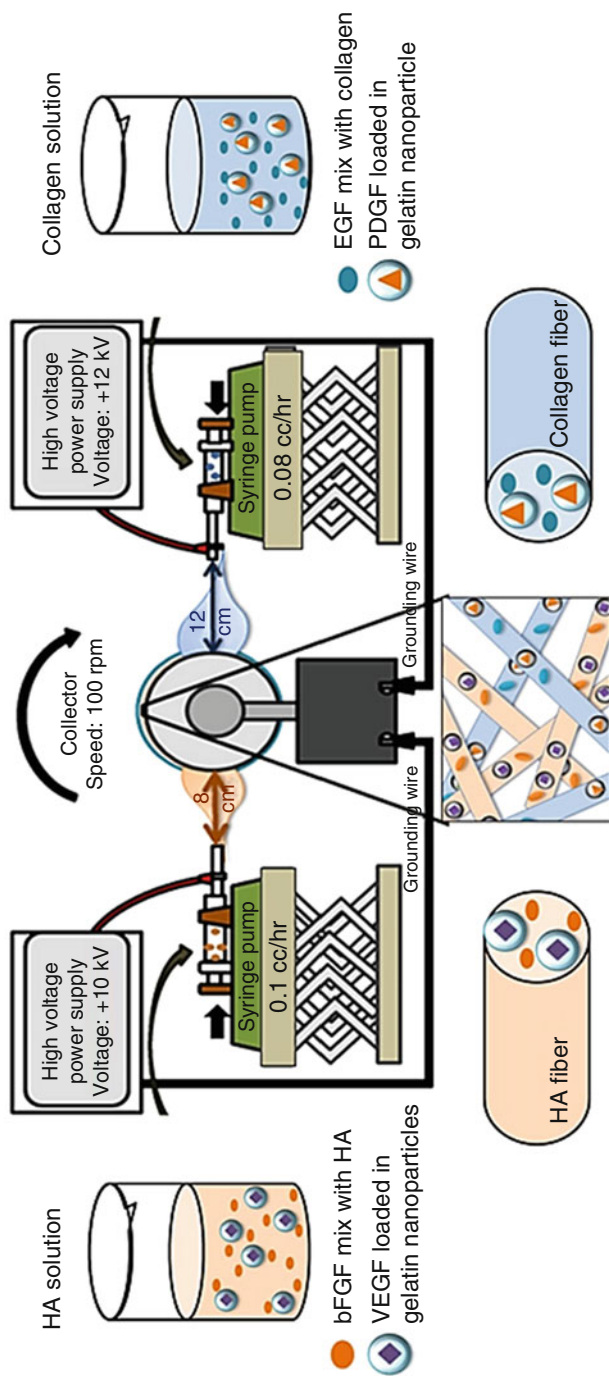
chitosan/polyethylene oxide (PEO) composite nanofibers and methoxypoly (ethylene glycol)-block-poly(L-lactide) (MPEG-b-PLA) micelles and fabricated a novel DDSs by incorporating two different model drugs (Fig. 11), cefradine (hydrophilic) and 5-fluorouracil (5-FU) (hydrophobic), for dual drug delivery [28]. The micelle-loaded nanofibrous membrane showed a significant sustained-release profile than the free drug encapsulated into the fiber matrix.

Natural polymeric nano-/microparticles were also used to incorporate therapeutic agents into the fibers. Lai et al. developed nanofibrous inter-stacking wound dressing based on collagen (Col) and hyaluronic acid (HA) for staged release of multiple angiogenic factors for diabetic wound healing (Fig. 12). Four angiogenic growth factors (GFs) were either directly embedded in the nanofibers or encapsulated in the gelatin nanoparticles (GNs), subsequently embedded in the fiber matrix by the single-nozzle electrospinning process. The designed particle-in-fiber structure provided a sustained release of growth factors up to 1 month [29].

Sustained local release of bioactive agents, e.g., growth factors, peptides, and proteins, has been utilized for acceleration of tissue regeneration in tissue engineering approaches. Since these factors have a short half-life, they may lose their bioactivity over a short time. Therefore, direct incorporation of bioactive agents in



**Fig. 11** Illustration of fabricating procedure used to load MPEG-PLA micelles into chitosan/PEO/nanofibers [28] (Copyright © 2014 Taylor & Francis)



**Fig. 12** Schematic representation of loading four different growth factors into fibrous structure. GFs either directly embedded in HA and Col nanofibers or encapsulated in gelatin nanoparticles and then incorporated into nanofibers [29] (Copyright © 2014 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved)



tissue engineering scaffolds does not always exhibit efficacy in tissue repair in vivo [30]. NP-embedded electrospun nanofiber scaffolds show good potential for controlled multiple deliveries of these kinds of bioactive agents. Li et al. developed a dual-drug-loaded poly( $\epsilon$ -caprolactone)-co-poly(ethylene glycol) (PCE) copolymer nanofiber scaffold for the repair of bone defects in bone tissue engineering. Bone morphogenetic protein 2 (BMP-2) was encapsulated into bovine serum albumin (BSA) nanoparticles to maintain the bioactivity of BMP-2, while dexamethasone (DEX), another commonly used bioactive molecule in bone regeneration, was loaded directly within the fiber matrix [31]. In vitro release profiles of DEX and BMP-2 demonstrated that the dual-drug-loaded nanofibrous scaffold showed a slightly slower than the single-drug-loaded one. Surprisingly, the release profiles of BMP-2 exhibit a slower zero-order-like release pattern, while the DEX release profile displayed a typical burst effect. It was confirmed that BMP-2 protection is afforded by the multi-barrier structure that supported continuous release for more than 35 days. Compared with the single or core/shell electrospun nanofibers [32], the results of this study demonstrated that the nanoparticle-embedded BMP-2-delivering scaffolds performed more effectively due to the dual-drug-loaded system, showing a sequential release pattern.

Inorganic NPs such as ceramic and metallic ones are widely studied as drug delivery carriers [33]. Loaded inorganic micro-/nanoparticles could also be incorporated into the electrospun fiber to improve the drug release pattern as well as tune the composite structure characteristics (e.g., mechanical properties).

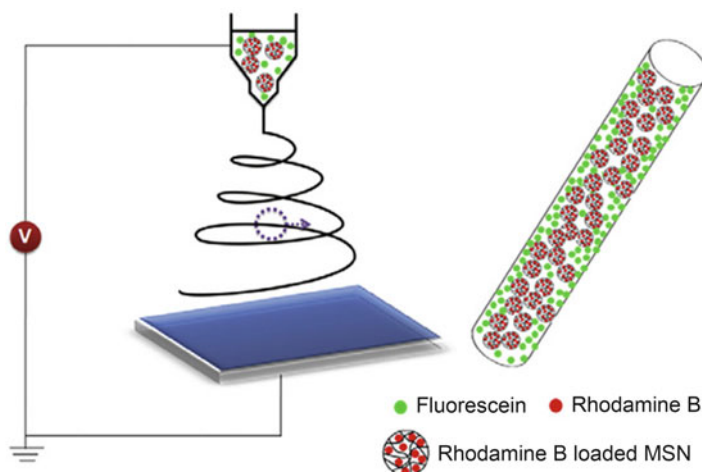
For instance, Chang et al. studied mesoporous silica nanoparticle (MSN)-incorporated poly(lactic-co-glycolic acid) (PLGA) electrospun mat. The composite fibrous mat was loaded by fluorescein (FLU) and Rhodamine B (RHB), as two model drugs, and their release profile was investigated [20]. Results showed that most of the FLUs (freely loaded in the shell part) were released rapidly, while RHB (MSN-loaded) showed a sustained-release behavior (Fig. 13).

The nanotube in the fiber composite seems a promising approach, which utilizes the capability of nanotubes and electrospinning technology. Inorganic nanotubes like carbon nanotube (CNT) or halloysite clay serve as a potent nano-container for drug delivery applications [34, 35].

Halloysite clay nanotubes doped into PCL/gelatin (PG) microfibers have been utilized for sustained delivery of metronidazole (MNA) from guided bone regeneration membranes. This nano-embedded microfiber architecture provided an extended release of metronidazole that prevented colonization of bacteria over a period of 3 weeks [36]. Incorporation of MNA into the halloysite nanotube, then adding to the fiber matrix, drastically slowed the rate of release, whereas without halloysite, around 90% of MNA was released from the membrane during 4 days.

Among the inorganic nanoparticles, carbon-based nanoparticles with high surface area like CNT or graphene have been successfully utilized to physically immobilize drugs [35, 37]. These kinds of particles show good potential to be embedded into the nanofibers during the electrospinning process. Shao et al. fabricated PCL/CNT composite electrospun nanofibers with green tea polyphenols (GTP) content of 0–10% for potential application in cancer therapy [38]. As depicted in Fig. 14, the in vitro GTP





**Fig. 13** A dual-drug-loaded electrospun composite fiber containing Rhodamine B-loaded MSN in the core and fluorescein in the shell [20] (Copyright © 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved)

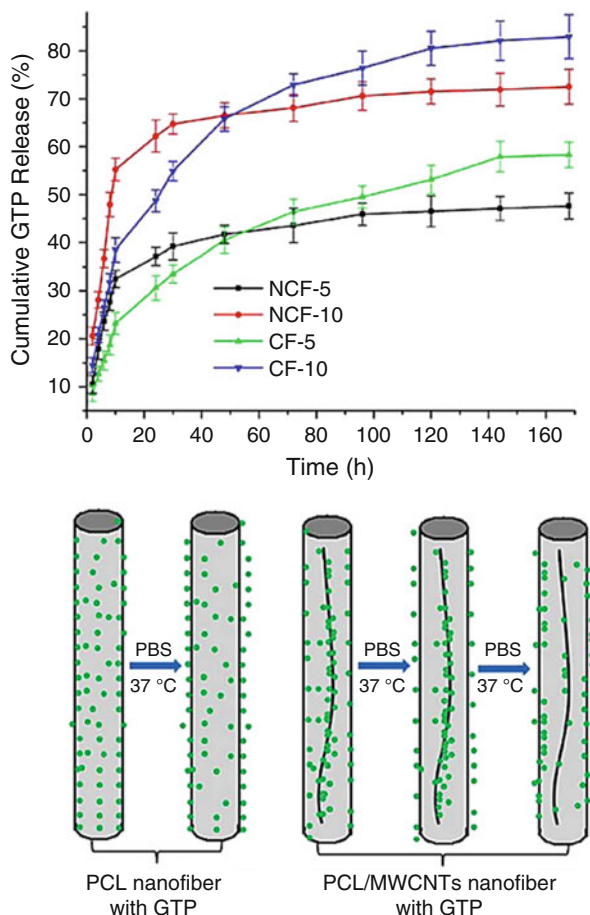
release study demonstrated that the cumulative drug release of PCL nanofiber containing GTP-CNTs (NCF) was significantly less than GTP-dispersed PCL nanofibers (CFs).

Although NPs embedded into the electrospun fiber can improve the release rate of encapsulated drugs compared to freely fiber-loaded drugs, the fiber matrix can improve some common nano-carrier drug delivery potential. For instance, lipid-based NPs (e.g., liposomes, niosomes, and solid lipid particles) have received widespread attention as carriers of therapeutic agents in regenerative medicine, whereas their applications are hampered by their short half-life, inefficient bio-stability, and poor control of drug release over prolonged periods [39]. Such disadvantages could be significantly improved by their combination with nanofibers through electrospinning.

Mickova et al. developed liposome-enriched nanofibers through two different electrospinning methods, blend and coaxial electrospinning, to incorporate liposomes into the nanofibers [40]. This study primarily aimed to investigate the delivery efficiency of horseradish peroxidase (HRP) as a model protein and delivered HRP enzymatic activity protection in samples prepared by blend or coaxial electrospinning with or without liposomes. The results demonstrated that in contrast with blend electrospinning, intact liposomes incorporated into nanofibers by coaxial electrospinning showed the highest potential for drug loading and sustained release. As the aqueous environment inside intact liposomes embedded in the nanofibers was retained during the release period, the fiber/liposome structure significantly enabled preserving HRP-specific activity. Moreover, nanofibrous scaffolds encapsulating recombinant GF (TGF- $\beta$ ) within the liposome were more potent at stimulating MSC proliferation than nanofibers without liposomes.

In another study, Li et al. developed a liposomal naproxen (NAP) releasing nanofiber mat for potential application as a wound dressing [41]. NAP-loaded

**Fig. 14** GTP release profiles from NFC samples and CF-10 nanofiber incubated in PBS (37 °C) (Top); the schematic diagram of GTP controlled release from PCL and PCL/MWCNTs nanofibers (Bottom) [38] (Copyright © 2011 Elsevier B.V. All rights reserved)



liposomes were embedded in the hyaluronic acid (HA) core, coated by cellulose acetate shell. NAP release behavior showed a specific pattern with a burst drug release at the initial stage and subsequently a sustained drug release for 12 days. Such burst release seems helpful to suppress the infection during the initial stage. In addition, the sustained drug release is necessary for efficiently supporting the wound healing for long periods without changing the dressing.

## Drug-Releasing Mechanisms and Rate Control Approaches

Controlled therapeutic agent release technology represents one of the advancing areas of biomedical and pharmaceutical sciences. Compared to conventional drug dosage forms, the advanced dosage form with controlled release rate capability offers numerous advantages including improved drug efficiency, reduced drug

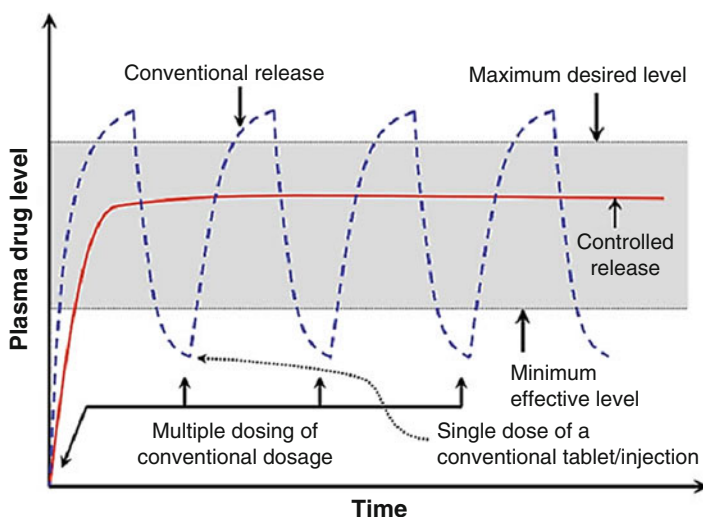
toxic side effects, reduced number of drug administrations required during treatment, and tuned release rate based on the disease condition [42].

In many traditional dosage forms, a sharp increase of drug concentration at potentially toxic levels accrues at the initial step of drug administration, followed by a relatively short period at the therapeutic level, and then drug concentration eventually drops off until re-administration (Fig. 15) [1].

DDSs employ electrospun materials to achieve controlled drug release. Using electrospun fibers for drug delivery applications has some unique advantages including efficient drug loading and encapsulation, diversity of material selection to be compatible with various drugs, simple modulation of the release rate, and simple processability [43].

### Controlled Release Mechanisms in Nanofibers

Here, specific attention is given to common mechanisms of sustaining the release of drugs loaded in the fiber-based formulations. The release mechanism is simply defined as “the way in which drug molecules are transported or released” [44]. Understanding the release mechanisms is a key step to developing the DDS dosage form. Regardless of the dosage forms, different release mechanisms or rate-controlling processes in the polymeric DDSs have been reported in the literature, mainly including dissolution of the drug (in combination with diffusion), diffusion



**Fig. 15** The drug release pattern of a traditional dosage form such as oral capsules or injection dosing (blue dashed curve) compared to a typical controlled release system (red continuous curve). Gray area indicates therapeutic windows [1] (Copyright © 2015, Springer-Verlag Berlin Heidelberg)

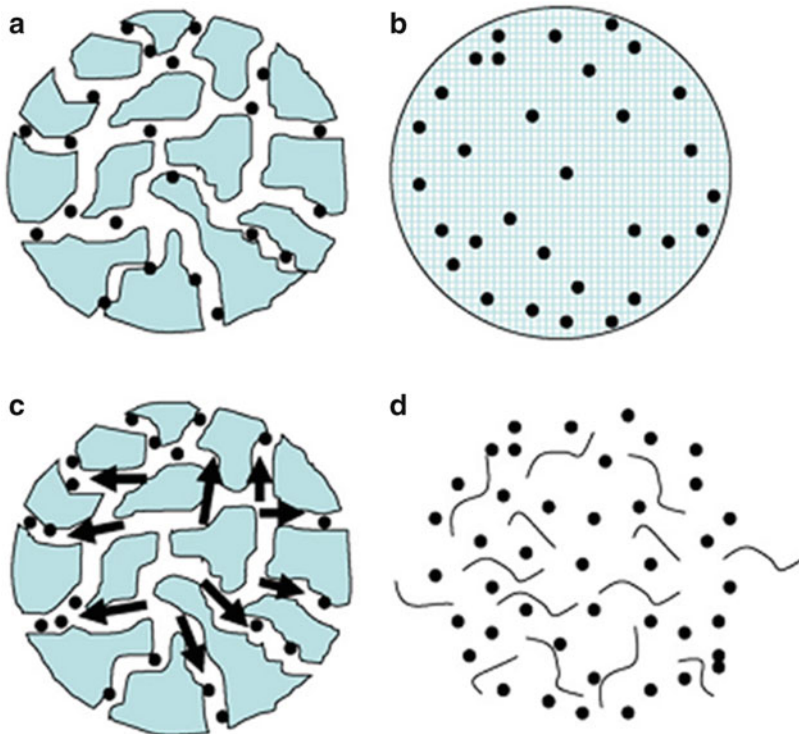
through water-filled pores, diffusion through the polymer matrix, degradation, erosion, swelling, and osmotic pumping [45].

However, the three main release mechanisms associated with drug release from common dosage forms are diffusion (through water-filled pores or the polymer bulk), degradation/erosion, and osmotic pumping (Fig. 16).

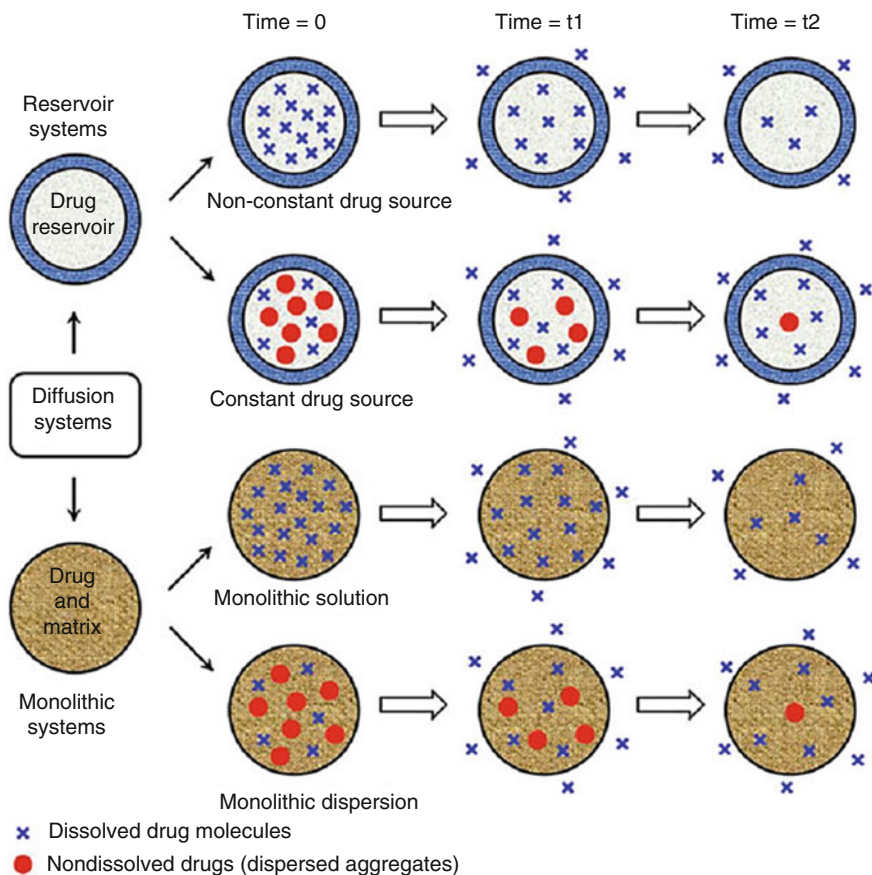
Among these mechanisms, the degradation/erosion does not require drug transport within the polymeric matrix, whereas in the other ones, the drug molecule transport is to be released.

In diffusion-controlled rate systems (Fig. 17), the drug molecules randomly move out of the device through a difference of chemical potential (concentration gradient) as a driving force. The diffusion can occur within a polymer matrix (monolithic matrix-based DDSs) or across a polymeric membrane, which surrounds a drug reservoir core (reservoir-based DDSs) [1].

In contrast, in degradation-/erosion-controlled release systems, drug reservoirs are encapsulated by dissolvable/degradable polymeric membranes (reservoir DDSs) or dispersed/dissolved within dissolvable/degradable polymeric matrices (monolithic



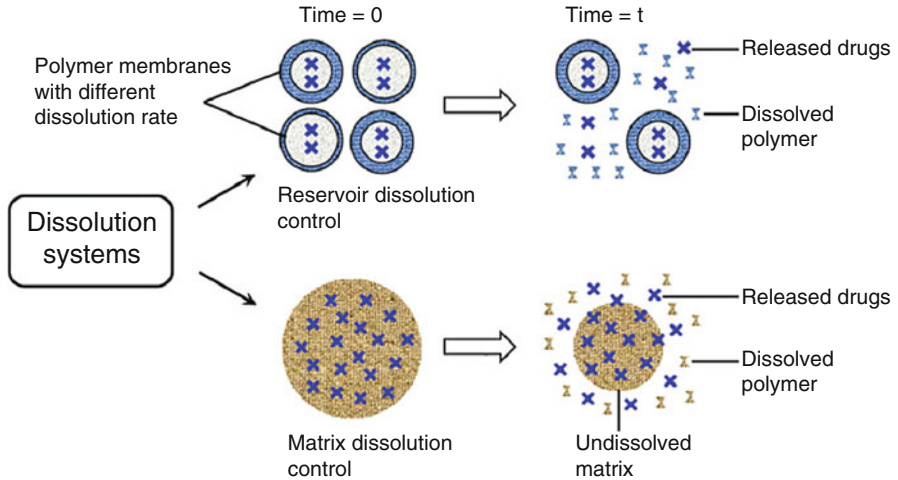
**Fig. 16** Common release mechanisms associated with various DDSs. Diffusion through water-filled pores (a) and the polymer, (b), osmotic pumping, (c, d) degradation/erosion [45] (Copyright © 2011 Elsevier B.V. All rights reserved)



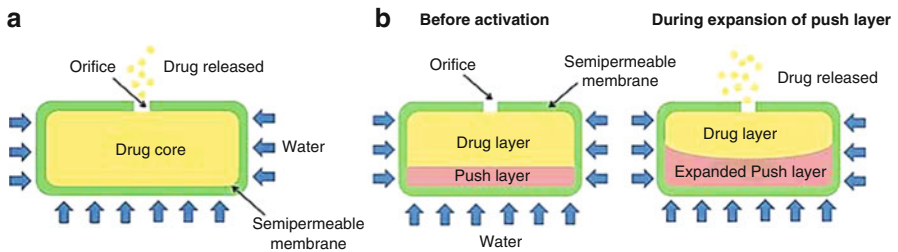
**Fig. 17** Major types of diffusion-controlled release systems [1] (Copyright © 2015, Springer-Verlag Berlin Heidelberg)

matrix DDSs). In such systems, the drug molecules can be released from the reservoir core by dissolution of encapsulating membranes, whereas in matrix degradation-/erosion-controlled systems, dissolution or degradation of the polymeric matrix drugs results in drug release (Fig. 18). If polymer undergoes a decrease in average molecular weight, the process is termed degradation, whereas if polymer undergoes a decrease in total mass, the process is termed erosion. Thus, usually degradation and erosion can occur at the bulk and surface of the polymers, respectively [46].

Convection, bulk water movement, is another way for transport into the polymeric DDSs through water-filled pores, which is mainly affected by the osmotic pressure-driven force. In osmotically controlled systems, it is necessary to have an osmotic agent (e.g., salts, sugars, PEG, PVA) within a semipermeable membrane reservoir [47]. The semipermeable membrane, which is permeable to water but not the loaded drugs, is a key component in osmosis-based DDSs (Fig. 19). However, this mechanism was rarely reported for the electrospun fiber-based-DDSs.



**Fig. 18** Schematic illustration of controlled release systems based on the matrix and reservoir dissolution mechanism [1] (Copyright © 2015, Springer-Verlag Berlin Heidelberg)

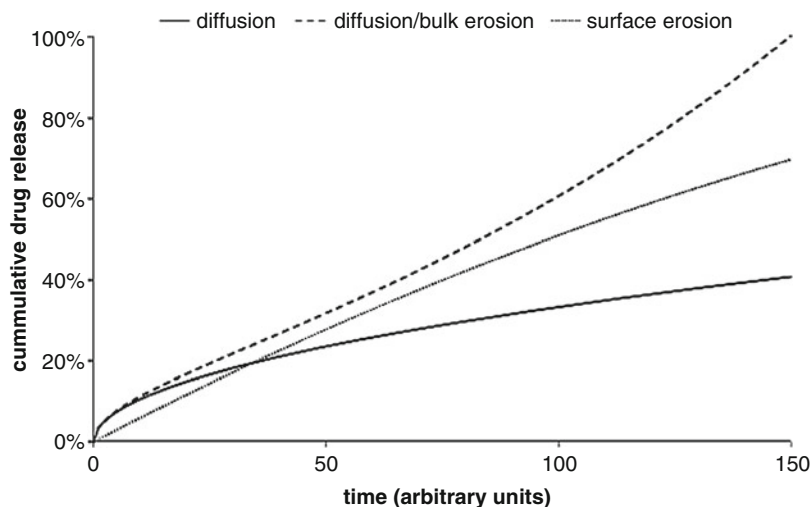


**Fig. 19** Schematic illustration of the (a) elementary osmotic pump and the (b) push-pull osmotic pump [48]???

Single-nozzle electrospun fibers usually serve as monolithic diffusion or degradation-based DDSs. In contrast, coaxial electrospinning typically produces a reservoir-like diffusion-type release system, where the drug molecules are encapsulated in the inner solution core and the outer shell forms the barrier layer surrounding core reservoir [49]. The release profiles of these systems are usually governed by diffusion through the shell membrane relative to the change of concentration gradient. Incorporating some porogen agents, e.g., salts, PEG, dextran, albumin, etc., can modify the diffusivity across the shell barrier [50].

The release profile is sometimes utilized for mechanistic evaluation of the studied dosage forms. Different release profiles due to diffusion, bulk degradation, and surface erosion for a typical uniform distribution of drug molecule in fibers are depicted in Fig. 20 [46]. The shape of the release profile does not often follow the pure diffusion or degradation pattern, where it consists of different phases.





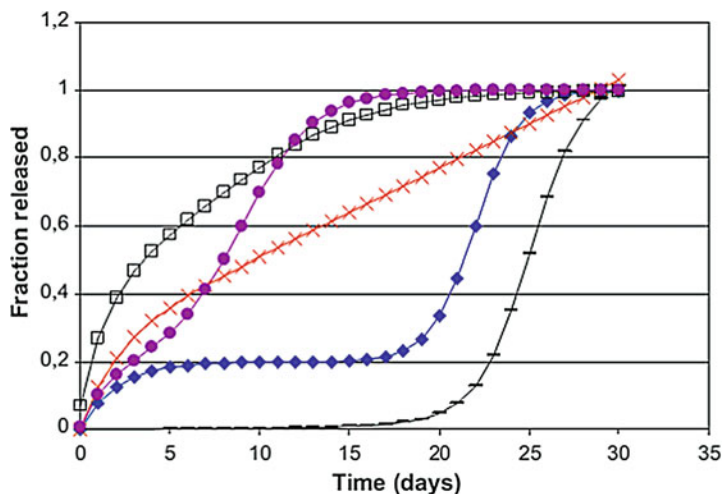
**Fig. 20** Different release profiles due to diffusion, bulk degradation, and surface erosion for a typical uniform distribution of drug molecule in fibers [46] (Copyright © 2010 Elsevier B.V. All rights reserved)

Since the drug release may proceed via a combination of two or more mechanisms, the release profile consists of different phases (Fig. 21) [45]. The first phase observed in the release profile is usually attributed to the burst release effect, where the non-encapsulated drug molecules on the surface or encapsulated drug molecules near the surface are easily released in a short time. However, sometimes, the observed burst release may be the result of cracks and the disintegration of formulation [51]. The release profile in the second phase often slowly proceeds, during which the drug gradually diffuses through the polymer matrix or through the pores or releases by slow polymer degradation. The last phase is sometimes called the second burst, during which the release profile shows acceleration due to onset of erosion or losing polymer integrity once again [45].

Besides studies that have experimentally worked on fiber-based DDSs, some studies utilized the modeling approach to investigate the release behavior of electrospun fibers with different fiber architecture or release mechanisms [49]. Developing an appropriate model to estimate the structural parameter effect on the release rate could be helpful to pre-adjust the electrospinning process variable or polymer characteristics, particularly when the dominant mechanism is diffusion.

## Factors Affecting Drug Release Mechanism and Kinetics

Besides the release mechanisms, understanding factors that affect drug release as well as physicochemical processes that influence the release rate is very important in order to be able to modify DDSs for a given application [52]. The properties of the



**Fig. 21** Typical drug release profiles including different phases.  $\square$ : burst release and a rapid release phase II.  $\bullet$ : triphasic release pattern with a short phase II.  $\times$ : burst release followed by zero-order release.  $\diamond$ : triphasic release pattern.  $-$ : biphasic release pattern without the burst release [45] (Copyright © 2011 Elsevier B.V. All rights reserved)

DDSs and the surrounding environment, which dominantly impact the drug release pattern, are listed in Table 1. However, these properties are not independently associated with the drug release rate; thus, understanding their effects on the release behavior could be complex. For instance, the complex interactions of the various parameters that influence drug release from PLGA, one of the most frequently used biodegradable polymers in DDSs, are depicted in Fig. 22.

Although the electrospinning process has various interconnected factors, which are simply tunable, polymer- and drug-related parameters must also be taken into account to achieve an optimized design for sustained drug release. Here, the most important factors discussed in the literature are briefly reviewed.

### Polymer Composition

Selection of a suitable polymer composition as well as altering the physicochemical properties of the selected composition is a simple mean to modify the release kinetics of a drug delivery system.

Affecting the rate of water diffusion into the electrospun fiber network is a strategy to control sustained release of drugs. Water diffusion into the fiber is mainly dependent on hydrophilicity/hydrophobicity of polymer-formed fibers [53]. Tuning hydrophilicity/hydrophobicity of synthesized polymers can also be utilized to control water diffusion into the polymeric matrix. Hydrophilic drug molecules can diffuse faster within the hydrophilic polymeric matrix. In degradable-controlled release fibers, wetting properties and solubility of the polymeric matrix mainly impact the drug release rate [54].



**Table 1** Properties of the DDSs and the surrounding environment that influence drug release [52] (Copyright © 2011 Elsevier B.V. All rights reserved)

The polymer	In vitro conditions
Molecular weight	Temperature
L/G ratio	Stirring
End-group capping	Composition of the release medium
Semi-crystallinity	pH
	Osmolality
Encapsulated substances	In vivo conditions
The characteristics of the drug	Sink conditions
Drug load and location	Enzymes
The characteristics of additives, such as salts, surfactants, and plasticizing agents	Lipids
	Immune responses
The DDS	
Size	
Porosity	
Density	
Shape	

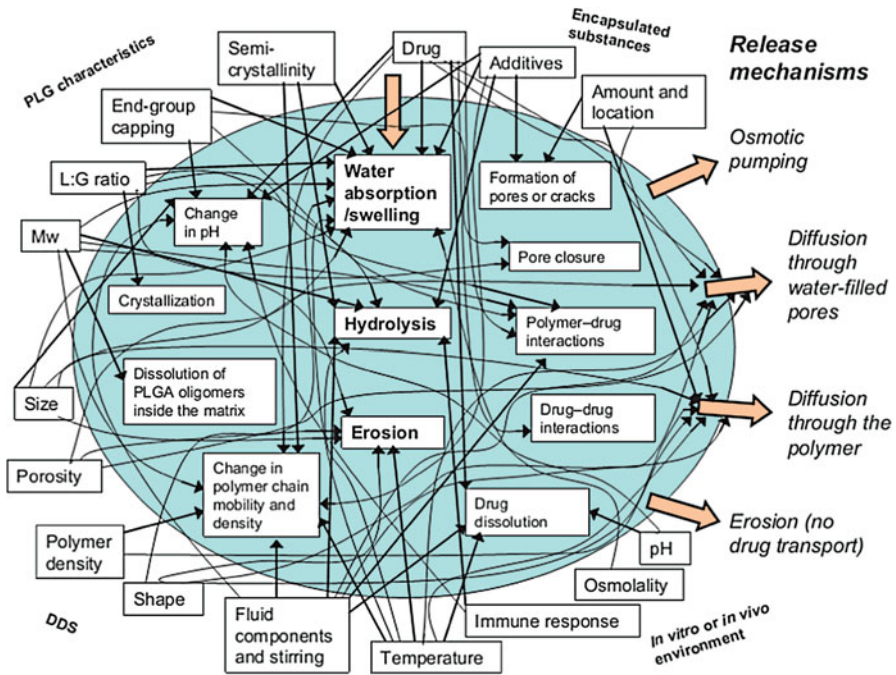
Crystallinity of polymers is a key structural parameter which will affect the drug releasing rate [55]. Increasing the crystallinity of the polymer matrix retards the rate of water diffusion into these materials. Consequently semi-crystalline polymers are often used for sustained drug release and show slower release rate than the amorphous structure [43].

In addition, cross-linking of polymer chains can also impede water penetration as well as drug diffusivity, which makes them useful materials for some sustained-release applications [56].

Glass transition temperature ( $T_g$ ), the temperature at which the polymer transitions from a hard, glassy material to a soft, rubbery material, serves as a structural property that controls the polymeric chain molecular motion at a given temperature. Consequently,  $T_g$  can impact molecular diffusion within the matrix polymeric chains in the release condition. In the high  $T_g$  polymers, the drug release rate can be sustained by hindering diffusion through the polymer chains. Some studies have investigated the effect of polymer  $T_g$  on drug release rate. In a study by Lyu et al. [57], two polyurethane (PU) fibers with low and high  $T_g$  were loaded by hydrophobic dexamethasone at 10 wt.% using uniaxial electrospinning. The results demonstrated that the PU fiber with higher  $T_g$  represented a lower drug release rate at the same condition. Interestingly, the intermediate release of dexamethasone was achieved by blending two PUs. Therefore, they could adjust the drug diffusivity using miscible polymer blends, where the drug diffusion coefficients were tuned from  $7 \times 10^{-23}$  to  $3 \times 10^{-19}$   $\text{cm}^2/\text{s}$ .

### Drug Properties

In addition to the polymer characteristics, properties of the loaded drug molecule as well as polymer/drug interactions effectively influence the drug release behavior.



**Fig. 22** Schematic illustration of the complex interactions of the various parameters that influence drug release from PLGA-based DDSs. Arrows indicate the effects of the properties of the DDSs and the surrounding environment on the processes [52] (Copyright © 2011 Elsevier B.V. All rights reserved)

Drug/polymer compatibility, which refers to the physical interaction between drug molecules and polymer chains, should be considered in designing the stage of fiber-based DDSs [43]. The drug/polymer compatibility will dictate how the drug molecules distribute in the final electrospun fiber matrix. Drug solubility in the polymer/solvent system will predominantly determine the compatibility. The lower solubility of drugs in the polymer solvent would cause some extent of phase separation during the spinning process that result in greater accumulation of the drug on the surface of the fibers, showing higher burst release. For example, paclitaxel is highly soluble in the organic solvent, whereas doxorubicin hydrochloride shows low solubility. Zeng et al. [58] utilized PLLA electrospun fibers to load these two anticancer drugs. They reported a preferable encapsulation of paclitaxel and doxorubicin due to their good compatibility with PLLA and solubility in the chloroform/acetone solvent. However, since doxorubicin hydrochloride has lower solubility in the solvents, it tended to accumulate on or near the surfaces of PLLA fibers. Consequently, an obvious burst release was found for doxorubicin than paclitaxel.

Another important characteristic, which affects drug distribution within the finished fibers, is the ionization degree of the incorporated drug. The ionization degree refers to the proportion of neutral molecules that are ionized to charged molecules.

The conductivity of the solution can be increased by the presence of ionized drug molecules [59], which increase the charge density of the jet resulting in the fibrous morphology. The drugs with higher ionic strength usually tend to be localized to the surface of the electrospun fiber. Particularly, during electrospinning of hydrophobic polymers, the majority of the drug molecules will migrate toward the surface of the nanofibers because the physical interactions between such polymer matrix and the drugs with high ionic strength are limited. Introduction of more hydrophilic parts such as amphiphilic block copolymers to the hydrophobic polymer structure can compensate the interaction and consequently lead to better drug distribution into the fiber matrix. Kim et al. [60] demonstrated that cefoxitin sodium salt, an antibiotic agent, incorporated into the PLGA nanofibrous scaffold showed more than 60% burst release in the first hour of incubation in the release media due to the high ionization degree of the drug and low compatibility with PLGA matrix. However, PLGA blending with the PEG-b-PLA amphiphilic copolymer improved the cefoxitin sodium dispersion into the fiber matrix and decreased the burst release effect.

Since the ionized drug mixing with polymer solution provides higher conductivity and the diameter of the electrospun fibers decreases at higher drug-loading levels, the drug release rate increases [60, 61]. In addition, increasing the drug content may impact matrix polymer properties, e.g., interrupting crystallinity, thus resulting in a faster release rate. For example, Zamani and co-worker reported that increasing the amount of metronidazole benzoate in the semi-crystalline PCL nanofibers caused a reduction in the crystallinity and consequently an increase in drug dissolution rate [62].

### **Fiber Architecture**

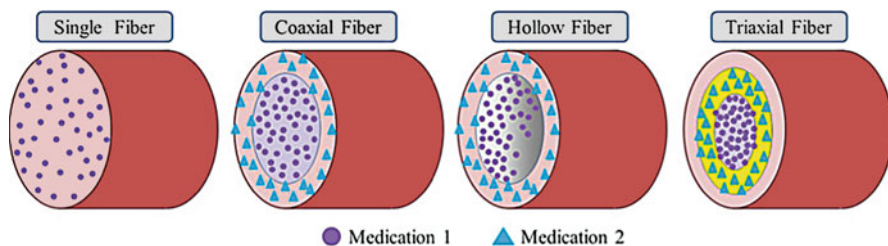
Fibrous nature of fiber-based DDSs serves as the simplest rate-controlling parameter. Considering the unique properties of the fibers such as high specific area and high porosity, the drug release profiles of the fibrous structure differ from other common dosage forms (e.g., film, membrane, slab, sphere, or cylinder), even with the same chemical compositions [63].

Besides the traditional single-nozzle electrospinning technique, multiaxial (e.g., coaxial or triaxial) electrospinning, as a major advancement in electrospinning, resolves the limitations in the traditional drug delivery methods [49]. The unique advantage of multiaxial electrospinning is the ability to simultaneously load various therapeutic agents and modulate the release behavior by altering the fiber properties, e.g., thickness and drug localization (Fig. 23).

Apart from the fiber composition, drug-loaded fibers with a multilayered structure offer unique opportunities to control the release profiles, including loading position, density of loaded drugs, and thickness of the fiber [6]. However, among the different fiber architectures, single uniaxial and coaxial fibers are most frequently used to develop fiber-based DDSs.

### **Uniaxial Electrospun Fibers Architecture**

Uniaxial electrospun fibers represent a relatively simple method to disperse drug molecules within the polymer matrix and achieve rapid and sustained release of the



**Fig. 23** Schematics of drug (medications) loading within the electrospun fibers in various configurations [49] (Copyright © 2016 Elsevier B.V. All rights reserved)

encapsulated drugs. Processing parameters and injected solution properties such as polymer concentration, solvent type, electric field strength, and feeding rate can impact the drug molecules dispersion, which in turn can affect the release kinetics [43].

For example, fiber diameter, which can be simply adjusted by electrospinning processing and solution parameters, can impact the release rate of the drug encapsulated into the polymer fiber [64]. Xie and Buschle-Diller [65] studied tetracycline and chlortetracycline release from PDLLA fibers, prepared with different diameters by adjusting the cosolvent/solvent ratio. Release studies indicated that for tetracycline, smaller fibers (around 200 nm) yielded threefold faster release compared to larger diameter fibers (around 800 nm) after 24 h. Surprisingly, in the case of chlortetracycline, the result demonstrated that the release rate from thicker fibers was faster than smaller ones. These differences may be a result of swelling behavior and drug solubility in the different fiber formulations. For the same polymer/drug systems, it would be expected that for pure diffusional release, the thicker fibers would create a longer path length for the drug to diffuse. However, the drug release mechanisms are often very complex. Sometimes the drug release follows a combinatorial pattern due to different possible mechanisms such as swelling, degradation, and diffusion as well.

Carson et al. developed antiviral fibers based on PCL/PLGA compositions safely releasing anti-HIV hydrophilic drugs to sustain the HIV inhibition effect [66]. This study focused on investigating the drug release patterns as a function of PCL/PLGA ratio (100:0, 80:20, 60:40, 40:60, 20:80, and 0:100) and drug molecule properties. The obtained release pattern showed that tenofovir (TFV)-loaded fiber (15 wt%) compositions containing higher PCL content resulted in more significant burst release, whereas fibers with higher PLGA content provided more sustained-release kinetics. The incremental tuning of TFV drug release was achieved by another composition in between. Furthermore, they examined three other highly water-soluble antiretroviral drugs, azidothymidine, maraviroc, and raltegravir, loaded into 80:20, 20:80, and 10:90, 5:95 PCL/PLGA fiber to investigate the effect of structural differences of the drugs, which have a similar molecular weight to TFV but have important physicochemical differences, including ionization state, functional groups, and solubility. Although the differences in the drug solubility or ionization

state showed some differences in the drug release pattern, fibers with more than 90% PLGA content also sustained the release of all three drugs, where they did not show total drug release by 72 h.

### Coaxial Electrospun Fiber Architecture

More recently, the coaxial electrospinning process to produce a core/shell fiber has been explored as an alternative strategy to provide a sustained drug release pattern from electrospun fiber. As discussed before, the coaxial electrospinning system ran different solutions (at least two) in separate nozzles as well as separate flow rate control to configure the core/shell fiber architecture [49].

Compared with uniaxial electrospinning, the integrity of the final core/shell fiber architecture is a challenging issue, which is influenced by miscibility of the polymers and the solvents used in the core and shell solution. Similar to uniaxial electrospinning, drugs are mixed with polymer solutions, while they are loaded into the polymer solution that forms the inner core. Therefore, the outer shell would be free of drug and serves as a diffusive barrier against the drugs transportation. The presence of such a barrier can help to delay the fast drug diffusion, and consequently burst effect. The shell thickness and core diameter, which are controlled by flow rate of the shell and core polymers, can determine the extent of the drug release delay. Although the core/shell fiber encapsulating drug can provide more prolonged release conditions, the electrospinning process may require more optimization than the uniaxial process to adjust the release rate [7].

An important factor associated with drug release behavior of coaxial fibers is distribution of the drug within the core or shell part, as well as final morphology of these hybrid fibers. Integrity of the core/shell structure and uniformity of fiber diameter and morphology are dependent on solvent volatility, evaporation rate, and solvent miscibility. For the immiscible core and shell solutions, if the shell solvent evaporates faster than the core solvent, it likely forms hollow fiber morphology [67]. Indeed, interfacial compatibility of the core and shell solutions plays a key role in the core/shell integrity, where insufficient compatibility may tend to delaminate at the interface, even in the absence of hollow fiber morphology.

For immiscible core and shell solutions, if the evaporation rate of the shell solvent is faster than the core solvent, some portion of the solvent remains in the core part. The entrapped solvent may partially dissolve the shell polymer; consequently, the shell structure gets porous. The resulted porosity also affects the drug diffusion into the shell and increases the release rate compared to the nonporous shell. Therefore, choosing compatible solvents and polymer solutions is an essential step to form integrated coaxial fibers [43].

One of the weaknesses in the integrity of the core/shell architecture will take place when the core and shell part are partially mixed in the interface due to mixing of the core/shell solvents during electrospinning. As a result of such inconvenience, the shell layer often contains an amount of drugs from the core part. For example, Sohrabi et al. [68] reported 30% initial burst release from poly (methyl methacrylate)-nylon6 core/shell fibers encapsulating ampicillin in the core part. They anticipated that such burst release effect may be originated from the accumulation of drug

molecules at or near the surface of the fibers during coaxial electrospinning due to core/shell mixing in the interface. Tiwari et al. [69] developed PVA–PCL core/shell fibers to deliver metoclopramide hydrochloride to investigate the factors that control the burst effect as well as the rate of subsequent release. Results of this study demonstrated that about 50% of the loaded drug released as the initial burst effect. This is most likely due to the presence of micron or nano-sized pores in the PCL shell, which allows easy penetration of water to the core, facilitating the rapid release of the drug.

In coaxial fiber in which drugs are incorporated in the core, predominantly, diffusion through the shell polymer shows a rate-limiting effect [70, 71]. The shell thickness and composition play a key role and should be adjusted to achieve a desirable release rate. In Wang et al. [72], the release rates of dimethyloxalylglycine (DMOG) from PLA and poly (3-hydroxy butyrate) (PHB) core/shell electrospun fiber with various shell thickness were investigated. The DMOG release profile demonstrated that the fibers with PHB core and PLA shell showed a burst release, where about 60% of DMOG was released during 2 h. In contrast, the fibers with PLA core and PHB shell provided a two-phase sustained release over 30 days, where a small amount of DMOG release in the first stage is followed by the zero-release order of a majority of DMOG in the second stage. Comparing samples with various shell thickness demonstrated that the shell thickness did not have any significant effect on the burst release phase, whereas the linear release in the second phase was dependent on the shell thickness. Increasing shell thickness from 120 to 230 nm sustained DMOG release (70%) from 11 to >30 days.

Besides the shell thickness, similar to uniaxial fiber, the hydrophobicity of the shell layer strongly impacts the release rate of hydrophilic small molecules. The surface hydrophilic–hydrophobic properties of the coaxial fibers can control the fiber wetting mechanism with which drug release is associated. For example, He et al. [73] investigated the release behavior of metronidazole, loaded in PCL core, gelatin shell fibers. They have changed the hydrophobic of gelatin shell by the cross-linking process, where more cross-linked gelatin resulted in less hydrophilicity, measured by the contact angle test. Interestingly, the cross-linked gelatin shell sustained the metronidazole release for up to 6 days, whereas for an uncross-linked gelatin shell, 80% of the loaded drugs were released after 1 day. However, in addition to increasing hydrophobicity, the degradation behavior of the gelatin shell may affect cumulative release results.

#### Posttreatment and Release Media

The drug release kinetics could also be modified, even after fiber formation by physical or chemical posttreatment techniques such as cross-linking [74]. However, maintaining the chemical and physical stability of the drug during the treatments is a challenging issue.

For example, Stephansen et al. [75] showed that release of insulin from fish sarcoplasmic protein fibers was affected by surfactants in the release media. Their study demonstrated that interactions between anionic surfactant (e.g., sodium taurocholate and sodium glycocholate) in the solution and the electrospun protein



had a concentration-dependent effect on insulin release, so that the fiber stability, porosity, and fiber surface properties were significantly influenced in the presence of the surfactants. However, the addition of cationic and neutral surfactants did not have any significant effect on the amount of released insulin.

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## Smart Active Drug Release Systems

For more capabilities of electrospun nanofibers, there are some variant-reported ways to make the drug-loaded nanofibers responsive to its environmental stimuli for releasing. In particular, smart or stimuli-responsive or on-demand delivery polymers could be used as effective carriers with controlled release. Their ability to respond to small changes in the environment such as pH, temperature, light, electric field, magnetic field, or multiple stimuli makes them smart and intelligent nanofibers. Due to the exclusive properties of electrospun nanofibers, these are very promising candidates for drug delivery.

### pH-Responsive Nanofibers

The pH of the media is a common stimulus for drug release. The human body is regulated by acid–base homeostasis, which keeps the pH of the arterial blood between 7.38 and 7.42. Nevertheless, many tissues or cell compartments have their own distinctive pH environments for normal functioning [76]. In tissues and cellular compartments, the pH varies from acidic to slightly alkaline. For example, the gastrointestinal tract in the stomach is acidic (pH 2), while it varies to more basic in the intestine (pH 5–8). Endosome and lysosome are acidic (pH 4.5–6.5). pH-triggered DDSs have been clinically used, and recently, it has been a lot of research for gene delivery. Materials responding to pH variations mainly undergo two mechanisms: pH influences the protonation/deprotonation balance and pH-dependent hydrolysis kinetics. Protonation/deprotonation is strongly associated with pH variations. Therefore, polymers containing functional groups with the acid dissociation constant  $pK_a$  close to the physiological/pathophysiological pH can be used as pH-triggered DDSs. Changing of water absorption, swelling ratio, and solubility of the polymers could result changing the pH [42].

Demirci et al. [77] synthesized poly(4-vinylbenzoic acid-co-(*ar*-vinylbenzyl)trimethylammonium chloride) [poly(VBA-co-VBTAC)] as a pH-responsive polymeric carrier for release study. The ciprofloxacin was chosen as the model drug to encapsulate into poly(VBA-co-VBTAC) by electrospinning. The nanofibers were found to be able to reversibly swell–deswell between a pH of 5.4 and 8.8, due to the protonation/deprotonation of 4-vinylbenzoic acid (VBA), and change the release profile of ciprofloxacin correspondingly.

Chemical reactions like hydrolysis are dependent on the pH. Therefore, polymer-containing acid-labile bonds such as hydrazone or acetal groups are sensitive to speed degradation in acidic conditions [42].

Increment of drug release rate in acidic media have been demonstrated for biodegradable pH-sensitive polymers containing ortho ester groups such as D, L-lactide. Qi et al. [78] electrospun biodegradable acid-labile polymers with the encapsulated paracetamol as a model drug. The total amount of drug released from these polymeric fibers was accelerated after incubation into acid buffer solutions in *in vitro* release study. For matrix polymers with hydrophilic acid-labile segments, the amount of initial burst release and sustained-release rate were significantly higher. It was indicated that the fibers containing acid-labile segments were stable in neutral buffer solution, but the molecular weight reduction of matrix polymers, the morphological changes, and mass loss of fibers were enhanced in the acidic environment.

Yuan et al. [79] constructed an acid-responsive poly-L-lactide (PLLA) nanofiber via doping sodium bicarbonate ( $\text{NaHCO}_3$ ) for faster release of ibuprofen which are used to intelligently regulate the anti-inflammatory agent release with the change of acid microenvironment in regions where the pH is reduced below 7.4, leading to a good restrain of inflammation on the early stage and a scarless repair on the later stage. The *in vivo* study showed that nanofibers containing  $\text{NaHCO}_3$  resulted in skin scarless healing and prevented excessive inflammation compared to drug-loaded nanofibers without  $\text{NaHCO}_3$ .

The air-plasma treatment is also an alternative method for introducing pH-sensitive groups to electrospun nanofibers. The air-plasma treatment of PCL and PLA nanofibers can generate carbonyl, carboxyl, and hydroxyl groups on their surfaces. Jiang et al. [80] proposed that air-plasma-treated PCL or PLA nanofibers coated with polydopamine could be pH-responsive. *In vitro* release profiles demonstrate that the positively charged molecules are released slowly in neutral and basic environments than in acidic environments within the same incubation time. It was demonstrated that a mussel-inspired protein polydopamine coating, serving as a mediator, can tune the loading and release rate of charged molecules from electrospun PCL nanofibers in solutions with different pH values.

## Thermo-responsive Nanofibers

Some polymers are responsive to environmental temperature which will affect the drug release rate from its matrix. Polymers which exhibit changes at temperature close to the human body temperature of  $37^\circ\text{C}$  are particularly suited for temperature-responsive drug release. These polymers undergo abrupt changes in solubility, that is, the affinity of water. This is the result of competition between hydrophilic and hydrophobic moieties on the polymer chain. The balance point is called the lower critical solution temperature (LCST), at which the polymer neither favors hydrogen bonding with the polymer nor with water. Thus, it could be stated that temperature can be manipulated and used as a stimulus to modulate the drug release.

Among temperature-sensitive polymers, poly (N -isopropylacrylamide) (PNIPAM), PDEA, PVCL, and PMVE have been widely explored as components of the thermo-responsive system because their LCSTs are close to normothermia [76].

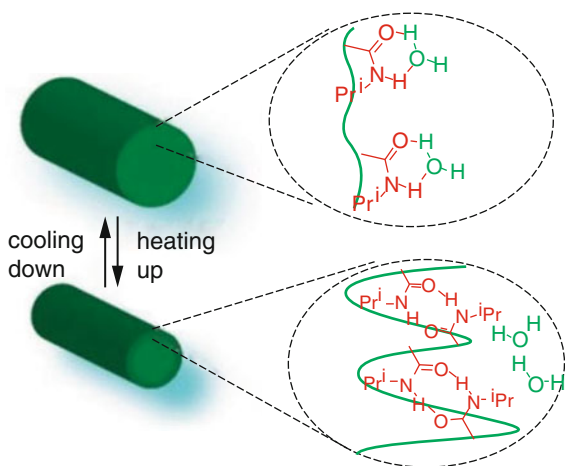


PNIPAM is one of the most studied temperature-sensitive polymers, as it will exhibit thermal reversible volume phase transition at LCST. Due to intermolecular hydrogen bonding between the polymer chains and water molecules, PNIPAM is hydrophilic below the LCST. However, above the LCST, the hydrogen bonding along the PNIPAM chains is replaced by intramolecular hydrogen bonding between C=O and N-H groups as it is illustrated in Fig. 24, resulting in aggregation of the polymer in water. Simultaneously, as the polymer is not in the solution, the water is less ordered. As a result, the volume phase transition between the swelling and deswelling states of the PNIPAM as drug carriers will affect positively or negatively the release of the encapsulated drugs. The former is as at the deswelling state at high temperature, and the drug is expelled out quickly. The latter is explained as the heterogeneous deswelling of the carriers which induced formation of a less permeable and dense surface layer, described as a skin barrier for drug release [42].

The potential toxicity of this polymer has been tested subcutaneously, and results did not show any toxic effects.

Azarbayjani et al. [81] used a mixture of polyvinyl alcohol (PVA) and biocompatible thermo-responsive PNIPAM to control the release of levothyroxine [3, 5, 3', 5'-tetraiodothyronine ( $T_4$ )].  $T_4$  is a synthetic hormone used for the treatment of hypothyroidism and goiter, and it stimulates lipid metabolism and induces lipolysis. The co-electrospun technique can overcome the barrier of high aqueous solubility of PNIPAM. PVA is a hydrophilic polymer with distinct properties such as high degree of swelling, non-toxicity, and good biocompatibility, and PNIPAM is a thermally reversible hydrogel with a LCST of around 32 °C. When heated above 32 °C, PNIPAM undergoes a reversible phase transition from hydrophilic to hydrophobic, losing ~90% of its volume, resulting in the change of drug release rates. The PNIPAM nanofibers are soluble in water when the temperature is below LCST; however, it loses its fibrous feature at temperatures above LCST as well. The cross-linked gel of this material swells below this temperature and shrinks above it.

**Fig. 24** Hydrogen bonding changes between LCST [42]  
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The drug release is expected to be increased while the material shrinks. It was claimed that these polymeric nanofiber delivery systems may have potential use in skin formulations containing active ingredients that are meant to be concentrated on the skin surface and can help to increase the retention of the drug on the skin layers. However, due to the high water permeability of hydrophilic PVA, there were serious burst effects at 25 °C and 37 °C.

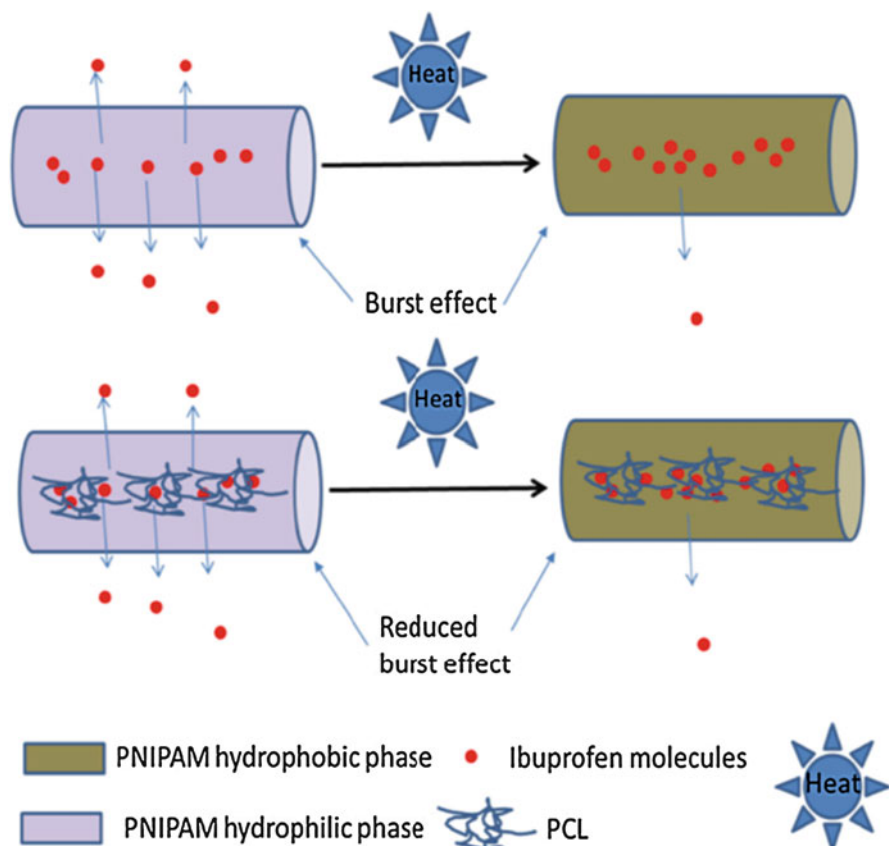
Tran et al. [82] similarly used a combination of PNIPAM and hydrophobic poly ( $\epsilon$ -caprolactone) (PCL) to control the release of ibuprofen (IP) from the nanofiber matrix and utilized it for controlled and on-demand release of the drug without burst effect. They study PCL, PNIPAM, and PNIPAM/PCL composite electrospun nanofibers containing IP. The release rates of IP from PCL nanofibers are not affected between 22 and 34 °C, but in PNIPAM nanofibers, the release rate is very sensitive to the change in temperature. It was found that it is five times higher at 22 °C compared to 34 °C. At a temperature of 22 °C, PNIPAM nanofibers showed a burst release while it demonstrates a gradual release at a temperature of 34 °C. For a composite PNIPAM/PCL, the release of IP is gradual even at 22 °C, although its release rate is faster than at 34 °C. The presence of PCL effectively suppressed the burst release of IP at lower temperature, but the rate at 22 °C is still 75% faster compared to that at 34 °C in this composition (Fig. 25).

The release rates of ibuprofen from three types of nanofibers were investigated in a pH of 7.4 deionized water at 22 °C and 34 °C as shown in Fig. 26. It is seen that in PCL/IP nanofibers, in the first 1 h at 22 °C and 34 °C, about 15% IP was released, and for both temperatures, there was less than 10% change in delivery rates. About 34% IP was released in 4 h, on average.

For PNIPAM/IP nanofibers, 1  $\mu$ mol of IP was quickly released in the first 1 h at 22 °C, and then the rest was released at a much slower rate of 0.05  $\mu$ mol/h, and it was found that 24% IP was released in 4 h. In comparison, when the temperature was increased to 34 °C, IP released mode was more controllable, and it was released in the first 1 h, and only 17% IP was released in 4 h. In the case of PNIPAM/IP/PCL nanofibers at both 22 °C and 34 °C, the diffusion rates were linear and without burst effects. Compared to the IP release rate at 34 °C, the average IP release rate from this composite nanofiber was 75% faster than at 22 °C. Such kinds of controllable and switchable delivery systems could easily find many practical applications in both pharmaceutical and medical sciences, but still more studies should be done.

The core/shell nanofibers were prepared with PNIPAM as core and hydrophobic ethyl cellulose (EC) as shell by coaxial electrospinning. Analogous medicated fibers were prepared by loading with a model drug ketoprofen (KET). Water contact angle measurements proved that the core–sheath fibers from hydrophilic were transformed into hydrophobic when the temperature reached the lower critical solution temperature. Compared to the blended nanofibers, the coaxial nanofibers have similar regular morphologies in drug sustained release and biocompatibility. However, the coaxial nanofibers show very clear thermo-sensitive drug delivery with sustained release than the blended nanofibers.

Thus, the coaxial nanofibers have both thermo-sensitive and sustained-release properties, which could be good thermo-responsive carriers for the sustained release,

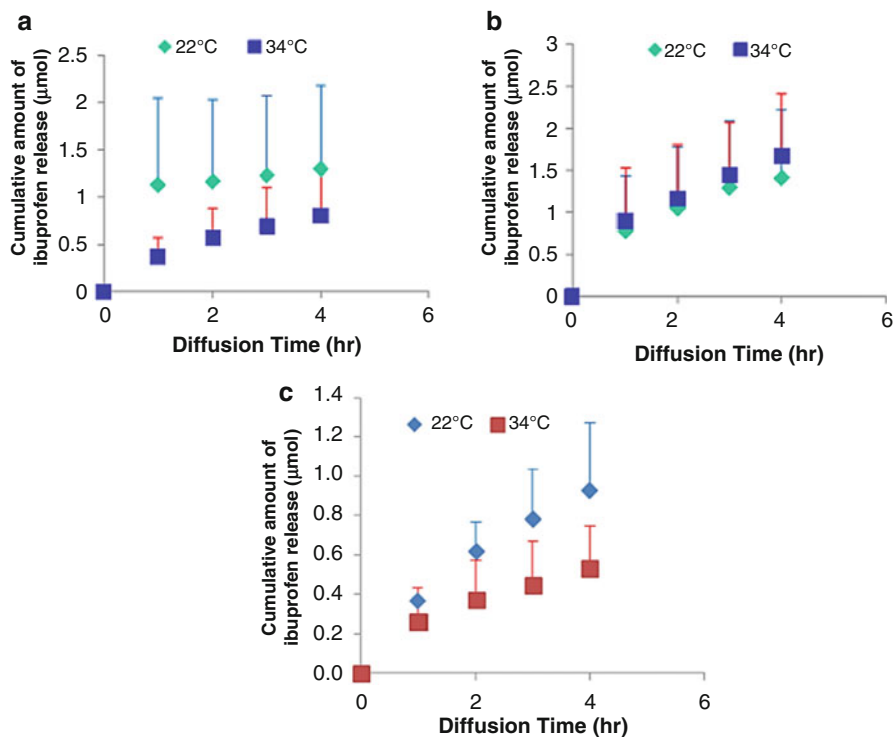


**Fig. 25** The schematic diagram to indicate the mechanism of reduced burst effects from PNIPAM/IP/PCL composite nanofibers [82] (Copyright © 2015, Tran et al.; licensee Springer)

especially for poorly water-soluble drugs, and are potential biocompatible nanofibers in the biomedical field. The system reported was claimed to prevent the undesirable side effects that may sometimes arise from non-localized drug release [83]. Polystyrene (PS), PCL, poly(2-acrylamido-2-methylpropanesulfonic acid), poly(ethylene oxide) (PEO), and PLCL have been co-electrospun with PNIPAM to achieve a thermo-responsive effect. Many of them are considered biocompatible and biodegradable, which makes them excellent candidates for controlled release [76].

Another well-known thermo-sensitive polymer which was approved by US Food and Drug Administration (FDA) and has been applied in drug delivery systems is Pluronic or the PEG–PPG–PEG triblock copolymer. The gelation is considered to respond at elevated temperature by a 3D packing of micelles due to the hydrophilic–hydrophobic balance of the amphiphilic molecule [42].

Hydrogel nanofiber based on multiblock poly(ester urethane)s comprising poly(ethylene glycol) (PEG), poly(propylene glycol) (PPG), and poly( $\epsilon$ -caprolactone)



**Fig. 26** Ibuprofen release profiles from (a) PNIPAM NFs, (b) PCL NFs, (c) PNIPAM, and PCL composite NFs, all containing 50 mg ibuprofen [82] (Copyright © 2015, Tran et al.; license Springer)

(PCL) segments were fabricated by electrospinning as thermo-responsive material. Under cold conditions, the hydrogel nanofibers absorbed more water and shrunk when exposed to higher temperatures. By changing the environment temperature, the rate of protein release could be controlled. The volume of water trapped reduced twice as low by increasing the temperature. That's because at higher temperatures, the PPG segment in the copolymer is becoming more hydrophobic. The encapsulated protein, bovine serum albumin (BSA), was released with water, and a higher rate of release was observed at 37 °C [84].

## Light-Responsive Nanofibers

Human bodies are often exposed to light (e.g., sunlight and artificial light). The wavelength of light encountered in daily life ranges from 3000 nm of the infrared heater to 315 nm of ultraviolet light A (UVA) in sunlight. Below 315 nm, the ultraviolet (UV) light is not suitable for therapeutic purposes since the high-energy photons directly start to damage DNA. Light-responsive drug-loaded electrospun

nanofibers respond faster, avoiding chemical stimulants and by-products. For safety considerations, light-responsive nanofibers should be able to respond to light with a wavelength longer than 315 nm. The photo response of these materials is based on the photoisomerization of their constituent molecules which in response to the absorption of light at two different wavelengths undergo a large conformational change between two states.

Typically, trans-cis-isomerization of azobenzene chromophores has been incorporated into different drug delivery systems which give rise to changes of the dipole moments, polarity, or shape of the molecules. Under UV light, these molecules switch from its trans- to cis-form and switch reversely upon exposing to light with a wavelength above 400 nm or heating [42].

Cyclodextrins (CDs) have been extensively studied mainly because of their well-hosting properties. This material is made of glucopyranose units with frustum structure. The CDs have unique combination properties, with their outer surface being hydrophilic; where the hydroxyl groups are located, the inner cavity is hydrophobic to host various hydrophobic molecules and form water-soluble inclusion complexes. Azobenzene can efficiently bind to CD in its trans-isomer but not in cis-configuration.

The electrospun nanofibers showed well-controlled release of 5-fluorouracil upon the irradiation of UV light. The drugs were released quickly and reached the maximum of release amount after 30 min of UV irradiation. It was found that the delivery system had a quick and specific response to the UV stimuli and stopped immediately after exposure off, and it demonstrated that a CD drug could be used as photo-triggered effective and controlled release material [85].

The UV has quick attenuation in tissues, so the near-infrared (NIR) light could be an appropriate alternative light source for biological applications, which has low risk of damage to healthy tissues and a deep penetration depth into tissues. Usually, by incorporating photo-sensitive nanostructures which have intense absorptions in the NIR light range, the NIR light-responsive materials were synthesized.

The electrospun polymer can be incorporated with light-sensitive additives like gold nanoparticles or nanorods to initiate changes in response to light. Au nanorods were able to strongly absorb near-infrared red light to generate heat, and this triggered a thermal transition in the polymer matrix [86].

## Electric Field-Responsive Nanofibers

The electrical field can lead to swelling, shrinking, or bending of the polymeric drug carriers, in some cases the process of ionization and trigger redox reactions. Based on the mechanisms, electric field-responsive polymers are mainly classified into the following categories: electroactive polymers, ion-doped conducting polymers, and polymer composites/bends/coatings.

Electroactive polymers (e.g., piezoelectric polymers, electrostrictive, and dielectric elastomers) display a change in their size or shape when stimulated by an electric field, which has not been investigated for controlled release by an electric field. Ion transport

takes place in conducting polymers during the electro- and/or chemical oxidation and reduction. The reversible intercalation motion of the ions results in a volume change of conducting polymers. The polymeric nanofibers incorporated with carbon nanotubes operating in electrolyte can lead to volume changes because of capacitive charging. Both conducting polymer-coated electrospun nanofibers and carbon nanotube-encapsulated electrospun nanofibers have been examined for controlled release under electrical stimulation [76]. Yun [87] prepared the electro-responsive transdermal drug delivery system by electrospinning of poly(vinyl alcohol)/poly(acrylic acid)/multi-walled carbon nanotube (MWCNTs) nanocomposites. The MWCNT content and oxyfluorination that were used for improving the MWNTs dispersion played important roles in the swelling and drug release characteristics of nanofibers. Due to the variation of ionization of functional groups in the polymer structure depending on the electric voltage applied, swelling and drug release of nanofibers varied sensitively.

### **Magnetic Field-Responsive Nanofibers**

Substantial interests in magnetic materials have been devoted to their potential biomedical applications. The magnetic field has unmatched advantages over other options. Living tissues are magnetically transparent since their compositions are mainly water, which is diamagnetic and negligibly repelled even in a powerful magnetic field, like a clinical magnetic resonance imaging machine, while applied light or heat can only reach up to 4 in. beneath the skin. In addition, the human body is able to tolerate a magnetic field of high strength. Humans can tolerate magnetic fields of up to 7 tesla, while a strong light or heat source usually leads to DNA damage and cell death [76].

Superparamagnetic nanoparticles could be incorporated into nanofibers during electrospinning. Superparamagnetism appears in small ferromagnetic or ferrimagnetic nanoparticles that randomly flip their magnetization direction under the influence of temperatures. This property guarantees SPNs to be aligned with the applied alternating current magnetic field (ACMF) without showing magnetic hysteresis that is not desirable by the magnetic field-responsive drug-loaded electrospun nanofibers. Liu [88] prepared magnetic nanofibers by electrospinning of polyacrylic acid (PAA)/polyvinyl alcohol (PVA) aqueous solutions with homogeneously dispersed magnetite  $\text{Fe}_3\text{O}_4$  nanoparticles. This nanofiber showed a soft ferromagnetic behavior. Wang [89] added  $\text{Fe}_3\text{O}_4$  nanoparticles and indomethacin and aspirin to electrospun dehydroxypropyl methyl cellulose phthalate and CA nanofibers. They showed that the presence of  $\text{Fe}_3\text{O}_4$  nanoparticles had no influence on the release profiles, though it was possible to move nanofibers to the target site under the guidance of an external magnetic field.

### **Multiple Stimuli-Responsive Nanofibers**

Multi-stimuli-responsive electrospun fiber systems that respond to a combination of two or more signals have been developed to extend the already broad tunability over

the drug delivery. These combined responses can occur at the same time or in a sequential way. For instance, dual-stimuli-responsive drug-loaded electrospun nanofibers can activate the release of drugs to an infection site whenever the local pH or temperature shifts from the normal value [76].

Chen [90] generated electrospun nanofibers composed of PNIPAAm/PVA blends responsive to both temperature and pH. At room temperature and at a pH below 4, the fibers showed nearly no swelling, whereas at room temperature and at a pH above 4, a high degree of swelling was observed. In contrast, at a pH above 4 and at elevated temperatures (e.g., 70 °C), the swelling ratio was reduced from 15- to 2.6-fold.

Zhang [91] fabricated pH and temperature dual-responsive poly(methyl methacrylate/*N*-isopropyl acrylamide/acrylic acid) (P(MMA/NIPAM/AAC)). The fibers showed reversible and positive temperature-controlled release of Rhodamine 610 chloride as a model drug, and it was found that it had faster release above LCST. By decreasing the ratio of the two monomers, NIPAM and MMA, from 7:3 to 5:5, the LCST of the nanofibers was tuned from 38 to 52 °C. The acrylic acid (AAC) and PAA molecules adjust their conformation in aqueous solutions because of the protonation/deprotonation equilibrium. These nanofibers shrank upon both decreased pH and elevated temperature. The shrinkage pH thresholds could be adjusted by changing the ratios of NIAPM, MMA, and AAC. Although the concepts of smart nanofibers for controlled release have been demonstrated in some studies, translation of these smart nanofibers to clinical applications could take a long way to go. Future efforts may be devoted to the development of smart electrospun nanofibers that are responsive to multiple stimuli under normal physiological conditions.

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## Applications of Nanofibers in Drug Delivery

Regarding the unique properties of electrospun fibers as well as controllability of drug-loading capacity and releasing behavior in the fibrous mat, the drug-incorporated fibers have a wide range of biomedical applications. Biodegradable fibers are more biocompatible due to elimination of a second surgery to remove the implanted system. The vast spectrum of biodegradable materials from natural polymers (such as collagen, gelatin, zein, silk fibroin, chitosan, cellulose, alginate, etc.) to common synthetic polymers (including poly(D-lactic acid) (PDLA), poly(vinyl alcohol) (PVA), poly(lactic-co-glycolic acid) (PLGA), poly(L-lactide-co-caprolactone) (PLCL), etc.) are widely used in fiber-based drug delivery systems [7]. However, hybrid blends of natural and synthetic polymer are usually desirable. In this section, some common applications of electrospun nanofibers in therapeutic agent delivery have been reviewed.

### Anticancer Drug Delivery

Systemic administration of anticancer drugs commonly results in the inefficient therapeutic effect due to their poor solubility and instability in body fluid, low



absorption and concentration in tumor site, and high rate of elimination. Therefore, using advance DDSs such as particulate base carriers for efficient targeted delivery of the anticancer drugs has attracted much attention with the great market acceptance. Considering multifarious parameters including limited drug-loading capacity, undesirable burst release, and targeting difficulties, the utilization of locally administered drug-loaded nanofiber scaffolds can be suggested as an alternative approach, particularly for chemotherapy in the postoperative area [5]. Drug-loaded nanofibers conveniently cover the tumor site for prolonged release with maximized efficiency and minimized adverse effects. In fact, not only does this system provide high local dosage needless of the large amount of drug, but it also increases the patient's quality of life because of the reduction in administration repetition and exclusive delivery to the cancerous tissues.

Numerous drugs with different water affinities (including doxorubicin hydrochloride and paclitaxel) can be incorporated in nanofibers using blend or coaxial electrospinning for sustained release [92]. There is also a possibility to apply natural anticancer compounds such as green tea polyphenol [38], curcumin [93], etc., in order to decrease the side effect of usual chemical drugs. Moreover, a vast number of studies have represented the high efficacy, solubility, and compatibility of antitumor drugs in polyester-based nanofibers including poly(l-lactic acid) or PLLA and its copolymers [94].

For highly hydrophobic antitumor agents, overcoming poor solubility and instability can be provided by either usage of solubilizer compound in the electrospinning mixture or core–sheath electrospinning techniques to have sustained and sufficient release of the active drug. It is worth mentioning that in the case of the large or inaccessible tumors, which the delivery of drug into the site is hindered, the fibrous-based DDSs may be regarded as imperfect.

## Antibiotic Drug Delivery

Antibiotic biocides for either killing or inhibiting bacterial growth can play an important role in subsiding infections caused after surgery or by pathological cues. The electrospinning fibers containing antibiotics are considered as suitable systems for in situ and sustained release in the form of wound dressings or other implants.

Until now, a significant number of antibiotic agents against *Staphylococcus epidermis*, *Pseudomonas aeruginosa*, *Listeria innocua*, and *Escherichia coli* such as levofloxacin, gentamicin, ampicillin, tetracycline hydrochloride, ciprofloxacin, silver nanoparticles (AgNPs), etc., have been encapsulated into nanofibers for multifarious applications [5, 7].

Several studies have utilized a mixture of hydrophobic and hydrophilic polymers for controlled release of antibiotic agents. For example, Torres et al. [95] made a coaxial PLA/collagen fiber containing gentamicin. Drug-loaded fibers showed sustained drug delivery instead of burst release (only 33% of gentamicin was released in the first 50 h, which is followed by 85% in 500 h). This result may be originated from the hydrophobic nature of PLA core.



Among the aforementioned drugs, AgNPs have also attracted much attention in researches. Core/shell nanofibers, consisting of PLLA as a shell and AgNPs blended PVP as core, have been reported by [96] with high effectiveness. Moreover, there are some polymers (mostly polysaccharide based) representing the antimicrobial entity. For example, chitosan, a popular biodegradable polymer, has been applied in tissue engineering scaffolds and wound dressing with high drug-loading capacity as well.

## Growth Factor and Protein Delivery

Growth factors (GFs) are a group of protein-based biomacromolecules with the regulation capability of biological processes by binding the cell surface receptor and transferring signals between cells and their extracellular matrix (ECM), which pave the way for regulating growth, proliferation, migration, and differentiation of cells, thereby enhancing tissue regeneration.

Thus, incorporation of GFs (from natural to recombinant sources) into tissue engineering scaffolds is recommended for fast and effective regeneration. From different properties of GFs affecting their delivery approach, their short half-life in a biological environment and fast rate of inactivation should be considered as the most important factors. Moreover, studies have proven that without both a slow and sequential releasing profile of GFs, the scaffold cannot perform effectively. For this reason, electrospun nanofibers have been employed in the scaffold's structure for sustained and controlled release of GFs.

Several techniques including blend electrospinning, coaxial electrospinning, emulsion electrospinning, and a combination of electrospinning with other conventional techniques were applied for GF incorporation alone in nanofibrous scaffolds (alone or in combination with hydrogels) [9]. In order to create efficient drug loading, and protection of GF molecule while exposing it to cell receptors, surface-modified nanofibrous scaffolds are more appropriate for GF delivery, which is economical and both morphologically and biochemically similar to native tissues.

Among the different substances for conjugating GFs in a structure, polysaccharides and sulfated glycosaminoglycans (GAGs) (like heparin) should be regarded as the perfect choice, since not only do they provide a mimicked ECM composition but can also efficiently interact with GF via negatively charged sulfate groups on their backbones [97].

As mentioned before, the preservation of bioactivity of GFs and their controlled release are considered important factors, which can be provided by using protective strategies such as coaxial or emulsion electrospinning [98] and also combination of nanofibers with other existing forms of biomaterials (e.g., hydrogels).

Another interesting technique for sustained release with high efficiency is immobilization of GFs onto nanofibers, which expose their active motifs to be targeted to a specific site. Moreover, only a small amount of GF is required to achieve similar

results to its soluble form in the medium. Notwithstanding, it is so striking that the chemical immobilization of these molecules can damage second or third protein structures as well as their active domain, which is sometimes out of control. Thus, an efficient approach, which is appropriate with such applications, should be regarded.

## **Nucleic Acid Delivery**

Nowadays, with the benefit of gene therapy and delivering DNA or interfering RNA and short interference RNA (siRNA), we are able to adjust both cellular responses and signaling pathways by enhancing or preventing a specific protein, which is valuable in regenerative medicine.

Commonly, gene delivery systems based on their carriers, can be categorized into two main groups: viral and nonviral delivery systems. Despite the high specific transfection and being needless for multiple dosages, viral delivery systems can transfer a limited size of the gene, while they may cause acute immune response and mutations. Hence, developing novel nonviral gene delivery systems is necessary.

Electrospun nanofibers are a novel class of potent materials as a carrier or in the form of scaffold for delivery of nucleic acid base therapeutics because of their unique features such as high surface area and high porosity with interconnected pores. Several studies have investigated DNA-functionalized nanofibrous systems for gene delivery in tissue engineering. An influential factor in this field of research is proper encapsulation and protection of therapeutics, which would not come true via simple blending of DNA with electrospinning solution. Therefore, employing techniques such as incorporation of DNA-loaded particles into the nanofibers, coaxial electrospinning, and surface modification is considered to overcome low transfection efficacy and other problems [3, 9].

It has been represented in different studies that incorporation of therapeutic agents in the core with polymer sheath can extend their releasing period of up to several months. Thus, core/shell structures are necessary for the protection of nucleic acid from degradation and unwanted release as well as making it possible for multiple drug loading [99].

Among different nucleic acid-based therapeutics, siRNAs are in spotlight, particularly in the tissue-repair process prohibited by the secretion of inhibitory factors, or in cancer therapy, where specific genes can enhance tumor growth [100].

## **Miscellaneous Drug Delivery**

Drug-loaded nanofibers have also been employed for the delivery of miscellaneous therapeutics including neurotransmitter or receptor blocking, anti-inflammatory, and antiepileptic agents.

For example, PLGA nanofibers with aqueous solution of levetiracetam were prepared and underwent solvent evaporation, which creates microcavities as drug reservoirs [101]. It was documented that alteration of the disperse-to-continuous

phase ratio in electrospinning solution has a direct connection to the size of cavities and consequently both the diffusive length and order of release. This system, intended to be implanted into an adult's brain for treatment of epilepsy, has shown linear and sustained release for over 21 days.

Anti-inflammatory activity of both nanofiber-loaded non-/steroidal drugs like ketoprofen, ibuprofen [102], and DEX have been studied in several studies. For example, [103] incorporated DEX in silk fibroin/poly(ethylene oxide) (PEO) fibers via emulsion electrospinning without any organic solvent usage. In vitro results showed reduced porcine hip artery endothelial cells inflammatory damage.

In another research work, a nanofiber patch for effective ocular drug delivery was synthesized by electrospinning poly(vinyl alcohol) (PVA) and poly(caprolactone) (PCL) incorporating timolol maleate and dorzolamide hydrochloride as drugs. Results suggested that the patch has great drug-loading capacity and prolonged duration of action in the intraocular area [104].

In the case of periodontal diseases, in which controlled local administration of antibiotics is crucial, and in viral infection and anti-HIV drugs, where pH-dependent solubility of fibers is determinant, the usage of nanofiber drug delivery systems is feasible [105].

## Cell Delivery and Tissue Engineering

Appropriate tissue responses to cell delivery treatments are mostly dependent on the type of carrier to transfer cells to the exact location. Thus, numerous materials and scaffolds, such as macroporous hydrogels, sponges, in situ gels, and nanofibers (especially self-assembling peptide nanofibers), have been studied for cell-based therapy. Moreover, these delivery systems should be flexible, smooth, and biodegradable [92].

The electrospun fibers have also been served as potent scaffolds for regeneration of tissues such as bones, cartilage, nerves, blood vessels, cardiac muscles, skins, etc. In addition to high surface-to-volume ratio, which is appreciated for biomolecule delivery, cell attachment, proliferation, and differentiation, their ECM-mimicking properties all along with the tailor-made ability make nanofiber-based scaffolds very interesting in the field of regenerative medicine. The coaxial fibers with controlled release potential of tissue regenerative agents demonstrated better performance than monolithic fibers on tissue engineering. Moreover, biocompatible, biodegradable, and hybrid materials are preferred in this field as well.

Numerous studies have utilized the fibrous-based scaffolds with sustained controlled release potential to improve the tissue regeneration process. For instance, McCullen et al. [106] employed tricalcium phosphate (TCP) nanoparticle-loaded coaxial fibers, which provide sustained release of calcium ions at a constant concentration with no burst release, to improve bone tissue regeneration. In a study by Su et al., the bone morphogenetic protein 2 (BMP-2) to the accompaniment of a steroid, dexamethasone (DEX), has been loaded into a poly(l-lactide-co- $\epsilon$ -caprolactone) (PLLACL) core/shell scaffold [107]. Controlled release of

BMP-2 and DEX increased mineralization, and osteoblast marker expression was observed on *in vitro* and *in vivo* evaluations.

Comprising striated active muscle fibers, cardiac tissue is another appropriate option for electrospun nanofiber-based scaffolds. Prolonged release of the bioactive growth factor can promote the angiogenesis response, which will be potential substrates for cardiac tissue regeneration. For example, Tian et al. [108] developed a dextran-protected VEGF-loaded poly(lactide-co-caprolactone) (PLCL) fiber, which can improve attachment and proliferation of bone marrow-derived mesenchymal stem cells.

Another important application of electrospun nanofibers is in nerve guidance conduits (NGC), which have a tubular structure bridging the gap between damaged parts of the nerve. In this prospect, aligned PLGA coaxial nanofibers releasing nerve growth factor (NGF) were investigated by Wang et al. [109]. In another research, dual-gradient NGF-loaded silk fibroin nanofibers were successfully utilized for nerve regeneration applications [110]. Skin tissue engineering scaffolds are one of the most important fields of application of nanofibers due to their positive effects on wound healing from hemostasis to reepithelialization. Various GFs such as EGF, bFGF, VEGF, PDGF, etc., can be incorporated into the fibers in order to stimulate the proliferation and cell migration (keratinocytes, fibroblasts, and endothelials), angiogenesis, and accelerating skin regeneration [111].

## Wound Dressing

Among common skin products, advanced wound dressings have attracted great attention as they can protect the wound from infection, absorb exudates while moisturizing the wound bed, and accelerate wound healing. Electrospun nanofibers have shown great potential as wound dressing due to their high surface area and porous structure, which can absorb exudates, as well as their ability for incorporation of therapeutic agents (such as drugs and growth factors).

Several studies showed the effective role of electrospun wound dressings in hemostasis, antibacterial properties, prevention of scar formation, and skin regeneration. On the other hand, transdermal drug delivery systems (TDDS), which are designed to support the delivery of target agents through the skin into the body, can also be fabricated from electrospun nanofibers. With the benefit of TDDS, researchers are able to administer sensitive drugs, which cannot be transferred orally [112]. However, considering the barrier-like nature of skin, a finite number of drugs limited to low molecular weight (up to a few hundred Daltons) and hydrophobic drugs can effectively pass through the skin. Therefore, the transdermal delivery of large hydrophilic drugs still remains problematic.

There are numerous researches that have applied herbal pharmaceutical compounds (e.g., curcumin (from turmeric), aloesin (from aloe vera), thymol (from thyme), etc.) incorporated in electrospun nanofibers in order to develop TDDS and/or active wound dressings [9].

## Naturally Derived Nanofiber

Besides electrospinning, which is a versatile method to produce fiber structure, nature also provided some fiber-based features that could be utilized for drug delivery applications. The naturally derived fibers entirely come from natural sources such as animal or plant. Unlike the electrospun fibers, properties of the naturally derived fibers are rarely tailored because they have preformed structure. However, using various modification strategies may help to adjust some properties such as surface functional groups, wettability, and charge.

Among the naturally derived fibers, cellulose and silk are two main nanofiber structures which are, respectively, extracted from plant and animal sources and used in drug delivery applications. Self-assembled peptide nanofiber (SAPN) is a new class of fibers, which are inspired from the naturally derived fibers. Recently, the SAPNs are widely used in the biomedical applications. Here, we briefly introduced these naturally derived nanofibers and review their applications in drug delivery systems.

### Cellulose Nanofiber

Bacterial cellulose (BC) is one such biopolymer that fulfills the criteria for consideration as a drug delivery material. It has already been approved by the FDA as a component of other products used for various clinical indications. There are lots of cellulose sources in nature, and numerous applications are reported for this material especially in the pharmaceutical and biomedical fields. There are many variations of cellulose due to the availability of extremely heterogeneous sources. Cellulose is a polysaccharide with a  $\beta$ -1,4-glycosidic linkage which is formed after condensation polymerization of anhydroglucose units. The cellulose may exist as cellulose nanowhiskers (CNWs) and nanocrystalline cellulose (NCC), with negatively charged form. The purely synthesized BC is unlike the plant cellulose which is produced as lignocellulosic polymer, and its degree of polymerization, crystallinity, high surface area, wet tensile strength, purity, and nanostructured fibers make it different from plant cellulose. The BC shows resembling properties of collagen in the human body with biocompatible flexibility and porosity. That is why the BC has been shown to have been used in several studies to fabricate drug delivery systems [113].

Hydrogen bonding is the main parameter of the existence and properties of BC. It has achieved smaller diameters with more fibrils which lead to even stronger hydrogen bonding. Many ions, including calcium (mineralization), can chemically modify the surfaces of these fine fibers and can also be found beneath the surface [114]. BC has been used in several systems for drug delivery after some sort of physical or chemical modification or else in the form of nanocomposite materials with diverse polymeric matrices. Furthermore, these systems have been mainly tested in *in vitro* transdermal drug delivery, oral drug delivery, and tissue engineering [115].

It is obvious that BC has been useful in wound healing for skin substitute products. The properties of this type of wound healing system can be oriented toward transdermal drug delivery, since it avoids external contamination, prevents moisture from evaporating, and maintains intimate contact with the exposed, inflamed, or diseased area which helps localized drug delivery to the target site. The use of BC with antibacterial materials such as silver nanoparticle has been used for fabrication of materials with antibacterial properties [116]. In composite layer of BC membrane with methacrylate, the S-enantiomer of propranolol, an antihypertensive drug, has been released. It applies to transdermal application where primary control of drug release came from the BC. Transdermal delivery systems that can work bilaterally, both to deliver drug and absorb exudates, represent a very exciting opportunity for the application of BC membranes [117]. BC could also be used as electrically stimulated drug delivery device in conjunction with a conducting polymer, such as polyaniline [118].

A series of cellulose hydrogels were made into membranes by the same investigators and examined for permeation of the lipophilic drug. BC can be used to generate multifunctional tissue engineering scaffolds (TES) from polymeric materials. A number of different methods can be employed, each of which depend upon the type of drug molecule and the features of TES [113]. In conclusion, the BC could be used for transdermal applications and as a pharmaceutical excipient in drug delivery systems and tissue engineering scaffolds, and it has the potential to couple tissue engineering with drug delivery for proteins and others.

## Silk Nanofiber

Silk is a fibrous high molecular weight (200–400 kDa) biopolymer naturally produced by *Bombyx mori* silkworm or spiders and identified by repetitive hydrophobic–hydrophilic peptide sequences. Representing biocompatibility, biodegradability, thermal stability, excellent mechanical properties (strength and toughness), and mild processing conditions, silk fibers have attracted much attention in the biomedical fields. The raw silk consists of two parallel fibroin fibers with a layer of sericin that held them together on their surfaces. Because of the immunogenicity of the sericin part, removing procedures should be done by degumming clean cocoons in boiling alkaline solution of sodium carbonate [119]. The resulting silk fibers are mostly used as suture or woven biomaterials. The structural composition of the natural fibroin mainly consists of glycine, serine, and alanine repeating sequence, which creates  $\alpha$ -helix and  $\beta$ -sheet crystallites with strong disulfide and hydrogen bonds and raises the tensile strength of the fiber up to five times higher than steel but extendable as synthetic rubber [120].

The extracted silk fibroin fiber can be used either without any further processing (as mentioned before) or by regenerating the silk fibroin (solubilizing the degummed silk fiber in hot salt solution and then dialyzing out the salts) and electrospinning the fiber solution in order to make desired morphologies for different applications. However, electrospun fibroin shows weaker mechanical properties than natural fiber which can be attributed to the nonuniform micro-/macro-orientations [121].

Silk fibroin unique properties lead to unfold numerous application for this fibrous protein, namely, surgical sutures; drug delivery carriers; tissue engineering scaffolds used for regeneration of the skin, corneal, and vascular and neural tissues; as well as load-bearing parts including the tendon, ligament, cartilage, and bone [122].

Studies demonstrated that the silk fibroin fibers as an ideal carrier can be applied for systemic/localized delivery of the variety of therapeutic agents including drugs, growth factors, genes, etc. Depending on the release kinetic pattern, amount of drugs, and the intended application, the drugs may be loaded onto the surface or inside the bulk of fibers. While in bulk loading, drugs are entrapped in the regenerated fibers by blending electrospinning or soaking native silk fibers in drug solution, surface loading includes direct coating or conjugating therapeutic agents onto the fibers. Sustaining the drug release, covalent conjugation of therapeutics such as proteins to the silk fibers can increase both their stability and half-life compared to simple adsorption [122, 123]. For example, [124] modified the silk fibers with sulfonated groups suggesting improved adsorption of fibroblast growth factor 2 (FGF-2) to the substrate. However, washing steps and harsh reaction condition may reduce the activity of drug in this type of loading, effectively.

Not only dose bulk loading method prevents destroying therapeutic agent during the fabrication process, it is also more suitable for delivering high doses. On the other hand, studies have demonstrated that native silk can strongly absorb the low molecular weight therapeutics specially with positive charge, through the electrostatic interaction between the drug and the negatively charged side chains of the hydrophilic spacers of its heavy chain, which usually occurs above the isoelectric point of silk (3.5–4.4) [125]. In addition, hydrophobic interactions between silk fibers and hydrophobic drugs represent another drug-loading possibility appropriate for lipophilic anticancer drugs [126]. It is worth mentioning that the crystallinity of fibroin (i.e., amount of  $\beta$ -sheet crystallites) can play crucial role in lowering initial burst release effect; the more  $\beta$ -sheet crystallites in fibroin, the more sustained-release pattern will be created.

Choi and co-workers used silk fibers to incorporate two antibiotics (doxycycline and ciprofloxacin) via different strategies including the simple loading (by dyeing fibers in various temperature, pH, and duration) and treatment of silk with NaOH solution for varied time leading to chemical and conformational changes [127]. It has been shown that the fibers can inhibit local growth of the *Staphylococcus* for more than 24 h.

As an alternative route of drug loading, composite systems of silk fibers which are typically achieved by integrating multiple silk formats (fibers, yarns, particles, etc.) into the implants, combinations of silk with other natural or synthetic polymers, all together with therapeutic agent incorporation in to the composite structure, indicate promising approach for tissue engineering and controlled drug delivery.

## Self-Assembled Peptide Nanofibers (SAPNs)

Self-assembling peptides are a category of peptides which undergo autonomous assembling process into ordered nanostructures such as nanofiber, nanorods,



nanotubes, nanospheres, nanofibrils, and nanotapes [128]. Molecular self-assembly is a spontaneous process in which the molecules are organized into an ordered structure, driven by free-energy. The main driving forces which are involved to start assembling process are van der Waals, electrostatic, hydrogen bonding, and  $\pi$ - $\pi$  stacking interactions [129]. In this “bottom-up” process, peptides as simple building blocks interact with each other to form large and more complex supramolecular structure. Interestingly, the essence of this technology is to mimic what nature does: for instance, fibrin clot formation as a response of vessel injuries or actin microfiber assembly in various cellular biochemistry processes. The peptides undergo self-assembling process that could be formed from natural or synthetic amino acids. Synthetic polypeptides which are usually derived from natural amino acids are the more preferred building block for biomedical or pharmaceutical applications because they are physicochemically stable, have variety of sequence and shape, and are suitable for large-scale synthesis [129]. A specific type of peptide amphiphiles could be self-assembled into the supramolecular structures under physiological conditions, mainly nanofibers with a cylindrical geometry.

PSANs are highly attractive nano-materials for many drug delivery applications. Drugs commonly are loaded during the formation of SAPNS by simple mixing of the drug molecules with the peptides. By modifying the amino acid sequence and adjusting the concentration of the peptide to form SAPNs, the proper drug loading and controlled release pattern then can be successfully achieved. Recently, the use of SAPNs as “smart” drug delivery platforms which can release the therapeutic components in response to environmental cues is very attractive. The amphiphilic peptide with pH-responsive self-assembling nature can be utilized as a pH-responsive drug delivery system that can release the drug content in response to environmental pH changing [130]. Furthermore, the SAPNs could be designed with novel peptide motifs, which are modified to make them stimuli-responsive [131].

Regarding the hydrogel applications in biomedicine, the SAPN hydrogels represent a promising alternative to current drug delivery approaches due to their encapsulation capability, water solubility, and biocompatibility [132]. Several studies have investigated SAPN hydrogels which were chemically conjugated with drugs, particularly anticancer drugs for chemotherapy applications [133, 134].

Based on the literature, SAPNs have been used to deliver the wide range of drugs and biomolecules such as anticancer agents, growth factors, and nucleic acids. For example, Ashwanikumar et al. developed a SAPN sustained-release DDS based on the RADA-F6 peptide with pH-responsive self-assembling nature to deliver 5-fluorouracil (5-FU) as an anticancer drug at basic pH [135]. Wang et al. developed a RGD peptide-based SAPN hydrogel for sustained drug delivery to the rabbit-eye posterior segment that was degraded gradually and exhibited great biocompatibility [136]. SAPNs are utilized to encapsulate the hydrophobic chemotherapy agent, e.g., camptothecin, to improve their solubility [137]. Studies also have reported the potential of SAPNs as the tissue engineering scaffold to deliver growth factors or bioactive biomolecules [138].

## Future Trends

Undoubtedly, drug delivery methods have experienced rapid transition to advanced systems, increasing the efficacy of therapeutic agents by controlling the site, time, and rate of release in the body and alleviating drug side effects by sustaining drug concentration in blood plasma. Employing porous micro-/nanostructured devices have received much attraction in biomedical applications, particularly tissue engineering and drug delivery. The reasons behind this fact include high surface area-to-volume ratio (enhances drug dissolution rate), ability of surface functionalization, adjusting surface morphology, and structural similarity to the ECM.

Considering its simplicity, cost-effectiveness, potential to scale up, and ability to spin a broad range of polymers from natural to synthetic and copolymers, electrospinning is one of the useful methods for micro-/nanofabrication in biomedical applications. Using this method, scientists are able to direct encapsulation of both hydrophobic and hydrophilic drugs (including anticancer drugs, antibiotics, etc.) and biomolecules such as proteins and nucleic acids into electrospun fibers.

Compared with other approaches, electrospinning affords a facilitated drug release system (due to high surface area and porous structure of fibers) and the ability of controlling the distribution state of drugs within fibers while decreasing the required dosage of the drug, leading to a less systemic absorption. Moreover, due to the high porosity of fibers, degradation products will not accumulate in the device and electrospun membranes can be tailored into any size and shape.

Despite being excellent drug carriers, electrospun fibers still have some limitations, which should be addressed. Initial burst release of the drug from fibers, which can occur in directly mixing drugs into the polymer solution, is considered a main problem due to the aggregation of drug molecules near the surface of nanofibers. Using super-hydrophobic polymers (i.e., doping electrospun fibers with hydrophobic agents) is suggested as an alternative approach to slow the burst release as well as prolong the sustained release of drugs. Although the sustained-release behavior has been usually achieved from uniaxial fibers with low loadings and hydrophobic molecules, optimization of the discussed designing parameters will increase the possibility of achieving sustained-release behavior for both hydrophilic and hydrophobic small molecule drugs at high loadings. Therefore, a deep understanding of the drug/polymer/solvent interactions at all stages of the electrospinning process is required to analyze the drug release behavior. Finally, fiber-based DDSs seem very promising combinatorial technology for biomedical applications.

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