Fiber Based Approaches as Medicine Delivery Systems

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ABSTRACT: The goal of drug delivery is to ensure that therapeutic molecules reach the intended target organ or tissue, such that the effectiveness of the drug is maximized. The efficiency of a drug delivery system greatly depends on the choice of drug carrier. Recently, there has been growing interest in using micro- and nanofibers for this purpose. The reasons for this growing interest include these materials' high surface area to volume ratios, ease of fabrication, high mechanical properties, and desirable drug release profile. Here, we review developments in using these materials made by the most prevalent methods of fiber fabrication: electrospinning, microfluidics, wet spinning, rotary spinning, and self-assembly for drug delivery purposes. Additionally, we discuss the potential to use these fiber based systems in research and clinical applications.

KEYWORDS: drug delivery, micro- and nanofiber fabrication, microfluidics, electrospinning, wet spinning, rotary spinning, self-assembly
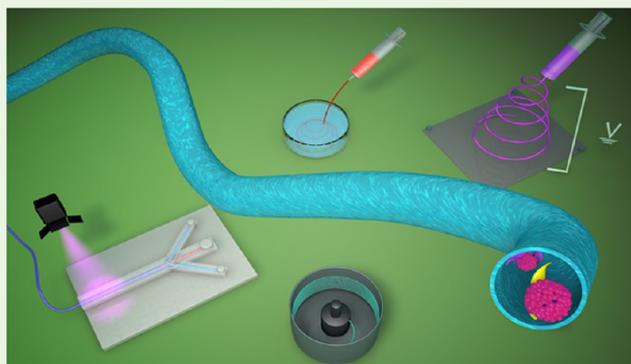
1. INTRODUCTION

Since the beginning of the 20th century, efficient drug delivery has been a topic of continuous study and research. Regardless of developments in areas such as cancer therapeutics and drug delivery, progress in certain aspects of each area has been dampened by the inefficiency of the carriers used in these drug delivery systems. The importance of the drug carrier can be attributed to four factors, which are (i) targeting of the drug to the intended organ for maximum effect, (ii) evasion of the immune system of the body to reach the final target, (iii) retention of the therapeutic molecules from the preparation and processing to the final target of the drug, and (iv) release of the drug molecules at the destination organ such that the molecules can exert the intended therapeutic effect. Therefore, the success of an extant or potential application of a drug delivery system innately depends on the choice of the drug carrier.[1−4]

Researchers have considered numerous carriers over the past few decades,[5,6] and micro- and nanofibers have become an attractive prospective carrier option.[7−13] This could be attributed to both the nature of the material used to fabricate the fiber and the nature of this very fabrication process. Additionally, the low initial burst rate compared to spherical vesicles and the controlled zero-order drug release profile, seen in drug loaded fibers, make them more suitable for drug delivery applications.[14−16] Materials such as alginate and gelatin used to fabricate these fibers are biocompatible,[17,18] thus causing no harm to the tissue of the host. Such fibers are also

biodegradable and do not accumulate in the human body, disrupting its biochemical and physiological processes. Furthermore, these materials exhibit low immunogenicity. This means that they do not provoke major immune responses from the host's immune system. As a result, fibers composed of such biomaterials help create effective carriers of therapeutic molecules.

The morphology of the fibers makes them ideal candidates for drug delivery systems. By virtue of the cylindrical shape of the fibers, they possess a high surface area to volume ratio.[7,19] This provides the fibers the ability to release the drug into the medium over a large surface area. Furthermore, unlike spherical vesicles, where the surface area to volume ratio can only be controlled by varying the radius, both the length and the cross-sectional radius can be varied in fibers. This adjustability is vital for a drug delivery system in applications in which the functional parameters are to be precisely controlled. Additionally, several applications of drug delivery systems are seen where the drug delivery function occurs alongside a structural role. Tissue scaffolds, wound dressings, and other tissue engineering applications can be cited as prime examples of such applications.[7,20] For these roles, the shape and mechanical properties of micro- and nanofibers, composed of biomaterials,
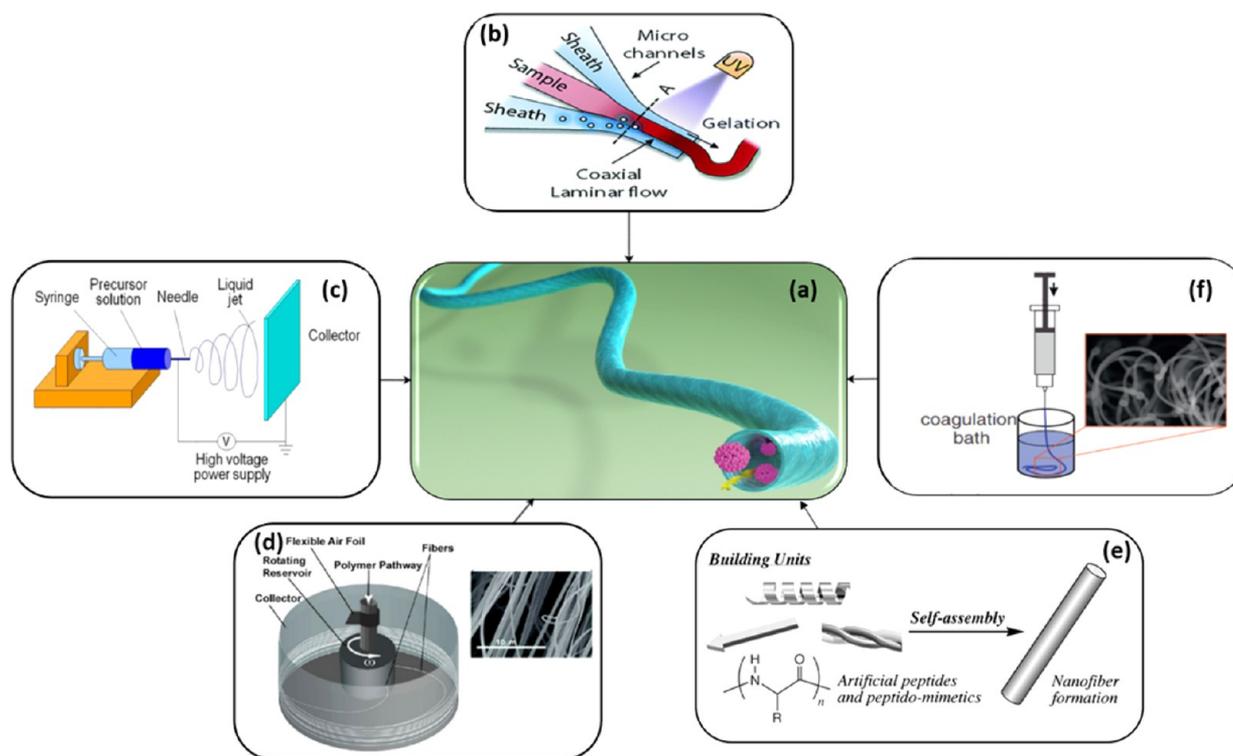
Figure 1. Most common methods used to fabricate fibers for drug delivery. (a) Illustration depicting the incorporation of drug molecules into a microfiber. (b) Schematic of the microfluidic fiber fabrication approach. The manner in which the sheath and the core fluid flows are directed by microchannels to generate the fiber is depicted.[24] (c) Schematic of fiber fabrication by electrospinning. The electrically ground plate collects the fiber.[25] (d) Rotary spinning method where the solution is spun at high speeds and the centrifugal force causes the solvent to evaporate, which results in fiber fabrication.[26] (e) Schematic of the building units which contribute to the formation of self-assembled nanofibers.[27] (f) Wet spinning method, where the fibers are injected into a coagulation bath.[28]

are essential. The shape and arrangement of such fibers could be easily changed, which makes them more suitable for drug delivery systems than micro- and nanovesicles. Fibers with different shapes and structures, such as hollow, flat, and ribbon shaped, can also be fabricated depending on the intended application.[21−23]

Various methods have been used for the fabrication of these micro- and nanofibers over the past few decades. Microfluidic fiber fabrication, electrospinning, rotary spinning, self-assembly, and wet spinning are the most common methods. These five approaches are schematically depicted in Figure 1. Moreover, variants of these methods have been developed to cater to the needs of different applications. Among these methods, electrospinning and microfluidic fiber fabrication approaches are predominantly employed in research related to drug delivery. Each of these methods have some advantages that make them suitable for specific drug delivery applications.

The purpose of this review is to categorize research developments in employing micro- and nanofibers for drug delivery applications. The different fiber fabrication techniques are reviewed, and further innovations in fiber based drug delivery systems are discussed. For example, in discussing microfluidic fiber fabrication for drug delivery applications, structural developments, incorporation of stimuli-responsive properties, and innovations in the fabrication methodology were explored in detail. Furthermore, special emphasis is given to the potential applications of these approaches in clinical practice. Finally, each of the applications are described in detail and tabulated to obtain a general overview of fibers utilized for drug delivery purposes.

2. MICROFLUIDIC FIBER FABRICATION

Microfluidics is a promising approach that uses a small amount of materials for various applications such as biomedical areas and energy devices.[29−35] This approach is the most recent of fiber fabrication methods applied to research in utilizing fibers as drug carriers.[36]

In this method, fibers are fabricated by means of coaxial flow of prepolymer (core fluid) and sheath fluid in a microchannel. Microfluidic fiber fabrication methods are particularly useful for drug delivery related applications due to the versatility, simplicity, and continuity of the process. There is no need for high electric currents, pressures, and temperatures, which improves the biological compatibility of the fiber fabrication process. Additionally, a variety of biocompatible and non-cytotoxic substances can be used in this approach. The size and shape of the fiber can be tuned by simply changing the parameters involved in the process as well as a solidification strategy. Submethods of microfluidic fiber fabrication can be categorized based on the solidification strategy: photopolymerization, chemical reaction, and phase inversion approaches. Photopolymerization involves solidification of prepolymeric molecules by means of free-radical polymerization reaction within the microchannel. This method results in rapid and easy generation of solid fibers while maintaining size and shape.[24,37] In the chemical reaction method, the bonding of prepolymer molecules is facilitated by using small molecules or ions, such as Ca^{2+}.[24,38] In the phase inversion method, the solvent in the core stream of the microfluidic chip is rapidly removed by means of evaporation or extraction to expedite solidification of the polymeric fiber.[24,31,32,39]
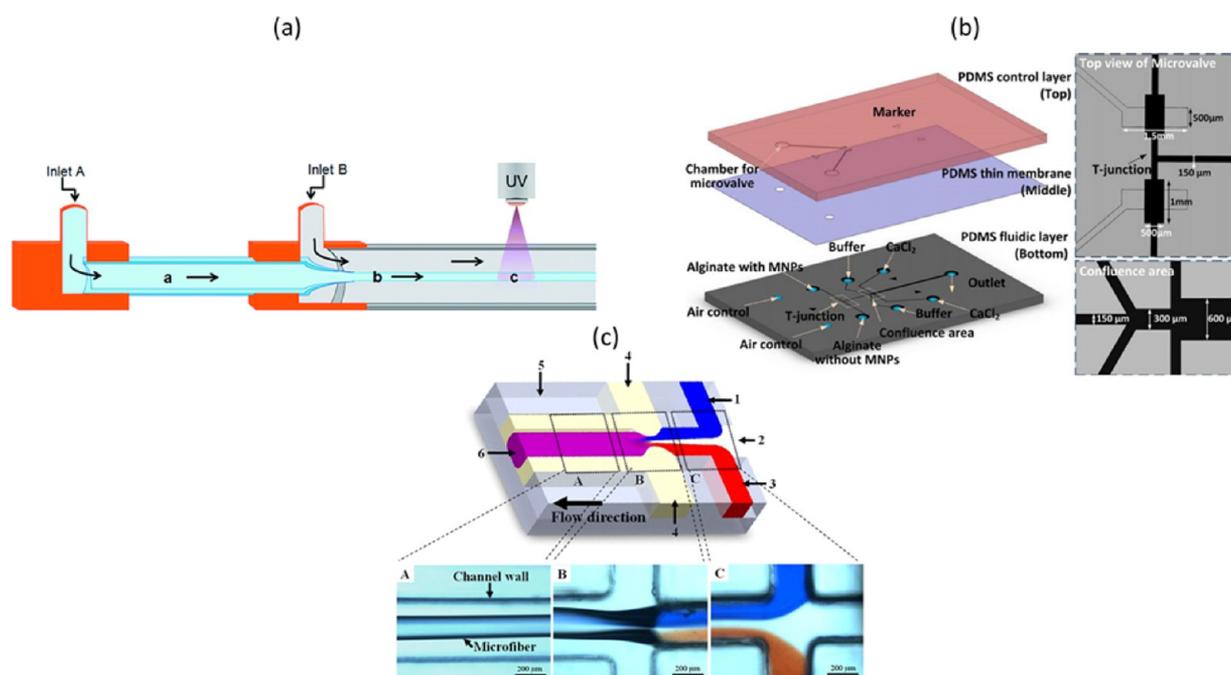
Figure 2. Different fabrication methods of magnetic stimuli-responsive micro- and nanofibers: (a) Use of magnetite nanoparticles in hydrogel cell encapsulation. A mixture of sodium alginate, N-iso-propylacrylamide (NIPAm), cross-linkers, and photoinitiator in aqueous form was inserted at inlet A. At inlet B, calcium ions were injected to diffuse into alginate and form calcium alginate.[19] (b) The pneumatic microvalve structure used in microfiber fabrication.[49] (c) Microfiber fiber fabrication system accompanied by photographs of the microfiber in the channel and two different junctions.[45]

Each of these submethods have distinct advantages and disadvantages. In particular, photopolymerization produces fibers in less than a second, and control over the fiber diameter over large spans of the fibers is significant. However, the degradability of the fibers fabricated by photopolymerization decreases, which could damage living organisms. Biodegradability and biocompatibility are the primary advantages of fibers fabricated using chemical cross-linking and phase inversion strategies. However, there are some limitations and difficulties associated with shape formation of the fibers due to the slower solidification rate of these two submethods.[24]

Microfluidic fiber fabrication is a promising platform to fabricate fibers with a wide range of characteristics. However, the production rate in this technique is relatively slow mainly because the flow has to be in the laminar regime. Otherwise, the fluids introduced in the microfluidic device become mixed together and the diffusion will not occur only at the fluid/fluid interface. Moreover, the fluids, i.e. core and sheath fluids, have to be matched in terms of viscosity in order to keep the shear force at the fluid/fluid interface in the stable flow regime. In addition, there is always a possibility of the microchannel clogging due to undesirable shear force, which is originated from the mismatch between the properties of the fluids or from inappropriate flow rate ratio. This issue can be minimized by adjusting the flow rate ratio between the fluids, the concentration of polymer and cross-linking agent, and the UV intensity in a suitable range.[31,34,40]

2.1. Magnetic-Responsive and Photoresponsive Drug Delivery Systems. Incorporating stimuli-responsive properties to micro- and nanofibers significantly increases the utility of such materials within biological environments. Such stimuli-responsive nanoparticles have been successfully used in drug/gene delivery,[41] bioseparation,[42] and magnetic resonance imaging,[43] but rarely with micro- and nanofibers. This is

particularly true in drug delivery, as the environment itself and the requirements for therapeutic material are constantly changing. These stimuli-responsive characteristics, such as photoresponsiveness,[44] magnetic manipulation,[45] and temperature sensitivity,[46] are achieved by the incorporation of minute particles into the fiber structure during the fabrication process. The advantages of fabricating such stimuli-responsive therapeutic-incorporated materials and scaffolds are numerous. This work provides controllability, response properties, attenuation, and rapid drug release to micro- and nanofibers. The advantages of such stimuli-responsive fibers are ease of fabrication, high production rate, low cost, biocompatibility, and uniform distribution of magnetic particles in the fibers.[47] However, there are unique challenges associated with utilizing these fibers for actual drug release applications *in vivo*. One obvious practical difficulty would be implementing an optimum configuration of magnets when administering drugs using magnetic-responsive fibers.[48] Photoresponsive drug loaded fibers are relatively easy to fabricate but challenging to deploy as drug carriers. Nevertheless, once these challenges are overcome, stimuli-responsive drug incorporating fibers have the potential to change the way that therapeutic substances are delivered to various cells and tissues in the body.

The use of magnetite nanoparticles in hydrogel spheres for cell encapsulation related studies has been discussed as well. However, Lim et al. extended the method to microfibers.[19] The focus of the study was to incorporate stimuli-responsive features to hydrogel microfibers fabricated by a microfluidic approach with controllable size and morphology. As shown in Figure 2(a), a microcapillary device was used to generate Ca-alginate templates. In this process, hydrogel monomers were included and subjected to UV radiation (photopolymerization) to create poly(N-isopropylacrylamide) (PNIPAm) based hydrogel microfibers. PNIPA was chosen for this study because
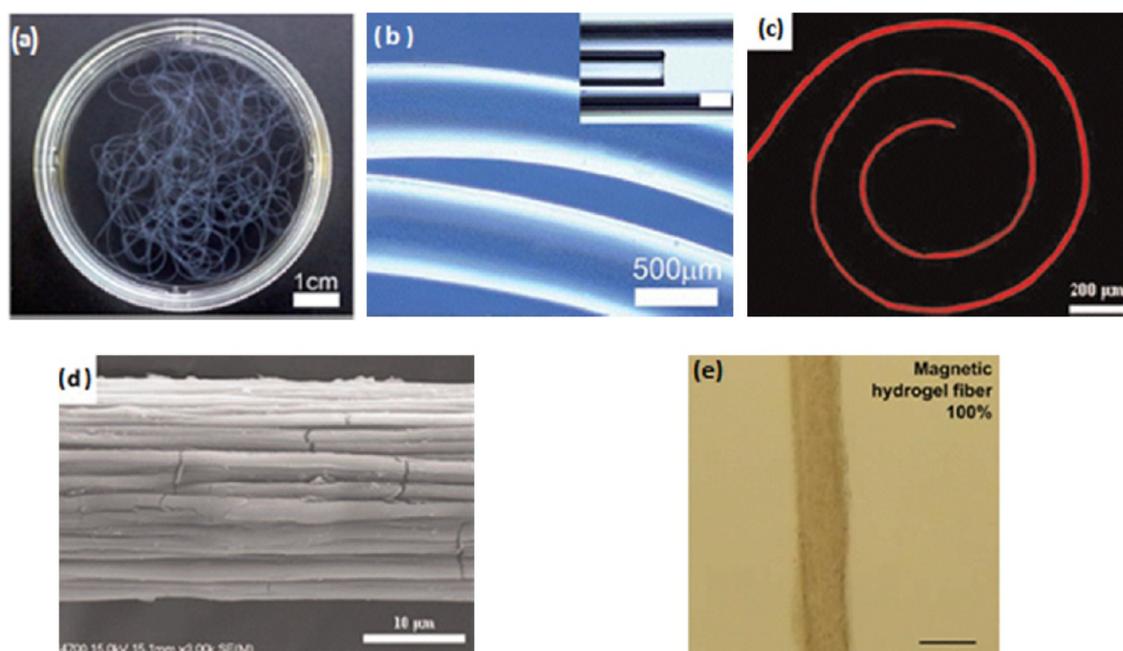
Figure 3. (a) EDTA treated poly(*N*-isopropylacrylamide) (PNIPAm) microfibers fabricated by the microfluidic approach.[19] (b) Optical micrograph of PNIPAm microfiber with an inner capillary diameter of 500 μm.[19] (c) Alginate microfiber for magnetic-responsive controlled drug release.[45] (d) SEM image of the fiber shown in part (c).[45] (e) 100% alginate hydrogel microfibers fabricated by a multilayered pneumatic microvalve based fabrication methodology. The horizontal scale bar represents 50 μm.[49]

of its temperature-responsive nature. Furthermore, the resulting microfibers were photoresponsive due to the inclusion of photothermal magnetite nanoparticles. Ionic attractions were observed between the polymer and calcium ions, facilitated by the capillary tubes and coaxial flows. This aided the uniformity and the small diameters required for the templates. The microfiber diameter was controlled by adjusting the capillary tube sizes. Hollow fibers were obtained by changing the order of the inlets in microfiber fabrication. Functional materials were either blended into the core fluid or copolymerized. The response of PNIPAm microfibers, with blended in magnetite nanoparticles responsive to light and temperature, was observed in the form of volume change.

The controllability of the microfiber could also be achieved by including magnetic nanoparticles in the alginate fiber fabricated with the microfluidic approach. Hu et al. obtained this result by evenly dispersing magnetic nanoparticles in alginate solution and subjecting it to a microfluidic fabrication process, illustrated in Figure 2(b).[49] This process was enhanced by incorporating hemicylindrical channels of multilayered pneumatic valves. The channels were capable of fully closing and regulating the flow rates of magnetic and nonmagnetic alginate. Through this process, microfibers with different magnetic properties were produced. Importantly, there was no aggregation of magnetic nanoparticles produced by a precipitation method inside the alginate solution. This aided the uniformity of the final product during the fabrication process. The ability of the microfibers to be utilized in a magnetic field, to assist drug targeting, growth factor delivery, and possibly other kinds of therapeutics, makes them candidates worthy of further investigation. This method could potentially address controllability, actuation, and response properties in drug delivery systems.

Lin et al. also focused on the use of magnetic nanoparticles for fabricating stimuli-responsive fibers for drug delivery. Their emphasis was laid on utilizing the unique stimuli-responsive characteristics in drug release and cell encapsulation.[45] As shown in Figure 2(c), a microfluidic method that involved multiple inlets at different points along the center channel was utilized. In this design, alginate solution was controlled at different points along the channel in a laminar flow regime. The diameter of the fibers was varied from 211 to 364 μm by changing the alginate solution flow rate. The magnetic iron oxide and diclofenac, the model drug, were incorporated into the alginate solution prior to the microfluidic fiber fabrication procedure. The drug release profile of the model drug demonstrated that the release process was linear and steady and could be controlled externally by a magnetic field. This control is achieved by the attraction of the magnetic nanoparticles toward the magnetic field, making the microfiber more porous. The initial burst rate observed in microfibers was smaller compared to spherical microvesicles. Furthermore, the microfluidic method of microfiber fabrication results in a high encapsulation rate of 90% for both the magnetic iron oxide nanoparticles and the drug itself. Therefore, this is an efficient, convenient, and controllable method for drug delivery.

The magnetic-responsive micro- and nanofibers generated by the aforementioned means do not display morphological changes that might adversely affect their function in drug delivery. The cylindrical forms of the fibers fabricated by Lim et al. are depicted in Figure 3(a) and (b).[19] Figure 3(c) and (d) show an alginate microfiber with diclofenac and magnetic iron oxide.[45] These microfibers are shown in Figure 3(e).[49]

2.2. Other Innovative Approaches to Microfluidic-Spun Fiber for Drug Delivery. Certain alterations have been introduced to this conventional microfluidic fiber fabrication procedure in order to ensure the enhanced functionality of fibers. These alterations include implementing a roller mechanism to draw out thinner fibers,[50] composing fibers of triblock copolymers as opposed to conventional PLGA,[51] and

enhanced continuous production methods.[36] In addition, attempts have been made to use glass for making microfluidic chips, instead of PDMS, as glass has more desirable optical properties.[52] Some research has been conducted on creating spherical vesicles from microfibers by drawing them out in a microfluidic arrangement. This method is unconventional in the sense that the fibers do not carry the drug to the target. In fact, they act as an intermediate stage in the final drug carrier fabrication.[53] Some studies focus on increasing the concentration of loaded drugs, which may be essential in curbing rapidly spread infections.[7] Each of these innovative approaches also have shortcomings, which shall be discussed on a case by case basis.

From a drug delivery system perspective, innovative methods for microfiber fabrication are important. Toward this end, Kang et al. described a solely PDMS based method of fabricating microfibers utilizing the cylindrical channel created by the deflection of a thin PDMS layer.[54] The principle was extended for creating rectangular molds, and an additional 12 rectangular "micromixers" were created on a single chip with 5 coaxial flow channels. In these channels, microfibers with a different chemical composition were fabricated. The process and resulting fibers are schematically depicted in Figure 4. The
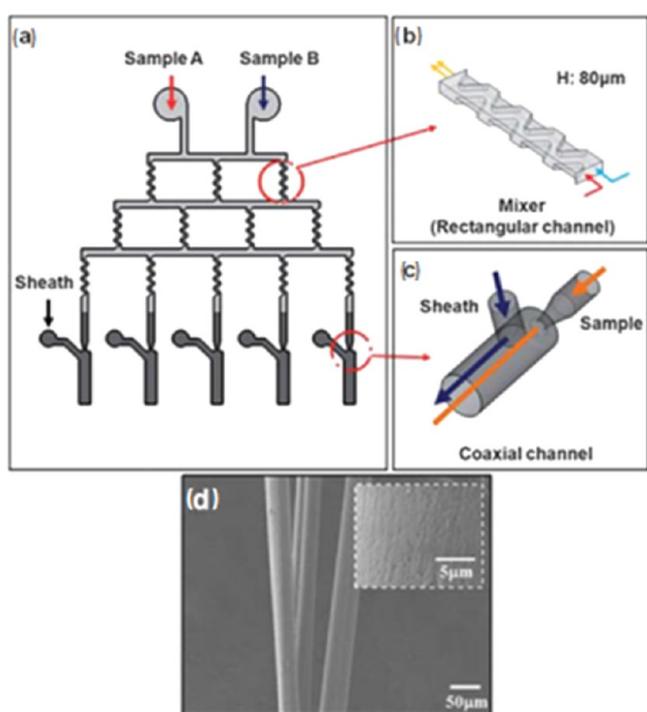

Figure 4. (a) Microfluidic fiber fabrication platform in which 5 fibers of different composition are fabricated in parallel. A stepwise gradient across 5 output solutions is achieved with 12 rectangular micromixers, and fibers were generated from these solutions through 5 coaxial flow channels. (b) Illustration of the alligator teeth micromixer. (c) Coaxial flow channel with a single sheath inlet. (d) SEM image of alginate fiber.[55]

diameters of the fibers fabricated were 75 to 115 μm. The core solution was sodium alginate, and the sheath fluid was calcium chloride. Bovine serum albumin (BSA) was successfully included in the fibers via the core fluid to demonstrate the ability of the fibers to carry therapeutic agents. However, the disadvantage of this method is the size limitation of the fibers,

which could potentially be addressed by adjusting the flow rate and channel size of the coaxial flow.

A higher degree of control over fiber dimensions is important in creating fibers for drug delivery applications. Su et al. have investigated the possibility of using a roller assisted microfluidic system for generating alginate microfibers, where it is possible to exert such a degree of control.[50] The alginate solution with the monomers and other particles, such as nanoparticles for drug delivery or cells for cell based therapy, was passed through a single microchannel. Then, calcium chloride solution was used to cross-link the alginate, which was collected with a roller, resulting in a microfiber. The roller was the critical component that reduced the diameter of the fiber to the order of 1 μm, and it also affected the shape of the fiber. Silver nanoparticles are important antimicrobial agents and possess wound healing properties. These particles were included by diffusing silver ions to the alginate microfiber and subjecting it to UV light. Such nanoparticles could be potentially released in low concentrations to create antimicrobial activity in wound care applications. Biomaterials were included in the microfiber by blending with the alginate solution, which results in a successful method of incorporating anticancer drugs in drug delivery applications. This method could be applied to other hydrogel fiber types, which may increase the range of microfibers capable of incorporating drug delivery systems into their composition.

In the field of drug delivery systems, controlling the release rate of an encapsulated drug or a protein in the microfiber is an important factor. Marimuthu et al. successfully conducted a study where microfibrous scaffolds composed of amphiphilic triblock copolymer were fabricated utilizing microfluidics and the porosity was controlled.[51] This controllable porosity was obtained by combining the effects of immersion precipitation and solvent evaporation with the microfluidic generation of fibers. It was demonstrated that the porosity of the fiber has a notable effect on the release of fibronectin, which was the model protein used. In principle, the method could be extended to use with gene therapy and other therapeutic agents in drug delivery systems. The copolymer used was an amphiphilic ABA copolymer (PPDO-co-PCL-b-PEG-b-PPDO-co-PCL) capable of facilitating drug delivery due to its hydrophobic (PPDO/PCL) and hydrophilic (PEG) segments. Along with the enhanced drug encapsulation and release characteristics, the method is cost-effective, is robust, and can be modified for other therapeutic applications.[56]

As Berthier et al. have pointed out, there are advantages specific to both polystyrene and PDMS as materials for microfluidic apparatus as well as disadvantages.[52] Of the two, polystyrene is more often used in conventional biorelated laboratory activities, but it has proven to be a difficult material to engineer. The same difficulties have been faced by researchers intending to use polystyrene in microfluidics, which has led to more prevalent use of other materials for research. Johnson et al. developed an innovative method to use PDMS molds to make polystyrene based microfluidic devices.[57] Powdered polystyrene in a Petri dish was melted against a mold made out of PDMS to fabricate a microfluidic chip with channels and grooves. The absorption levels of drugs by fabricated devices were clearly demonstrated and compared to conventional PDMS devices. The results indicated that clopidogrel, the drug of choice for the study, is not absorbed by the PDMS material. Therefore, microfluidic devices could be used for laboratory drug delivery system related research, and in encapsulating drugs into microfibers.
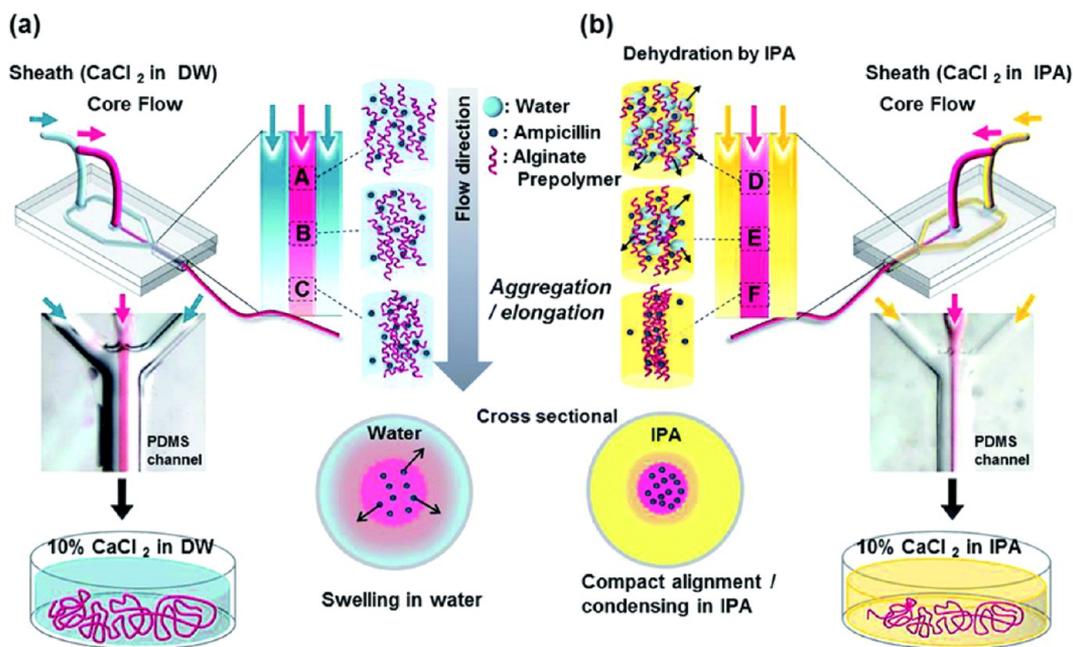
Figure 5. Schematic depicting the manner in which drugs are loaded into alginate fibers. The polymers aggregate and encapsulate the ampicillin molecules along the direction of flow in each groove. (a) Fiber is fabricated with a solution of calcium chloride in deionized water as the sheath fluid; (b) fiber is fabricated with a solution of calcium chloride in isopropyl alcohol (IPA) as the sheath fluid. In either case, the resulting fiber is passed onto a calcium chloride solution for further coagulation.[7]

The required concentration of a therapeutic substance has to be relatively high to have any effect on certain tissues or pathogens. Microfluidic fiber fabrication allows for creation of fibers with a higher capacity to carry drugs. The deviation from the conventional method does not necessarily have to be structural, and it could be a change in the constituent materials used. Ahn et al. investigated a process in which certain details of the conventional microfluidic approach were changed in order to make the intended effect.[7] Isopropyl alcohol was used as a sheath flow to create alginate polymer chains packed in a highly ordered and tight manner to form the fiber. This minimizes the swelling of the fibers and makes the concentration of the drug loaded in the fiber as high as possible. This overall arrangement of polymers within the fibers led to delayed degradation of the microfiber. The degradation was further slowed down by immersing the drug loaded fibers in a calcium ion bath. This was done to increase the cross-linking of the polymers, which results in a stronger polymer. The core fluid was alginate solution with Ampicillin dissolved in it. Figure 5(a) describes the fabrication of drug loaded alginate fibers with calcium chloride in deionized water as the sheath flow and in the coagulation bath. Figure 5(b) depicts the fabrication procedure with calcium chloride dissolved in isopropyl alcohol as both the sheath fluid and the coagulation bath.

Ampicillin is a widely used antibiotic that is active against Gram-positive and Gram-negative bacteria.[58] It was demonstrated that the drug loaded fibers were successful based on the antimicrobial action of drug loaded fibers placed in a bacterial culture. Further fibers were embedded in a chitosan patch and successfully used on a bacteria infected wound of a mouse. This experimental application is schematically depicted in Figure 6(a). The actual structure of the dressing scaffold and the excision wound are shown in Figure 6(b) and (c), respectively.

The essential details pertaining to separate cases where micro- and nanofibers fabricated by the microfluidic approach
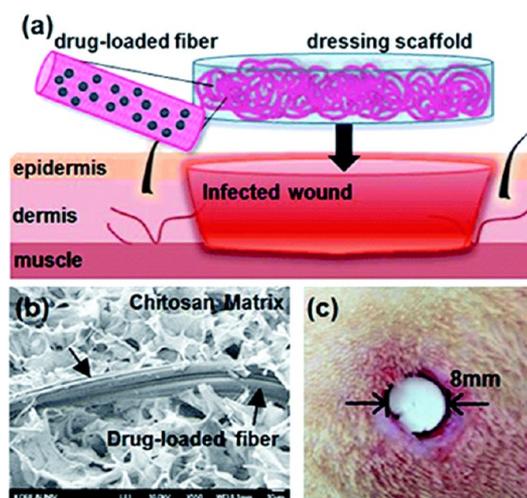

Figure 6. (a) Schematic of a bacterial wound with a fibrous scaffold containing drugs. The dressing scaffold is composed of alginate fibers with a high concentration of ampicillin capable of exerting the necessary antibacterial action to control an infection. (b) SEM image of the actual dressing scaffold with the chitosan matrix and the ampicillin loaded fiber. (c) Excision wound.[7]

for drug delivery applications are given in Table 1. The core fluid, sheath fluid, diameter of the cross section, and drug type (if indicated) used in each instance are indicated.

3. ELECTROSPINNING

Electrospinning is a widely used and thoroughly investigated method of micro- and nanofiber fabrication. In this method, the polymer is subjected to an electric field applied between a syringe containing the polymer and a collector. The jet moves in the air, and during this time, it is either electrically deflected, collected on a grounded stationary metal screen,[60] or collected

Table 1. Details of Fibers Fabricated by the Microfluidic Approach for Drug Delivery Systems

| Authors	Drug Type	Diameter (μm)	Core	Sheath
Lim et al.[19]	N/A	10−600	A mixture of Na-alginate, NIPAm, cross-linkers and photoinitiator in aqueous form	Ca^{2+} solution
Hu et al.[49]	N/A	45−50	Alginate solution with magnetic nanoparticles	CaCl$_2$ solution
Lin et al.[45]	Diclofenac	211−364	Alginate solution and model drug	CaCl$_2$ solution
Mazzitelli et al.[59]	Drug delivery systems CAM, ERSM, LS, and COBE	180−500	Na-alginate through one inlet, Na-alginate and drug delivery system (CAM, ERSM, LS, or COBE) through one inlet, Na-alginate and cell suspensions through one inlet.	N/A
Kang et al.[55]	BSA	75−115	Na-alginate solution and BSA	CaCl$_2$ solution
Su et al.[50]	Silver particles	∼1	Na-alginate solution	CaCl$_2$ solution
Marimuthu et al.[51]	Fibronectin	2−200	10% PPDO-co-PCL-b-PEG-b-PPDO-co-PCL copolymer in CH$_2$Cl$_2$	DI water
Ahn et al.[7]	Ampicillin	N/A	Alginate and Ampicillin solution	CaCl$_2$ in IPA or DI water
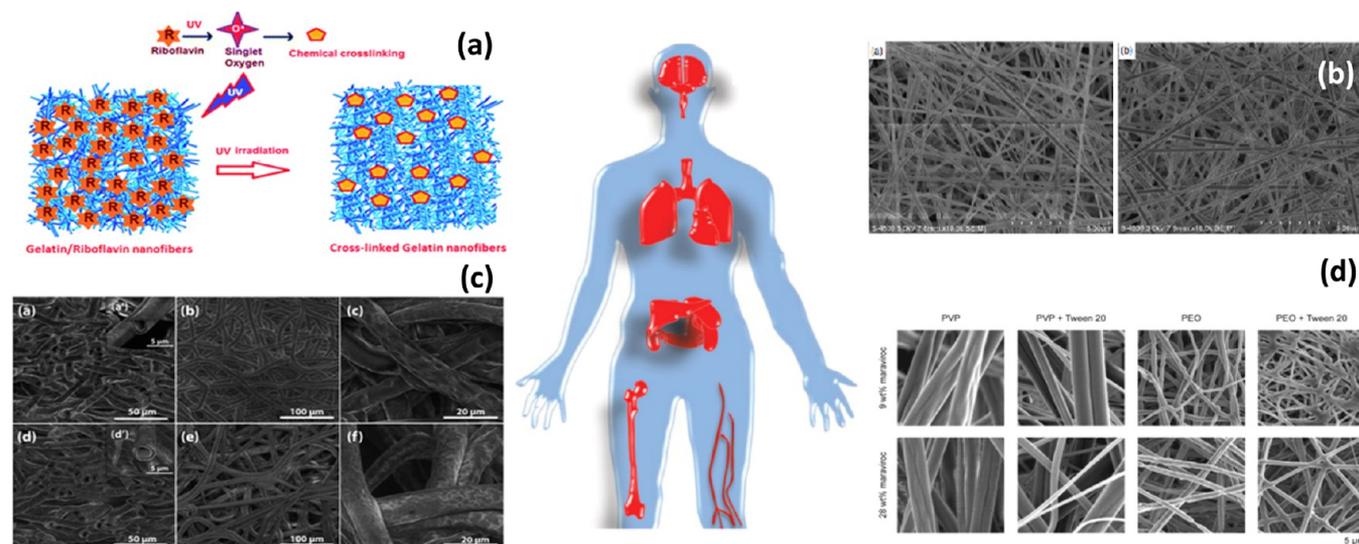
Figure 7. (a) Schematic depicting the cross-linking of gelatin nanofibers with riboflavin which may potentially be used in the dentin, pericardium, or eye.[78] (b) BUD-core/shell-nanofibers that could be potentially used for drug delivery.[81] (c) PVP and PEO fibers containing HIV prophylactic drug Maraviroc.[84] (d) Coaxial PCL/PEO hollow fibers which may be loaded with dexamethasone for inflammation treatment.[82]

on a grounded rotating or translating metal target.[61] Different variants of this method exist, but the core concept is the same. By varying the conditions of the process, including the voltage and the material, fibers with a range of cross-sectional diameters were obtained. The advantages of using electrospinning to fabricate macro- and nanofibers in drug delivery systems include the ease of fabrication of fiber with diverse morphology and dimensions, the ability to include the therapeutic molecules in the polymer solution, and the ability to orient fibers either randomly or in an ordered manner, for tissue engineering related drug delivery applications.[62]

Although electrospinning is a common approach for fabricating fibers, it has some disadvantages that adversely affect the biocompatibility aspect of this method. The diameter of the electrospun fibers is typically smaller than a single cell, which makes it challenging to encapsulate living cells and microparticles into the fibers.[28,63] Additionally, the common solvents that are used in this process, such as 2,2,2-trifluoroethanol (TFE), tetrahydrofuran (THF), dimethylformamide (DMF), dichloromethane (DCM), chloroform, acrylic acid, and hexafluoroisopropanol (HFIP), have high toxicity.[64]

Due to the surface tension at the liquid/air interface, the cross sections of the electrospun fibers are mostly circular, whereas, in the microfluidic approach, the shape and surface of the fibers can be simply tuned by changing the 3D hydrodynamic focusing force.[31,34,54,65] Besides the size and shape limitation and toxicity of the solvents, the utilization of high electric fields (∼1−2 kV/cm) in this technique makes electrospinning unsuitable for certain drug delivery systems where live cells need to be included in the fibers.[28] However, due to the functionality of the electrospinning method, many studies focused on improving the shortcomings that exist in a typical electrospinning process.[64,66−68] For example, some reports showed that by simultaneously elesctrospinning fibers and electrospraying the cell suspension, the cells will have high viability.[67,68] There are some studies in which drugs were encapsulated into the fibers, whereas, in other reports, the combination of both fiber and liposomes were used to encapsulate the drugs and control the rate of release.

3.1. Electrospinning Fiber Fabrication Technique in Drug Delivery Application. Usage of micro- and nanofibers in drug delivery is still an emerging topic in biomedical

research. Due to the structural advantages fibers offer, they could be used in specific sites in the body in conjunction with tissue. The range of molecules that could be delivered by electrospun fibers extends from small biomolecules to molecules as big as proteins and DNA plasmids.[69−75] Hence, this offers a significant advantage over conventional carriers.[76] Additionally, subcellular vesicles and stimuli-responsive time-variant morphological features could be incorporated into the fibers. However, further innovations could result in drug delivery systems designed for specific applications. Wound healing, for instance, is an area widely studied in applications of drug delivery systems which incorporate electrospun fiber structures. However, a single material may fall short in mechanical strength or may have less than optimal drug loading capacity in wound dressing applications. Bai et al. have succeeded in addressing both issues by fabricating a chitosan/polycaprolactone (CS/PCL) nonwoven mat utilizing the electrospinning method.[77] The arrangement of fabricated fibers provides a greater area for active ingredients in the fiber to interact with the surroundings. Tree oil and calcium ions were incorporated into the chitosan component of the structure, leading to increased platelet aggregation and antibacterial as well as anti-inflammatory effects, respectively.

Releasing hydrophilic therapeutic compounds from hydrophobic fibers is a challenge. PCL-riboflavin nanofibers with radii ranging from 267 ± 37 nm and gelatin-riboflavin microfibers with radii 2.18 ± 0.3 μm were fabricated by Sridhar et al.[78] Riboflavin is commonly known as Vitamin B2. It performs a range of critical metabolic functions as well as contributing to wound healing and maintaining tissue health.[79,80] Cross-linking was caused by the oxygen radicals generated by UV irradiation of riboflavin, which leads to an increase in mechanical strength of the fibers. This is schematically presented in Figure 7(a). The riboflavin release rate from these fibers was altered by treating the fibers with plasma and changing the plasma treatment duration. Therefore, noncytotoxic riboflavin can function as a cross-linker and a therapeutic agent whose release rate can be controlled. Such riboflavin cross-linked fibers could be potentially used for fibrous scaffolds in tissue engineering applications such as dentin, parts of the eye, and the pericardium.

Oral ingestion of drugs is the most prevalent form of drug delivery in the pharmaceutical industry. Toward this end, Xu et al. created and investigated a drug delivery system consisting of Budesonide (BUD) loaded core/shell nanofibers that follows the aforementioned oral colonic pathway.[81] Coaxial electrospinning was performed to prepare Budesonide loaded ethylcellulose(EC)-core/Euragit S100-shell nanofibers, shown in Figure 7(b). The diameter of these fibers averaged 190 nm, and the average core diameter, which is uniform throughout the length, was 74 nm. Budesonide-loaded Eudragit S100/ethylcellulose nanofibers, which are regarded as composite nanofibers, were fabricated utilizing blend electrospinning. The composite fiber was used as a control, and both were subjected to *in vitro* and *in vivo* tests, with the latter being carried out in rats. It was observed that the desired pH dependent behavior was observed from the Budesonide loaded core/shell nanofibers, and the encapsulated drug was shielded from the acidic contents of the stomach and small intestine until the colon was reached. Budesonide in nanofiber encapsulated form could potentially be used for future applications in an oral colonic drug delivery systems. This is a possibility due to the

advantages this particular method offers over the current conventional method used in the pharmaceutical industry.

Rubert et al. investigated fibroblast growth factor delivery and tissue engineering applications of PEO/PCL electrospun coaxial microfibers.[82] Fibrous cartilage in the human body heals at a slower rate due to the lack of cells which produce collagen. Figure 7(c) shows a method in which PCL/PEO coaxial microfibers were loaded with fibroblast growth factor. The fibers had an outer surface made of PCL, and the fiber diameters ranged from 7.49 ± 0.835 μm to 7.489 ± 0.445 μm. As noted in previous reviewed work, electrospinning parameters could be adjusted to change the fiber morphology to the desired form. The therapeutic substance was encapsulated properly, and the release lasted over 9 days. It was observed that the growth factor was expressed more after the first day, but reduced in release after day 9, proving that the method could be a potent form of growth factor delivery based on microfibers. Lei et al. utilized electrospun PLGA microfibers to deliver designer RNAi plasmid, complexed with a gene carrier polyethylenimine, to treat brain tumor by suppressing the expression of Matrix metalloproteinase-2 in tumor cells.[83] Anticancer drug paclitaxel and the RNAi plasmid were dual encapsulated in disc shaped implants composed of electrospun PLGA microfibers. The microfiber implant was able to release the drug and the gene in a sustainable manner. The gene/drug delivery was observed to be capable of greater tumor regression compared to the single delivery of a drug by a microfiber or commercial drug treatment currently available. The microfibers that constitute the disc shaped implant had diameters of 835 ± 92 nm.

Pre-exposure prophylaxis of HIV is an important step in preventing the spread of the HIV virus. Implementing such methods in precoital vaginal settings have unique challenges. Rapidly releasing a large volume of the drug without discomfort is difficult to accomplish with conventional drug delivery systems. Ball and Woodrow fabricated PVP and PEO microfibers loaded with maraviroc shown in Figure 7(d). Maraviroc is the prophylactic drug, while polysorbate 20 is the wetting agent which aids quick release of the drug.[84] The fibers ranged in diameter from 0.4 to 2 μm. The drug loading was up to 28 wt % and conditions of high moisture were facilitated to result in rapid release of the whole 28 wt % of the drug under 6 min under sink conditions. During the electrospinning process, the drug retained the original potency and had no side effects. This could form the basis of a novel prophylactic measure to curb the spreading of HIV due to the efficiency of the drug release mechanism.

3.2. Drug Delivery in Conjunction with Liposomes and Electrospun Micro- and Nanofibers.

Liposomes are spherical subcellular vesicles with at least a single lipid bilayer, and they have been extensively used for experimental and clinical studies in drug delivery.[85] The ability to load the vesicle with various molecules ranging from chlorine in wool chlorination[86,87] to chemotherapeutic nanomedicines to treat cancer, e.g. Camptothecin and platinum(II) drugs,[88] has made liposomes an ideal nanocarrier, particularly in drug delivery.

The reasons for the popularity of liposomes, for drug delivery, include the longevity of liposomes in the bloodstream, the ability to penetrate cells in the delivery of substances, and the stimuli-sensitive nature of liposomes. In research carried out by Mickova et al., horse radish peroxidase was used as the model encapsulate, and its enzymatic activity was preserved. This lead to the conclusion that the mesenchymal stem cell
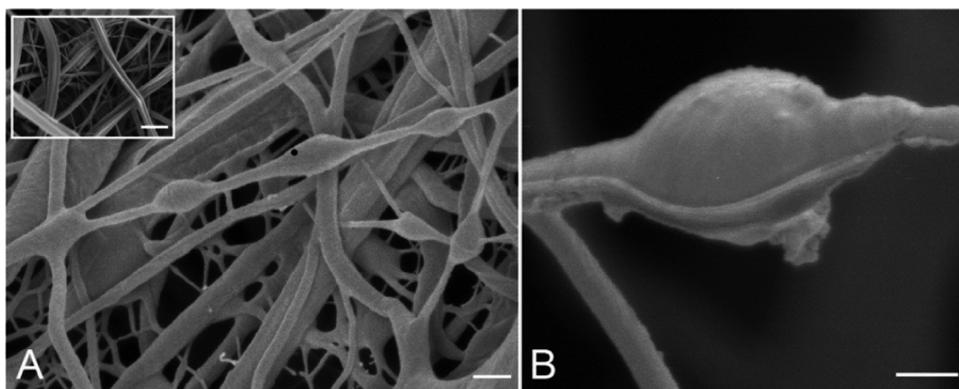
Figure 8. (a) FESEM image of coaxially electrospun PVA-core/PCL-shell nanofibers with liposomes encapsulated along the length of the fiber. (b) The bulge caused along the length of the nanofiber due to the liposome is clearly seen.[89]
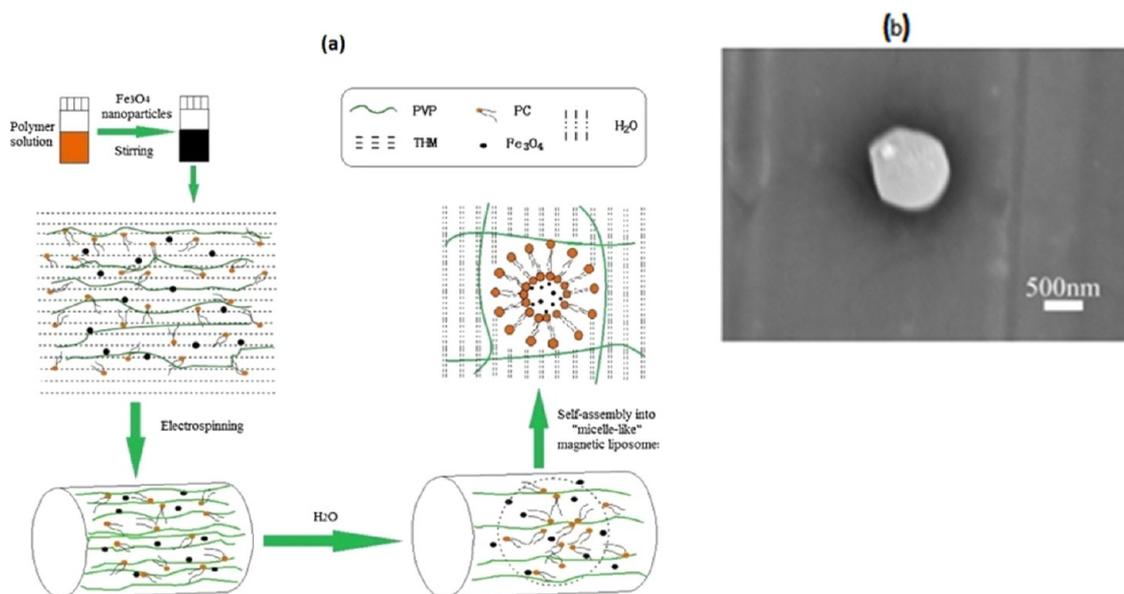

Figure 9. (a) Schematic of magnetic liposome self-assembly. Fe_3O_4 nanoparticles are stirred into the polymer solution, and then subjected to an electrospinning fabrication process. Once hydrated, liposomes form through self-assembly. (b) SEM micrograph of a magnetic liposome fabricated from the fibers by a self-assembly process, which results in stimuli-responsiveness in addition to drug delivery capacity.[90]

proliferation was enhanced by the delivery of recombinant growth factors provided by this drug delivery system.[89] In addition, there is potential for clinical applications based on the use of stimuli-responsive liposomes in drug delivery.[90] Liposomes, which are adherent to microfibers, are capable of encapsulating a range of important biomaterials ranging from drugs to DNA. Here, we have a closer look at the various fabrication methods in which liposomes have been incorporated to fibers.

Liposomes, blended with poly(vinyl alcohol)-core/poly-ε-caprolactone-shell nanofibers, were fabricated by coaxial electrospinning as well as controls with no embedded liposomes.[89] According to stereological measurements, the controls had nanofiber populations with peak diameters of 50 and 150 nm, while the liposome embedded fibers had bulges along the length with diameters 233.4 ± 36.9 nm with embedded liposomes at places. The appearance of such liposome embedded fibers is shown in Figure 8.

Incorporation of magnetic nanoparticles is a common way of introducing stimuli-responsive properties to drug delivery systems.[91,92] This is applicable to liposomes as well. For

example, fibers were electrospun from a core solution containing polyvinylpyrrolidone K90, phosphatidyl choline, and Fe_3O_4 nanoparticles, and then subsequently added to water.[90] It was observed that the fibers have the Fe_3O_4 particles uniformly distributed, which is illustrated in Figure 9(a). The fibers were observed to spontaneously undergo self-assembly to form liposomes. Additionally, the size was seen to vary with the Fe_3O_4 concentration. The retention of sensitivity to magnetic stimuli was observed to be retained throughout the electrospinning and self-assembly processes. An actual view of the liposomes obtained is shown in Figure 9(b). Similar but non-stimuli-responsive liposomes were fabricated through molecular self-assembly by adding electrospun amphiphilic nanofibers composed of hydrophilic polymer polyvinylpyrrolidone K60 (PVP) and soybean lecithin.[93] The liposomes were phosphatidyl choline (PC), and the diameter was varied by changing the PC content of the fibers.

Rampichova et al. utilized the process of microfiber fabrication by electrospinning to produce poly(2-hydroxyethyl methacrylate) (PHEMA) fibers to be used as a tissue engineering scaffold for cartilage. The fibers fabricated had
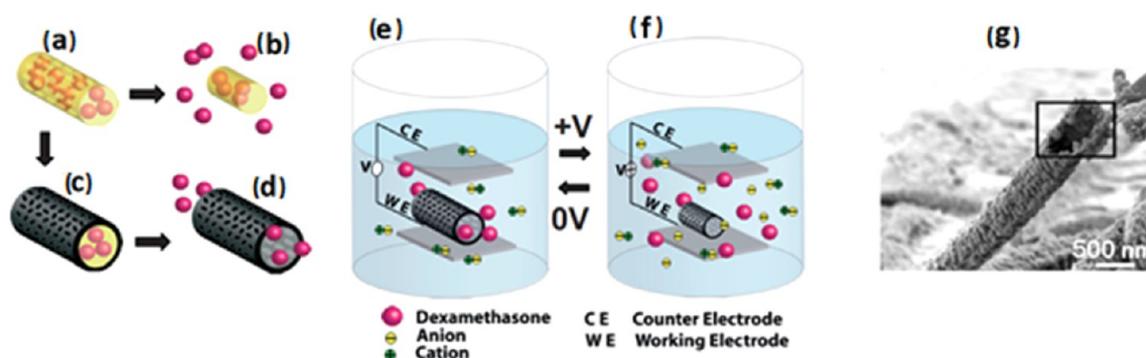
Figure 10. Schematic diagram of controlled release of dexamethasone. (a) Electrospun PLGA fiber loaded with dexamethasone. (b) Degradation of PLGA fibers by hydrolysis, which results in releasing the drug. (c) Electrochemical deposition of PEDOT around the PLGA fiber. (d) This results in the sustained release of the drug over time. (e) PEDOT nanotubes in a neutral electrical condition. (f) Applying a nonzero voltage allows exertion of control over the rate of dexamethasone release due to contraction or expansion of the PEDOT. (g) A PEDOT nanotube which was formed around a PLGA fiber. The PLGA solution of fiber was subsequently dissolved, resulting in this appearance.[96]

diameters in the submicron range.[94] In addition, a relatively straightforward drug delivery system was created in which fetal bovine serum loaded liposomes were anchored to the fabricated fibers. This anchoring occurs as a result of the adhesion of liposomes to PHEMA. An enhanced proliferation of chondrocytes, in the vicinity of such liposomes attached to the fibers, was found. This observation showed the development of controlled drug release mechanisms in conjunction with microfibers in tissue engineering applications.

3.3. Miscellaneous Innovations in Electrospun Fiber Based Drug Delivery.
Programmable transdermal drug delivery is one such exploratory application of micro- and nanofibers in drug delivery systems. Tran et al. incorporated two types of ibuprofen (an anti-inflammatory drug) into the microfibers using an electrospinning approach.[95] One type of microfibers were fabricated from polycaprolactone (PCL), while the other type was composed of poly(N-isopropylacrylamide-co-methacrylic acid) (pNIPAM-co-MAA). The average diameter of PCL fibers was 1237 nm, whereas that of pNIPAM-co-MAA fibers was 1608 nm. The drug release characteristics under different pH and temperature conditions, from both types of fibers, were investigated. It was revealed that the drug release rate from PCL fibers is largely unresponsive to both pH and temperature changes whereas pNIPAM-co-MAA drug release rates were highly sensitive to changes in the above-mentioned conditions. The drug release profile from the latter was linear and controllable at temperatures higher than the lower critical temperature of pNIPAM-co-MAA and at a pH higher than the pK_a of carboxylic acids. Furthermore, at room temperature, the drug release rate from pNIPAM-co-MAA was shown to be ten times higher than the release rate at a higher temperature. Therefore, the highly stimuli-responsive nature of ibuprofen loaded pNIPAM-co-MAA fibers can be utilized in future in vivo and potentially clinical applications.

A nanofiber based drug delivery system, capable of exercising precise control over drug delivery, by means of coating with nanotubes, has been investigated by Abidian et al.[96] Biodegradable drug loaded poly(L-lactide) (PLLA) and poly-(lactide-co-glycolide) PLGA nanofibers with diameters ranging from 40 to 500 nm were fabricated by electrospinning. The drug loaded into the fibers in the study was dexamethasone. The nanofibers were coated with poly(3,4-ethylenedioxythiophene) (PEDOT) nanotubes by means of electrodeposition. The process is detailed in Figure 10. This conducting nanopolymer coating significantly reduces the impedance and increases the charge capacity such that drug release from the fibers can be simulated to a desired extent, by means of electricity. Due to the controllability and precision of the mechanism, this can be a potential drug delivery system.

Zhou et al. devised a method to exert more control over drug release by fabricating water-soluble drug loaded ultrafine fibers by means of microsol-electrospinning.[97] Core–shell poly(L-lactic acid) microfibers loaded with chloroquine-hyaluronic acid nanoparticles were created by microsol electrospinning. Chloroquine phosphate, which is the therapeutic substance used in the study, is historically noted for being used in the treatment of falciparum malaria, vivax malaria,[98,99] infections caused by protozoa,[100] and certain other diseases. The fabricated fibers had diameters ranging from 1.33 ± 0.32 μm to 1.48 ± 0.44 μm and cores ranging from 0.29 to 0.83 μm depending on the composition of hyaluronic acid and the drug constituent ratio in the fibers. The morphology and physical features of such fibers were no different than those of fibers fabricated from conventional electrospinning. The loading efficiency of the microfibrous scaffolds was approximately 80%. The burst release was lower than that of conventionally prepared microfibers, and drug release occurred for 42 days. The rate of drug release could be adjusted by changing the concentrations of microsol and drug in the fibers.

Puhl et al. fabricated nonwoven PCL microfibers with diameters ranging from 1.6 to 10 μm by electrospinning, and lysozyme crystals with diameters in the range of 0.7–2.1 μm were encapsulated during the process.[101] Lysozyme, an enzyme in the crystalline form, is the most concentrated form of the protein, which makes for increased drug loading.[102] The enzyme itself is used for wound treatment, and electrospun chitosan mats, which are loaded with it, have been used for wound healing.[103] In the study, the fiber diameter and the lysozyme loading concentration were varied. Additionally, PCL/PEG and PCL/PLGA blends were used to enhance the hydrophilic nature, porosity, and degradability of the fibers, which in turn affects the drug release profile. It was observed that the bioactivity of the encapsulant was preserved during the electrospinning, and the burst release could be controlled by changing the aforementioned fiber and crystal properties. These factors did not affect the long-term drug release phase, but it was extended to over 11 weeks by PLGA inclusion during the electrospinning fabrication.
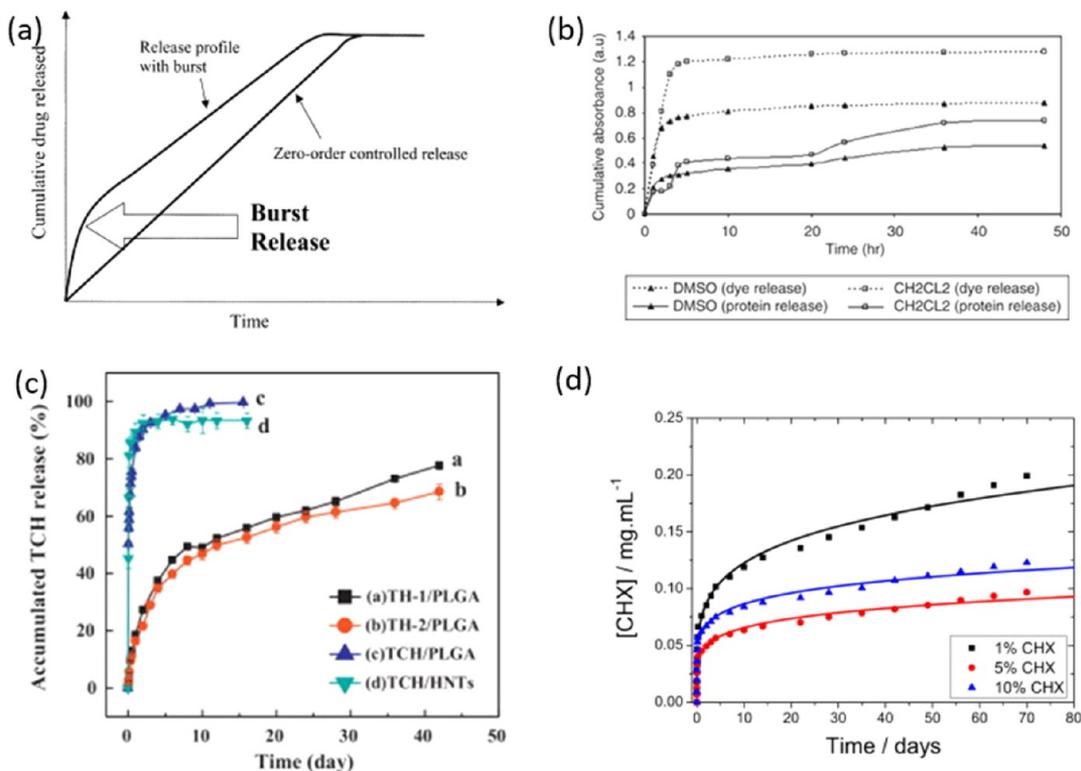
Figure 11. General overview of drug release profiles. (a) A schematic depicting the burst-effect in a zero order controlled drug delivery.[16] (b) The release profiles of protein and dye in DMSO (dimethyl sulfoxide) and dichloromethane from microfluidically fabricated fibers.[108] (c) The release profiles of tetracycline hydrochloride (TCH) from electrospun TH-1/PLGA, TH-2/PLGA, tetracycline hydrochloride loaded/poly(lactic-co-glycolic acid) composite (TCH/PLGA) nanofibers, and tetracycline hydrochloride loaded halloysite nanotubes (TCH/HNT) fibers.[109] (d) Release profiles of chlorhexidine (CHX) in poly(hydroxybutyrate) (PHB) and poly(hydroxybutyrate)/poly(ethylene oxide) (PHB/PEO) electrospun fibers.[10]

Llorens et al. obtained a method in which both antimicrobial and anticancer drugs were released from the same scaffold composed of microfibers fabricated using electrospinning.[104] In this study, uniaxial microfibers were fabricated by varying core−shell compositions and distributions. This was accomplished by subjecting ploy(ethylene glycol) (PEG) and poly(butylene succinate) (PBS) in a dichloromethane solution to coaxial electrospinning. The diameters of the core/shell fibers ranged from 4.40 ± 0.92 μm to 4.83 ± 1.27 μm, and for the uniaxial blended fibers were in the range of 0.43 ± 0.10 μm to 0.76 ± 0.18 μm. The core−shell microfibers were prepared such that the hydophobic drugs triclosan and curcumin were loaded into PEG and PBS, respectively. The triclosan incorporated into PEG lead to the rapid release often needed to combat microbial infections. Moreover, a slower sustained release required for anticancer therapy was displayed by curcumin loaded in PBS.[104] The drug loaded fibers were observed to be biocompatible upon investigation, and the release profiles of drugs in different media were compared. It was observed that the lowest release rate was found in PEG-rich uniaxial fibers in a buffer saline medium, whereas the highest release was obtained in coaxial microfibers in a buffer saline/ethanol mixture.

Fibers have also been electrospun from biological molecules. A prime example is the fabrication of hemoglobin and myoglobin mats by means of an electrospinning approach.[105] The fibers produced in this manner were ribbon-like. The dimensions varied with the concentration of hemoglobin and myoglobin in the electrospun solution. For hemoglobin concentrations from 150 to 225 mg/L, the average width and thickness of fiber mats changed from 2.68 ± 0.83 μm to $3.55 \pm$ 1.49 μm and from 0.49 ± 0.08 μm to 0.99 ± 0.41 μm, respectively. It was found that there is a correlation between the porosity of the fibers and the hemoglobin concentration. These fibrous structures could function as vehicles for drug delivery.

3.4. Controlled Drug Release with Electrospun Micro- and Nanofibers. Drug release profiles of micro- and nanofiber based drug delivery systems are an important factor. For example, acute microbial infection control requires the release of a large dosage of drug in a specific location over a short period of time. However, treatment of a chronic infection or containing the spread of a tumor requires a longer sustained release of the drug in controlled quantities.[106] The typical release profile of a drug delivery system consists of a rapid initial burst release followed by a longer period of controlled release.[16] This is shown in schematic form in Figure 11(a). The drug has to be administered less frequently to the patient because of the sustained release of the drug.[107] This sustained release resembles the flat portion of the separate plots depicted in Figure 11(b).[108] The release rates and the time at which the release rate plateaus out depend on the drug molecule, the concentration of the drug molecule in the fiber, and the nature of the fiber itself.[69−72,74] Luu et al. incorporated DNA into a fibrous scaffold made by PLGA and PLA−PEG block copolymers. They showed that the DNA release can be controlled by changing the block copolymer content.[69] Another example, i.e. a study by Qi et al. in which drug-fiber combinations drastically affect the burst and sustained release profiles for drug molecules, is shown in Figure 11(c).[109] The effect of drug concentration on the release profile is clearly observed in Figure 11(d).[10] These can be attained on a case by

case basis just by adjusting the varying burst release properties of the encapsulated drug or the sustained release.

When conventional methods of drug loading are followed with electrospun fibers, the burst release effect, observed at the outset, hampers the effectiveness of the blended or mixed drug. This is a major disadvantage in drug delivery system applications. Qi et al. addressed this issue by fabricating tetracycline hydrochloride (TCH) loaded halloysite nanotubes (HNTs)/poly(lactic-co-glycolic acid) composite nanofibers (TCH/HNTs/PLGA) with improved tensile strength, sustained 3D form, and cytocompatibility.[109] TCH, the pharmaceutical substance applied in the study, is an antibiotic which is extensively used to treat periodontal infections[110,111] and periodontal applications in veterinary medical applications.[112] Additionally, the composite fibers had the ability to overcome the initial burst release effect and release the antibiotic drug in a sustained manner for 42 days. Hence, the intended TCH induced therapeutic effect is sustained and lasts longer. The fabrication process involved TCH encapsulation within HNTs, and the composite fibers were electrospun from the solution with PLGA. The diameter of fabricated drug loaded composite fibers was 519 ± 133 nm.

Li et al. took a similar comparative approach to study the effects of binary fibers which were loaded with dexamethasone in anti-inflammatory applications.[113] Dexamethasone is a synthetic glucocorticoid, which is used primarily as an anti-inflammatory drug in a clinical context;[114] however, it may also be used for unconventional applications such as treatment of bacterial meningitis[115] and multiple myeloma.[116] Immiscible polymer blends of polycaprolactone (PCL) and poly(ethylene oxide) (PEO) were prepared with different compositions of the two constituents in each case. The general physical characteristics of the fibers were not changed in the direct loading of the drug during the electrospinning process. Depending on the relative composition of each component, the physical structure of the fibers varied from straight, straight with pores, to porous lamellar. The diameter of the fibers ranged from 0.92 ± 0.61 μm to 4.782 ± 0.37 μm. The nature of dexamethasone release was a function of the wettability of the fiber, with highly hydrophilic compositions leading to minimize the undesired burst release. Regardless of the morphology and other chemical properties, all fibers were biocompatible. The dexamethasone was effective in reducing inflammation caused by lipopolysaccharides.[113]

Inclusion of other nanostructures in microfibers generated by electrospinning could assist in a desirable drug release profile. In a study, drug-loaded halloysite clay nanotubes, with 50 nm diameter and length of 600 nm, were embedded into electrospun PCL/gelatin microfibers with mean diameter of 400 nm.[117] Prepared halloysite loaded microfibers were formed into a membrane with tensile strength doubling in the direction of the rotation of the collector. The embedding of drug loaded halloysite nanotubes into the fibers resulted in a drug release period of over 20 days compared to the control, in which the drug was directly loaded to the PCL/gelatin fiber, which lasted for a mere 96 h.[109] This microfiber-halloysite membranous structure had good biocompatibility, and eukaryotic cells were able to grow along the membrane. Furthermore, the drug acted to prevent the colonization of anaerobic Fusobacteria.

The same principle of including nanostructures in the micro- and nanofiber structures has been explored by Valarezo et al. by including layered double hydroxide (LDH) nanoparticles within electrospun PCL microfibers.[118] The drug Amoxicillin was interspersed within the nanostructures. The interspersion of the drug in LDH was done by a coprecipitation process. These PCL fibers were organized into nonwoven mats with individual fibers of an average diameter of 0.8 μm. The fibers were randomly oriented in these structures, and the drug loading along with the nanoparticles appeared to slightly increase the average cross-sectional area of the fibers. The initial burst release, followed by sustained release of the drug, was observed in this case as well. However, the intercalation of the drug within the LDH allowed for a slower sustained release. There is potential for successful use of this method for wound dressings, oral care, and dermatological treatment applications. Rubert et al. fabricated coaxial electrospun fibers with the same constituents in which dexamethasone was encapsulated.[82] The fibers were hollow fibers of the core–shell type with a highly porous morphology conducive to drug release. The diameter of the fibers was 8.255 ± 0.838 μm and 8.7 ± 0.813 μm before and after dexamethasone encapsulation, respectively. The release of the drug occurs in two stages; the burst release occurs in the first 0.5–3 h, and a late more stable release occurs over more than 12 days. This dual stage drug release property makes this drug loaded electrospun microfiber structure ideal for implantation and acute inflammation as well as for chronic inflammation control. The drug loaded fibers were successful in reducing the proliferation of lipopolysaccharide (LPS) stimulated macrophages and at expressing inflammation related genes.

Paclitaxel is an antitumor drug that acts to inhibit tumor cell growth by enhancing microtubule assembly resulting in blocking cell replication.[119] This drug has been widely used in clinical anticancer applications. Huang et al. successfully fabricated paclitaxel loaded poly(L-lactic acid-co-ε-caprolactone) (P(LLA-CL)) microfibers utilizing coaxial electrospinning.[120] The diameters of the fibers were 233 ± 68 nm for fibers with 4% P(LLA-CL) by weight and 1459 ± 150 nm for 10% P(LLA-CL). The solvent used in electrospinning was 2,2,2-trifluoro-ethane (TFE). As in previous cases, there was burst release initially for the first 24 h, and then sustained release for the next 60 days. The drug release involved polymer degradation and diffusion; however, this rate depended heavily on the concentration of initial drug loading. The accumulation release of the drug and the release rate are inversely related to the length of the hydrophobic polymeric chain and drug loaded concentration. The cytotoxic nature of the drug loaded fibers successfully inhibited HeLa cell growth, indicating the potential success of the method for anticancer drugs and other therapeutic substances with a hydrophobic nature.

Sabitha and Rajiv applied a different approach to include drugs into electrospun fibers by facilitating imbibition of tigecycline in PCL urethane urea microfibers.[121] This was performed by immersing the fibers in a tigecycline solution. The diameter of the fibers was 1.5–2 μm after drug imbibition has taken place. The imbibition of the antibiotic improved the thermal stability of the fiber. In addition, typical initial burst release followed by sustained release over a prolonged period of the drug was observed. The antibiotic activity was retained after the fabrication process. This method could potentially be utilized to create a scaffold to manage soft tissue infections and as a bandage to prevent such infections.

Although a survey of the literature relevant to micro- and nanofiber fabrication reveals the widespread use of certain materials for micro- and nanofiber fabrication, such as alginate and gelatin, other materials could be used, such as animal

Table 2. Details of Fibers Fabricated by Electrospinning for Drug Delivery Systems

Author	Material	Drug	Function	Diameter
Rampichova et al.[94]	PHEMA	BSA	Chondrocyte seeding and proliferation	2.1 ± 0.6 μm to 3.6 ± 1.3 μm
Bai et al.[77]	CS/PCL	tree oil, calcium ion	Wound healing	2.51 ± 0.69 μm
Qi et al.[109]	TCH/HNTs/PLGA	TCH	Antibacterial action	519 ± 133 nm
Li et al.[113]	PCL and PEO	Dexamethasone	Anti-inflammatory action	0.92 ± 0.61 μm to 4.782 ± 0.37 μm
Rubert et al.[82]	PCL and PEO	Dexamethasone	Anti-inflammatory action	8.255 ± 0.838 μm and 8.7 ± 0.813 μm
Valarezo et al.[118]	PCL	Amoxicillin	Wound dressings, oral care and dermatological treatment applications	0.8 μm
Huang et al.[120]	P(LLA-CL)	Paclitaxel	Anticancer therapeutic	233 ± 68 nm 1459 ± 150 nm
Sabitha and Rajiv[121]	PCL urethane urea	Tigecycline	Soft tissue infections and as a bandage	1.5−2 μm
Stephansen et al.[122]	Cod sarcoplasmic protein	Dipeptide Ala-Trp	Bioactive peptides for therapeutic purposes	100−1000 nm
Bottino et al.[123]	polydioxanone	Metronidazole, ciproflaxin	Inhibiting peridontopathogenic activity	765 ± 288 nm to 1158 ± 402 nm
Albuquerque et al.[124]	polydioxanone	Metronidazole, ciprofloxacin, Minocycline	Inhibiting actinomyces naeslundii activity	689 ± 312 nm to 718 ± 125 nm
Reise et al.[125]	polylactide	metronidazole	Peridontal disease treatment	0.64 to 1.2 μm
Rho et al.[126]	type I collagen		Early stage wound healing	100−1200 nm
Xu et al.[81]	EC/Eudragit S100	Budesonide	Drug dependent	74 nm-core 190 nm shell
Llorens et al.[104]	PEG and PBS	Triclosan Curcumin	Treatment of microbial infection and cancer	core/shell- 4.40 ± 0.92 μm to 4.83 ± 1.27 μm uniaxial blended fibers-0.43 ± 0.10- 0.76 ± 0.18 μm
Tran et al.[95]	PCL/pNIPAM-co-MAA	Ibuprofen	Anti-inflammatory drug action	pNIPAM-co-MAA fibers were 1608 nm, PCL was 1237 nm
Abidian et al.[96]	PLLA/PGLA, coated with PEDOT nanotubes	Dexamethasone	Antibiotic/antifungal action	40−500 nm
Mickova et al.[89]	PVA/PCL	Horseradish peroxidase/ growth factor	Mesenchymal stem cell proliferation	50 and 150 nm, peak diameters of 50 and 150 nm
Zhou et al.[97]	Core−shell PLLA microfibers	Chloroquine	Treatment of Malaria	core:1.33 ± 0.32 μm to 1.48 ± 0.44 μm shell: 0.29−0.83 μm
Puhl et al.[101]	PCL	Lysozyme	Wound dressing	1.6−10 μm
Sridhar et al.[78]	PCL/Gelatin	Riboflavin	Therapeutic action	1.7−2.2 μm
Rubert et al.[82]	PEO/PCL	Fibroblast growth factor	Cartilage`regeneration	7.49 ± 0.835 μm to 7.489 ± 0.445 μm
Ball and Woodrow[84]	PEO/PVP	Maraviroc	HIV prophylaxis	400−2000 nm
Xue et al.[117]	PCL/gelatin	Metronidazole	Antimicrobial action	400 nm
Lei et al.[83]	PLGA	RNAi plasmid	Brain tumor therapy (Matrix metalloproteinase-2)	835 ± 92 nm
Barnes et al.[105]	Hemoglobin and Myoglobin	Could Potentially be used	Could Potentially be used	Width and thickness: 2.68 ± 0.83 to 3.55 ± 1.49 μm and from 0.49 ± 0.08 to 0.99 ± 0.41 μm

proteins. For example, micro- and nanofibers from cod (*Gadus morhua*) sarcoplasmic proteins were electrospun by Stephansen et al. to investigate the bioactivity, the ability to encapsulate drugs, and the nature of drug release from drug incorporated fibers.[122] The fiber diameter was dependent on the cod sarcoplasmic protein concentration of the electrospun solution, with fiber diameters ranging from 100 nm for lower concentrations to 1000 nm and higher for higher concentrations. The water insoluble fibers were hydrolyzed by proteinases to result in small peptides which were the immediate product that successfully inhibited diabetes related enzyme DPP-IV, demonstrating its bioactive property. Dipeptide Ala-Trp encapsulated in the fibers was used to study the drug release profile from the fiber in both gastric and intestinal buffer. The drug release profile was different in this case, where the burst release phase took place within 1 min, resulting in release of 40% of the encapsulated substance, the next 30% within 30 min (gastric buffer), and 15 min (intestinal buffer) for gastric and intestinal buffer, respectively. The last

30% is assumed to be released in a sustained long-term manner, as it was not released within the duration of the experiment. The encapsulation of Rhodamine B was done to study the manner in which encapsulated compounds are distributed. This demonstrated that the distribution is largely uniform, except for certain regions, possibly due to the high density of the protein fiber network. The study demonstrates the potential use of the cod sarcoplasmic fibers for encapsulating and carrying bioactive peptides for therapeutic purposes.

The clinical applications of matrices composed of electrospun nanofibers are numerous. In this regard, biodegradable polydioxanone (PDS II) periodontal drug delivery systems, incorporated with either metronidazole (MET) or ciprofloxacin (CIP), have been electrospun. They were used to investigate the effects of antibiotics on oral commensal bacteria as well as pathogenic bacterial species.[123] The fibers were electrospun from PDS solutions containing 5 wt % MET, 25 wt % MET, 5 wt % CIP, and 25 wt % CIP. In this study, pure PDS fibers were fabricated as a control. It was noticed that while the highest
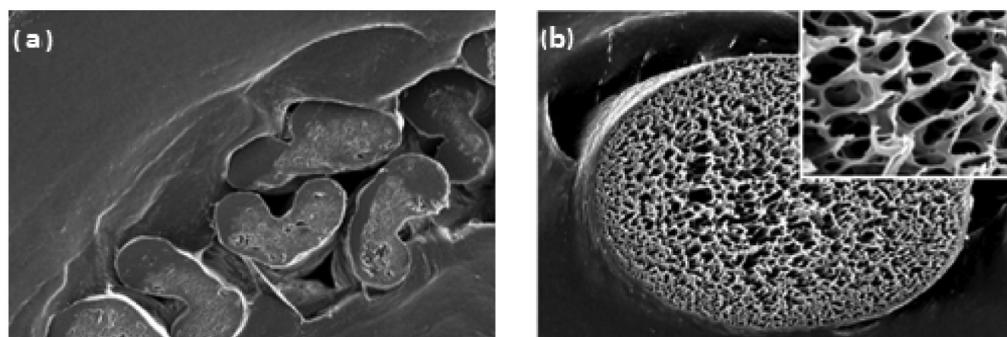
Figure 12. (a) Scanning electron micrographs under 350-time magnification BSA loaded PLGA microfibers fabricated by wet spinning.[133] (b) Surface and cross-sectional features of microfibers fabricated by wet spinning. Magnification value for the image is 1300-times.[134]

fiber diameters were observed in pure PDS fibers at 1,158 ± 402 nm, the lowest diameters were observed in 25 wt % CIP incorporated fibers. Furthermore, fibers with higher weight percentage of incorporated therapeutic molecules released drugs for longer than others. As desired, CIP fiber matrices significantly inhibited periodontopathogens without inhibiting the activity of commensal oral bacteria. Thus, it was recommended to do *in vivo* tests using animal models in order to test the viability of this method for clinical applications.

Additional research has been done on utilizing electrospun fibers for oral drug delivery applications.[124] A triple antibiotic paste-mimic scaffold was fabricated by adding metronidazole, ciprofloxacin, and minocycline to a polydioxanone (PDS) solution and then subjecting it to electrospun fibers. The diameter of the pure PDS scaffold was 689 ± 312 nm, whereas that of the TAP mimic was 718 ± 125 nm. The purpose of the study was to study the effectiveness of the TAP-mimic scaffold for drug delivery to Actinomyces naeslundii, often seen in traumatized permanent teeth diagnosed with necrotic pulps. Toward this end, a rapid burst release was seen in the first 24 h of application, whereas a slow sustained release was observed for the following 4 weeks of both drugs, save for minocycline. Compared to the negative control, which consisted of a 7-day old biofilm infected dentine and pure PDS scaffolds, the TAP-mimic scaffold was successful in reducing viable bacterial populations. The sustained drug release and the cytocompatibility of metronidazole(MNA)- loaded electrospun fiber mats made them significant candidates for clinical applications, particularly in the treatment of periodontal diseases. In research conducted by Reise et al., polylactide (PLA) fibers integrated with 0.1–40% (w/w) MNA were electrospun, and the release profiles of MNA from these fibers were investigated.[125] The diameters of the fibers fabricated ranged from 0.64 to 1.2 μm. MNA yielded fibers with the smallest diameter and the highest surface area to volume ratio, resulting in the highest initial release rate. This rate decreased over time until the third day and then followed a linear trend beyond that period. Furthermore, 32−48% of the drug was released in the first week and release of MNA lasted until the end of 4 weeks. It was observed that mats with 48% MNA resulted in effective action against F. nucleatum and P. gingivalis. Additionally, Rho et al. utilized electrospun collagen nanofibers for early stage wound healing and interaction with human keratinocytes.[126] Type I collagen in 1,1,1,3,3,3-hexafluoro-2-propanol was embedded into electrospun fibers, and the diameter ranged from 100 to 1200 nm. These nanofibers form a matrix that was cross-linked by glutaraldehyde vapor with a saturated aqueous solution. The

cross-linked matrix was then treated with 0.1 M glycine. The tensile strength and high cytocompatibility make these structures ideal for tissue engineering scaffolds. Furthermore, the interactions of keratinocytes and the nanofibers that constitute the matrix allow early stage wound healing.

The material composition of the electrospun fiber, drug used, and target organ or tissue and the diameter of each of the cases discussed in this section are detailed in Table 2.

4. WET SPINNING, ROTARY SPINNING, AND MOLDING APPROACHES IN DRUG DELIVERY

Wet spinning and rotary spinning have been used less often in fabricating fibers for drug delivery related research, but they are among the older methods used in fabricating fibers. In wet spinning, the biomaterial is dissolved in deionized water and stirred at high angular velocities to generate a viscous solution. The solution is then extruded into a coagulation bath and dried to obtain the fiber for the desired application.[127−130] Although this method is simple, there is potential for long-term exposure of cells to cytotoxic chemicals used during the fabrication process.[28] As a result, fibers used in drug delivery applications, with cell encapsulation involved, may not be fabricated by wet spinning. In rotary spinning, high-speed rotation of the microfiber constituent solution results in high centrifugal forces, and the ensuing solvent evaporation generates microfibers.[131] More novel methods such as mold based fiber fabrication for study of drug release characteristics have been explored recently. One such approach is fabricating hollow alginate fibers in a mold composed of a hollow fiber microfiltration membrane.[132]

Wet spinning produces microfibers that could form scaffolds with both tissue engineering and drug delivery applications. PLLA (poly(L-lactic acid)) and PLGA (poly(lactic-co-glycolic acid)) microfibers fabricated by wet spinning were loaded with insulin, lysozyme, and bovine serum albumin by means of a cryogenic emulsion technique (Figure 12(a)).[133] The molecular weights of insulin, lysozyme, and bovine serum albumin were 5.8 kDa, 14.3 kDa, and 66.0 kDa, respectively. It was apparent that the mechanical and drug release rates were highly dependent on the molecular weights of the encapsulated proteins for both the fiber types. Lighter hydrophilic proteins, such as insulin, remained encapsulated within the fibers longer (63 days) than the heavier molecules. This indicates that smaller therapeutic molecules are more suitable for applications such as drug delivery and tissue regeneration, both of which require long-term sustained delivery of drugs. Loading of BSA in PLGA resulted in a higher tensile strength compared to PLLA. It was concluded from the study that semicrystalline

fibers such as PLLA may be suitable for the encapsulation of lighter proteins, whereas amorphous porous microfibers composed of PLGA may be better candidates for heavier proteins such as BSA. The radius of fabricated fibers measured approximately 50 μm.

Lavin et al. demonstrated again that encapsulation of drugs in wetspun microfibers increases the mechanical properties of microfibrous scaffolds.[134] Hydrophobic anti-inflammatory drug dexamethasone was encapsulated in poly(L-lactic acid) (PLLA) wetspun fibers. In this research, the *in vitro* drug release kinetics was studied as well as the mechanical properties of the fibers. The cross section of PLLAfiber, shown in Figure 12(b), had an average diameter of 64.3 ± 7 μm. It was observed that the drug release profile was long-term and linear, releasing 28% of the encapsulated drug until the end of 56 days. Additionally, an increase in crystallinity of the fibers was observed due to encapsulation. The drug loaded fibers retained 97% of the tensile strength present at the outset compared to a control without the drug. It was concluded that loading therapeutic molecules less than 600 kDa might have a positive effect on the tensile strength of the microfibers.

In rotary spinning, the fiber morphology is primarily controlled by adjusting the rotary speed, polymeric solution composition, and inner diameter of the wall orifices.[135] Szabo et al. fabricated hydroxypropyl cellulose fibers by rotary spinning, which were subjected to a preformulation study. This is a stage in drug development where the morphological and chemical properties of a therapeutic substance are characterized.[136] This investigation is significant because microfiber based orodispersible tablets were prepared for *in vitro* dissolution enhancement. The drug used in the experiment was carvedilol. The orodispersible tablets were produced by compressing fibers that were milled, sieved, and mixed with excipients. The diameter of the resulting fibers ranges from 12.6 ± 4.8 μm to 13.5 ± 6.1 μm. The most interesting observation in the study was that the drug dissolution rate from the microfiber based formula was independent of the pH of the medium. Furthermore, drugs were found to be in an amorphous form in the fibers.

Hollow and solid microfibers can be generated by mold based techniques to possess mechanical and morphological properties desired to incorporate drug delivery systems. This method was investigated by Yoo et al.[132] They managed to use a hollow-fiber microfiltration membrane as the mold and to hold the calcium chloride solution which functions as the cross-linker. The diffusion of calcium ions occurs radially inward to the lumen, resulting in solid fiber formation. On the other hand, hollow fiber formation was affected by forcing out uncross-linked alginate from inside the lumen using calcium chloride solution. Figure 13 illustrates the steps by which seethe hollow fiber is fabricated. The diameters of the hollow fibers obtained in this manner ranged from 200 μm outer diameter (O.D.) and 50 μm inner diameter (I.D.) to 1.42 ± 0.06 mm O.D. and 0.65 ± 0.004 mm I.D. The outer and inner diameters were varied by changing the inner diameter of the mold and cross-linking time, respectively. Due to the ability to exert precise control over morphology and strength, and the fact that the fabrication process does not involve high pressures, voltages, or cytotoxic materials, this process is ideal for incorporating drug delivery systems into microfibers. Although the method is ideal for small scale fabrication of microfiber, mass production of microfibers is not possible with this
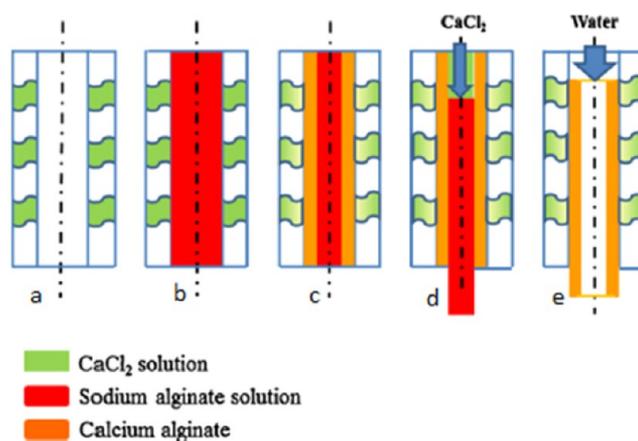

Figure 13. Mold based technique for fabricating hollow alginate fibers. (a) A vertical sectional view of the hollow fiber membrane with CaCl₂ solution filling the pores. (b) The lumen of the mold being filled with aqueous sodium alginate. (c) Calcium ions diffuse from the pores toward the central axis of the lumen resulting in the cross-linking of the alginate. (d) Un-cross-linked alginate solution is forced out of the lumen by the CaCl₂ solution. (e) The fiber is expelled from the mold with water.[132]

method. Furthermore, the length of the fibers produced is limited to the length of the mold.

The above-discussed applications of wet spun and rotary spun fibers are summarized in Table 3. The material composition and drug and target organ/tissues are indicated. The diameter of the cross section of the fiber is given if provided.

5. SELF-ASSEMBLING FIBERS: APPLICATIONS IN DRUG DELIVERY

The self-assembly of peptide amphiphile (PA) molecules is triggered by the ionic strength of the *in vivo* environment. This behavior allows the fabrication of nanostructures in the extracellular spaces found within numerous tissue structures that constitute the body. Due to the nature of the mechanism of self-assembly in fiber formation, self-assembled hydrogel fibers present unique qualities that make them ideal for drug delivery. Efficient delivery of drug carriers to intercellular compartments is difficult to perform using other fibers fabricated by other methods. Additionally, drugs incorporated with self-assembled fibers could be kept stable in intercellular compartments with properties intact. The advantage of using this method is that certain drug molecules that cannot be incorporated into fibers by covalent binding can be physically encapsulated within self-assembled hydrogel fibers.[137] Moreover, fibers with a higher loading capacity for drugs and efficiency can be fabricated by self-assembly.[138] This was demonstrated by Zhang et al. in fabricating paclitaxel loaded self-assembled microfibers composed of Tat Cell Penetrating Peptide Units.[139] The self-assembly of these molecules to fibers is schematically depicted in Figure 14. Also demonstrated was the possibility of transporting encapsulated drug particles into cells by means of an adsorptive-mediated endocytosis pathway. The efficacy of paclitaxel delivered in the fiber was found to be the same as that of free paclitaxel. Therefore, the intrinsic properties of the drug molecule loaded to the fibers were kept intact. The main disadvantages of self-assembled fibers include limitations, which are a consequence of the size and inability to

Table 3. Details of Fibers Fabricated by Wet Spinning and Rotary Spinning Methods for Drug Delivery Systems

Author	Material	Drug	Target	Diameter
Lavin et al.[133]	PLLA, PLGA	Insulin, Lysozyme, BSA	pancreas	N/A
Lavin et al.[134]	PLLA	Dexamethasone	Inflamed tissue	$64.3 \pm 7 \ \mu m$
Szabo et al.[135]	Hydroxypropyl cellulose	Semisynthetic alkaloid	N/A	$12.6 \pm 4.8 \ \mu m$ to $13.5 \pm 6.1 \ \mu m$
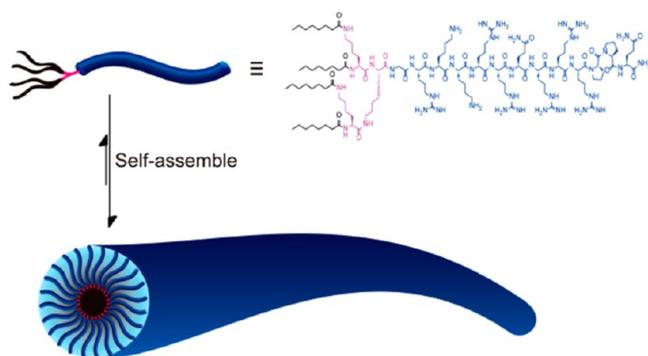
Figure 14. Schematic of self-assembly of Tat Cell Penetrating Peptide Units to form nanofibers where paclitaxel is encapsulated.[139]

incorporate certain molecules and structures in encapsulated form in self-assembled fibers.

The nature of self-assembly, to generate nanofibers, makes it an ideal technique to be used in other minimally invasive applications as well. PA molecules designed to self-assemble to nanofibers were investigated by Shah et al.[140] The nanofibers fabricated in this study were capable of cartilage regeneration through transforming growth factor β-1 (TGβ-1). This is accomplished by displaying a higher density of binding epitopes to the growth factor. The slow release of TGβ-1 from such fibers *in vitro* resulted in an increase in the survival rate and chondrogenic differentiation of human mesenchymal stem cells. The material is capable of articular cartilage generation regardless of the presence of the exogenous growth factor in a rabbit model. This means that the potential for the usage of this material for cartilage regeneration activities is significant. The application of self-assembling peptides to generate nanofibers capable of creating microenvironments within the myocardium was explored by Davis et al.[141] The microenvironments capable of promoting vascular smooth muscle cell recruitment were generated by injecting designer self-assembling peptide molecules. This enabled formation of functional vascular structures, suggesting potential for injectable tissue regeneration strategies in the future. In a separate study, Heparin-binding peptide amphiphiles were used to generate

nanofibers that interact with heparin.[142] A significant improvement in pancreatic islet engraftment was observed when vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2) were delivered from fabricated fibers. Hence, peptide amphiphile self-assembly based nanofibers could potentially be used for drug delivery applications. In addition, investigations carried out by Nagai et al. on self-assembling peptide nanofibers suggested that the release profiles of drugs, which are integrated to hydrogel scaffolds composed of self-assembled peptides, could be customized by controlling nanofiber-diffusant molecular interactions.[143] Single-molecule fluorescence correlation spectroscopy was used to study the release kinetics of functional proteins. These proteins span a wide range of molecular mass, hydrodynamic radii, and isoelectric points, and create a nanofiber hydrogel scaffold consisting of designer self-assembling peptides by Koutsopoulos et al.[144] The observations indicated that the protein functionality was unaffected by the encapsulation and release from the scaffold, demonstrating the suitability of such scaffolds for sustained delivery of drugs in a clinical context. Self-assembling peptide scaffolds, integrated with epidermal growth factor, were investigated as a method to accelerate wound healing by Schneider et al.[145] The scaffold was tested on a human skin equivalent model, and it was observed that the epidermal growth factor was only released when the scaffold was in contact with the tissue model. Furthermore, the scaffold demonstrated an accelerated rate of wound healing. The use of self-assembling peptide amphiphile nanofiber scaffolds for replacement of dental caries with dental stem cells demonstrates the versatility of the technique.[146] Instead of replacing decayed dental structures with inert materials, scaffolds of this nature could prove to be an effective biological substitute. Similarly, electrospun scaffolds of self-assembling peptides hybridized with poly(ethylene oxide) have been explored as a viable biomaterial for bone tissue engineering due to the biomimicry of self-assembled biological molecules[147]

Instances of self-assembled fibers with regard to specific applications are summarized in Table 4. The material composition and function are given.

Table 4. Details of Fibers Fabricated by Self-Assembly

Author	Material	Function
Jiang et al.[148]	laminin, isoleucine-lysine-valine-alanine-valine Peptide amphiphile (IKVAV PA)	Promoting neurite outgrowth and inhibit glial differentiation
Tysseling-Mattiace et al.[149]	IKVAV PA	regeneration of both sensory and motor neurons, reduction in cell mortality
Guo et al.[150]	RADA16-I peptide	Reknitting the injured spinal cord
Shah et al.[140]	TGFBPA	cartilage regeneration
Davis et al.[141]	RAD16-II peptide	Promote vascular cell recruitment in the myocardium.
Stendahl et al.[142]	Heparin-binding peptide amphiphiles	Improvement in pancreatic islet engraftment
Schneider et al.[145]	self-complementary peptides with 16 amino-acids (RADA16-I, Ac-RADARADARADARADA-CONH2)	Acceleration of wound healing
Galler et al.[146]	13-amino-acid peptide (GTAGLIGQERGDS)	Dental carrie replacement with dental stem cells
Brun et al.[147]	Several peptides with varying sequences.	Applications related to bone tissue engineering

6. CONCLUSION

Micro- and nanofibers are promising candidates for carriers in drug delivery systems. The surface area to volume ratio, morphology, material properties, and drug release profile can be easily tuned. In this review paper, we showed that electrospinning, microfluidic, wet and dry spinning, and self-assembly approaches are commonly used for fabricating fibers applied for drug delivery research. All methods are relatively straightforward and feasible under laboratory settings. Among these methods, electrospinning was found to be the most prominent approach, and has been used extensively to fabricate micro- and nanofibers. This method has demonstrated great controllability in creating ultrafine fibers, but the limitations in size, shape, biocompatible solvent, and process may render it unsuitable for certain applications. The microfluidic platform is relatively new with promising potential to fabricate fibers in a variety of dimensions, cross-sectional shapes, and biocompatible materials without changing the environmental conditions. This makes it a desirable approach for cell incorporation in drug delivery systems. Wet and rotary spinning were seen to be less commonly used for generating fibers for drug delivery applications. Micro- and nanofibers fabricated by these methods have been incorporated with stimuli-responsive characteristics, such as responsiveness to magnetism and light. Such stimuli-responsive fibers along with the drug carrying capacity have numerous potential applications in drug delivery. Additionally, the incorporation of liposomes with micro- and nanofibers were shown to enhance the drug carrying capacity in drug delivery systems. The use of self-assembly methods for fiber fabrication has proved to be a novel and effective method to create structures in the intercellular matrix while encapsulating drugs.

For each of these fiber fabrication methods, the constituent molecules are biocompatible. Thus, they are viable carriers for drugs *in vivo*. For example, the incorporation of liposomes into electrospun fibers, utilization of the burst release for HIV prophylaxis, and stimuli-responsive fibers are all promising prospects for drug delivery applications. A wide range of molecules could be delivered by these fibers. Additionally, it is possible to exert precise control over drug release profiles from fibers. There is a significant potential for fiber based drug delivery systems in modern clinical medicine. The above-mentioned advantages offered by fiber based delivery systems outperform current conventional drug delivery systems. Methods such as orodispersible tablets and vaccines could be incorporated with fiber based drug delivery systems in order to improve the efficiency of drug delivery. However, the majority of developments detailed in this review involve *in vitro* investigations of the efficacy and efficiency of fibrous drug carriers. Before clinical trials, *in vivo* studies must be performed extensively to identify the best candidates for drug delivery systems incorporated with fibers. Once extensive *in vivo* studies are carried out, manufacturing processes should be developed to commercialize these drug delivery systems in clinical medicine.

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Notes

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