Chapter 7
Electrospun Fibers in Drug Delivery

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Abstract Electrospun fibers have been very widely explored in the context of drug delivery. The rapid drying nature of the electrospinning process tends to result in amorphous solid dispersions, and hence the use of a hydrophilic filament-forming polymer can give significant increases in dissolution rate, apparent solubility, and bioavailability. Electrospun formulations thus have great potential to overcome the solubility challenges faced by > 70% of emerging drug candidates. Beyond this, by careful choice of the polymer carrier and the nanoscale architecture of the fibers (monolithic, core/shell, Janus, etc.) it is possible to precisely control both the drug release rate and location, and in a number of cases much sought after zero-order (constant rate) release has been obtained with electrospun systems. Fibers from electrospinning have thus been widely explored for drug delivery via a range of routes, including oral, transdermal, ocular, and implantation. In this chapter, we will review the body of literature in the area, focusing on the various types of release modality that can be obtained and the most exciting recent findings in the field. We will further consider issues of translation from bench to bedside, covering the great progress made in the scale-up of the electrospinning process in recent years, the need for production under Good Manufacturing Practice conditions, and evaluating how close electrospun formulations are to becoming marketed products.

Keywords Drug delivery · Polymer carrier · Electrospun systems · Drug release modality

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7.1   Introduction

The ultimate goal of drug delivery systems is to deliver the drug locally, safely and in a controlled fashion in order to minimize side effects often associated with systemic administration of active pharmaceutical agents (APIs). To achieve the desired therapeutic effect, the correct API must be delivered to the required site of action, at the correct time, and in an appropriate amount. Inability to meet these criteria will render the medicine either ineffective or toxic to the patient. Although medicines can take a wide range of forms and be administered via numerous routes, for reasons of patient compliance and convenience the majority of APIs are given orally as solid dosage forms. This has a number of benefits: for instance, it is simple for a patient to take two tablets three times a day, and oral solid dosage forms can be administered by the patient themselves rather than requiring a healthcare professional (as is usually the case for injections).

There are also drawbacks to the use of oral solid dosage forms, however. In order to be active in the body, the API needs to be in solution. This requires a solid dosage form to *dissolve* into the fluids present in the gastrointestinal tract. In the process of dissolution, the large aggregates of molecules that make up a solid material are separated out, resulting in a solution in which each API molecule is surrounded by water molecules. Thus, API-API intermolecular interactions in the solid-state are replaced by API-water interactions. The dissolution rate and maximum concentration of the drug in solution (the *solubility*) are determined by the balance of these energies. Further, the majority of medicines given orally are intended to act systemically (throughout the body) rather than locally in the gastrointestinal tract. Thus, after it dissolves, the molecules from a solid dosage form need to pass through the lipid biomembranes which line the intestinal tract, so that they can reach the bloodstream. This process is termed *permeation.*

Some APIs have both high dissolution rates and solubilities and high permeability, but in most cases, there is a formulation challenge that needs to be overcome to improve at least one of these properties. The Biopharmaceutical Classification System (BCS) helps pharmaceutical scientists to classify APIs in terms of their properties: BCS class I drugs have high solubility and permeability; class II are poorly soluble but freely permeable; class III APIs are highly soluble but poorly permeable, and class IV materials are both poorly soluble and poorly permeable.

Beyond BCS considerations, pharmaceutical scientists need to consider carefully where in the body the drug will be released. For instance, many APIs cause irritation to the stomach lining, and thus it is desirable to avoid release there and instead target delivery to the latter stages of the gastrointestinal tract. The rate of release of a drug from a medicine also needs to be established, since this impacts both the therapeutic efficacy and the dosage frequency required. The stability of the API must additionally be established and understood. While small-molecule APIs such as paracetamol or ibuprofen are held together by covalent bonds and thus are generally stable in vivo, more complex biomolecules such as proteins rely heavily on weaker hydrogen and van der Waals interactions to sustain their 3D structure. A loss of 3D structure will

result in a loss of activity, and since the interactions holding the structure together are weak proteins degrade easily. Great care must thus be taken in formulating, to ensure that the API delivered is therapeutically active.

Electrospinning offers routes to improve solubility and dissolution rate by processing the API into an amorphous solid dispersion (ASD), where there is a molecular dispersion of drug in polymer and thus no API-API interactions to overcome during the process of dissolution. The addition of a permeation enhancer into the formulation can improve permeability. Further, the choice of the polymer used as the filament-forming carrier can allow the drug release location and rate to be tuned. The fact that electrospinning does not require heat to evaporate the solvent can aid in maintaining the stability of protein APIs, but the use of organic solvents can be problematic in this regard. These topics will be discussed in more detail below, with illustrative examples presented. We will first consider small molecule APIs and the types of release profiles that can be attained. Later in the chapter, we will also consider the use of electrospinning to process more complex biologic-based therapeutics and consider the next steps in moving electrospun medicines towards the market.

7.2 Fiber Architecture

A range of fiber architectures can be achieved by using spinnerets with different needle arrangements, as shown in Fig. 7.1. The simplest experiment is mono-axial
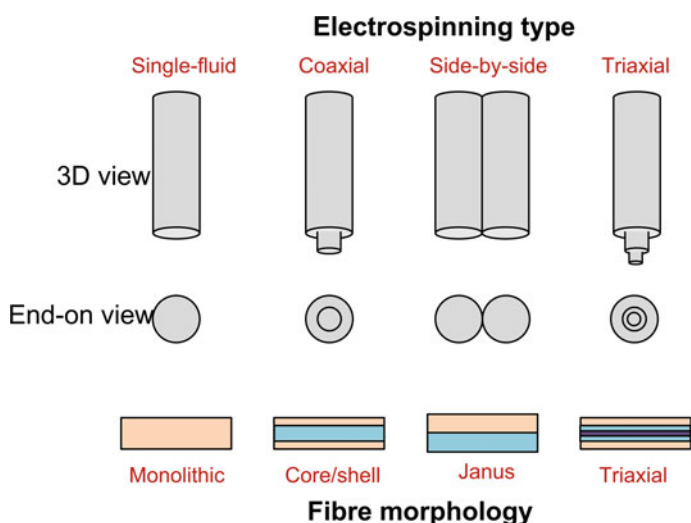
Fig. 7.1 Spinneret designs for different types of electrospinning, and the structures of the fibers produced. Reproduced from Williams G. R. et al. 2018. *Nanofibres* in Drug Delivery. London: UCL Press (https://doi.org/10.14324/111.9781787350182), under the terms of a CC BY 4.0 license

electrospinning, where a blunt-ended spinneret is used to generate monolithic fibers. These have a number of benefits, but their large surface area and the presence of drug at the fiber surface often results in an undesirable initial "burst" of release. To overcome this, co-axial spinning can be used to produce core/shell fiber architectures; if the drug is confined to the core then burst release can be reduced and/or release targeted to a particular part of the body. Tri-axial spinning allows the possibility of creating 3–layer fibers to provide further control over the drug release profile. Two-faced Janus fiber architectures can also be created using a side-by-side spinneret, resulting in two-compartment fibers where both sides can interact with their external environment.

7.3   Pharmaceutical Polymers

Several aspects need to be considered when choosing the polymer for the electrospinning solution. Probably the most important consideration is the intended application of the product. The polymer degradation half-life and by-products, biocompatibility, and solubility will heavily influence the potential applications of the product. For example, for fast-release applications, a polymer with a relatively rapid dissolution/degradation rate and high solubility in aqueous solvents (such as polyvinylpyrrolidone (PVP)) would be preferred [1]. In contrast, when designing a long-term surgical implant, a hydrophobic polymer with slow degradation rates would be more suitable. In some cases, polymers with special characteristics such as thermo- or pH-sensitivity are of interest, aiding targeted delivery to the action site [2].

One of the most commonly used pharmaceutical polymers in electrospinning is poly(lactic-co-glycolic) acid (PLGA) (Fig. 7.2a). PLGA is a synthetic copolymer formed of polylactic (PLA) and polyglycolic (PGA) acids. PLGA degrades by hydrolysis of its ester linkages via bulk erosion in aqueous environments. The rate of degradation can be controlled, for example by adjusting the molecular weight of the polymer or the molar ratio of the monomer components. As an example, PLGA copolymers with a higher content of lactic acid will degrade more slowly due to the presence of hydrophobic methyl groups [3].
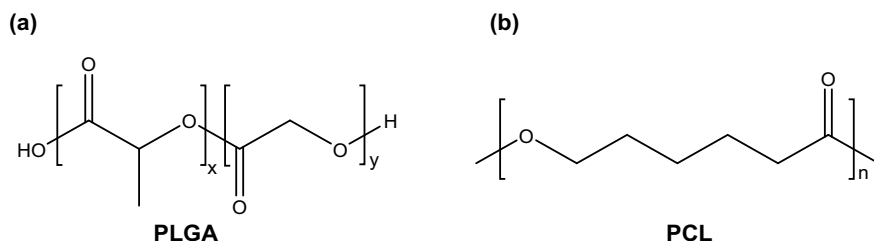

Fig. 7.2 Chemical structures of **a** PLGA and **b** PCL

Another medically important polymer is poly(ε-caprolactone) (PCL; Fig. 7.2b), which is an aliphatic polyester composed of hexanoate repeat units. It is a semi-crystalline polymer widely used in the manufacturing of surgical sutures, drug delivery systems and tissue engineering scaffolds, and biodegrades through hydrolysis over a time period ranging from several months to years, depending on the molecular weight [4, 5].

Biomaterials manufactured from PLGA and PCL follow a similar triphasic breakdown profile. In the hydration step, water penetrates into the amorphous region of the material, thus disrupting the van der Waals forces. Subsequently, the polymer chain starts to degrade either by end-chain or random-chain scission and the cleavage of covalent bonds. This leads to a decrease in the molecular weight [6]. The degradation process is then autocatalysed by carboxylic end groups and the particle structure is severely disrupted by the breakdown of backbone covalent bonds. The resulting metabolite monomers incorporate into the Krebs cycle and can be safely eliminated from the body [7, 8].

7.4 Small Molecule Drugs

There exist a range of drug release profiles which find utility in medicines development (Fig. 7.3). These range from very rapid release, aiming to deliver a drug cargo within a few minutes of administration, to formulations seeking to prolong release over days or weeks. Complex multi-stage profiles can also be desirable, for instance to provide an initial "loading" dose for rapid relief of pain followed by a maintenance dose to keep the concentration in the patient's bloodstream at a therapeutic level. Electrospun formulations have been explored for many of these modalities of small molecule API delivery, and we will discuss a series of examples below.

Fig. 7.3 Some common types of drug release profile. The plot depicts the percentage of drug loading freed from a formulation as a function of time
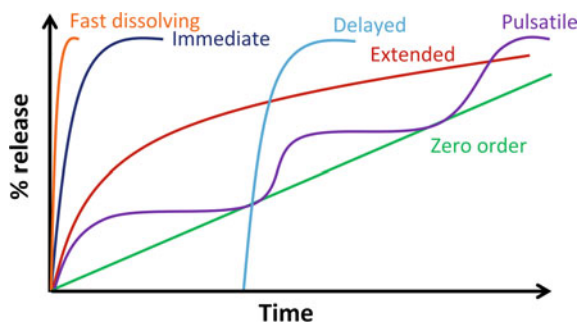
7.4.1 Fast Dissolving Drug Delivery Systems

Fast-dissolving drug delivery systems (FD-DDSs) offer a variety of advantages such as very rapid onset of action and enhanced bioavailability. This type of release is ideal for situations where instant drug dissolution is required to achieve rapid therapeutic effects. Electrospinning can be used to generate ASDs with very high surface area to volume ratios, and thus is ideal to achieve fast dissolution of otherwise poorly water-soluble drugs. Such electrospun FD-DDSs are commonly designed as solid films that undergo instant wetting by saliva to dissolve/disintegrate in the patient's mouth. These formulations are beneficial to administer drugs to children and patients with swallowing difficulties, as they can be used without consuming liquid or chewing [9].

Numerous electrospun FD-DDSs have been reported in the literature, often based on the hydrophilic and fast-dissolving PVP. For instance, fibers containing paracetamol and caffeine were generated by Illangakoon et al. The fiber mats disintegrated completely within a very short time (< 0.5 s) when added to simulated saliva solution and released the drug cargo within around 150 s in a dissolution test, giving notably faster dissolution compared to the pure drugs [10]. PVP fibers have also been used to enhance the dissolution rate of mebeverine hydrochloride [11], ketoprofen (KET) [12], indomethacin [13], ornidazole [14], borneol [15], emodin [16], sildenafil citrate [17], and loratadine [18]. Caution must be taken in designing the formulations, however: the drug loading in the system has been shown to be crucial in determining the release properties. In a very recent report, PVP was employed for the preparation of KET loaded fibers. ASDs were obtained, but while fibers with low KET loading (9% w/w) disintegrated quickly and hastened KET dissolution, fibers with 23% w/w drug did now show these benefits (Fig. 7.4) [12].

While PVP has attracted the most attention, other hydrophilic polymers can also be used to generate electrospun FD-DDSs. For instance, polyvinyl alcohol (PVA) fibers have been prepared loaded with caffeine and riboflavin [19]. Electrospun blends of polyethylene oxide are also reported to provide fast release of drugs such as lidocaine and diclofenac [20]. More recently, the natural polymers jelly fig polysaccharide and pullulan have been investigated for fast delivery of hydrophobic drugs such as ampicillin and dexamethasone [21].

7.4.2 Extended Release

Extended release systems (also termed sustained, controlled, prolonged, or slow-release) are designed to release their drug cargo over a prolonged period of time in the body, with the goal of maintaining a therapeutically potent dose over this period of time and reducing the required dosing frequency. For instance, electrospun (ES) mats capable of delivering analgesics or anti-inflammatory medications in a sustained manner could be very beneficial for patients suffering from long term
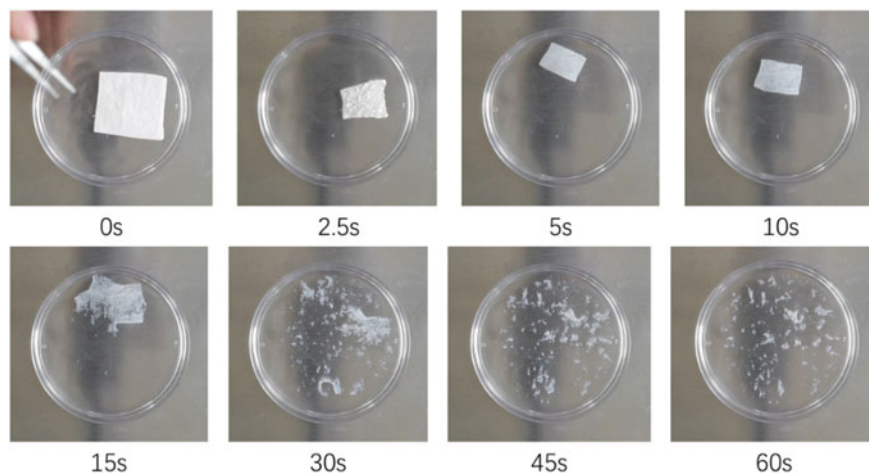
Fig. 7.4 Digital camera images of the disintegration of PVP fibers containing 9% w/w KET. Reprinted with permission from *Geng* et al. [12] Copyright 2020 Elsevier Ltd

diseases such as rheumatic arthritis. Thus, many publications report ES matrices for sustained release of analgesics over periods of hours (for oral delivery) or days (for wound care or cancer therapy), containing APIs such as diclofenac [22], naproxen [23], tramadol [24], ketoprofen [25], lidocaine [26], and steroidal drugs [27]. In addition to pain relief, ES fiber systems have been generated for sustained release of antibacterial agents (e.g. tetracyclines [28], gentamicin [29]), anti-viral drugs (e.g. acyclovir [30]), and anti-cancer APIs (e.g. niclosamide [31], hydroxycamptothecin [32], CPT-11 and SN-38 [33], oxaliplatin [34], 5-fluorouracil [35], paclitaxel [36], and doxorubicin [37, 38]). In the latter case, the formulations are often designed as implants to be placed for instance in a tumor resection site.

Suitable choice of polymer is key to develop an effective sustained-release ES formulation. Appropriate polymers are hydrophobic; they can be stable (in which case drug release occurs by diffusion out of the matrix) or degrade slowly into soluble monomers. Commonly explored biodegradable polymers include PLA [27], PGA, PLGA, and PCL [39, 40] while the non-degradable polyurethane [32], polycarbonate [32], and nylon-6 [41, 42] have also been investigated. Sustained release can additionally be achieved by using natural polymers like silk [43, 44], collagen [45, 46], gelatin [47, 48], alginate [49, 50], cellulose derivatives [23, 51], and chitosan [52, 53], either spinning them alone, or by blending with other components [54–59].

A widely observed phenomenon in fibers from mono-axial ES is an initial burst of API release due to the high surface area-to-volume ratio of the fibers and the presence of drug at or near the fiber surface. While this is not an issue with FD-DDSs (where release is intended to be rapid), it can be problematic when seeking to develop sustained release systems. Researchers worldwide have thus probed various strategies to overcome this effect. One strategy is to generate core/shell fibers, where drug loaded within the core has to diffuse through a drug-free polymer shell before

reaching the release media [60–63]. Designing composite ES fibers with drug-loaded nanoparticles can also be used to reduce the initial burst release. Silica nanoparticle (NP)-loaded PLGA fibers [64] and chitosan NPs in PCL fibers have both been explored to this end [65].

Core/shell systems can also be applied to deliver multiple APIs at different rates. Heydari et al. developed core/shell fibers composed of polyglycerol-sebacate as the shell and poly (hydroxybutyrate) elastomer as the core. Simvastatin, a drug known for accelerating diabetic wound healing by enhancing angiogenesis and lymphangiogenesis, was loaded into the fiber core, and the antibacterial drug ciprofloxacin included in the shell [66]. This resulted in a smart wound-healing system, since the fibers gave 60% ciprofloxacin release in 24 h, but simvastatin was released much more slowly [66].

7.4.3   Zero-Order Release

Therapeutic systems that can release an API at a constant rate are much sought after in order to minimize variations in plasma drug concentrations and help maintain the drug concentration within the therapeutic range [67]. Various strategies have been applied to achieve zero-order release using electrospun formulations. One of the earliest reports of this developed drug-loaded cellulose acetate (CA) nanofibers using a modified coaxial electrospinning process [61]. Core/shell fibers were produced with both compartments made of CA and the model drug KET confined to the core, and were able to provide zero-order release over 96 h [61]. Subsequent approaches using alternative core/shell fiber formulations have also been shown to yield zero-order release profiles [60, 61]. Three-layer fibers from triaxial spinning have additionally been investigated. By preparing a triaxial system with all three compartments made of ethyl cellulose (EC) and with an increasing w/w drug loading moving from the exterior to the core compartment, it was possible to achieve zero-order release of KET over 20 h (Fig. 7.5) [63].

7.4.4   Targeted Release

There exist a variety of different pH environments in the body, which can be used to target drug release. For instance, the stomach is acidic (*ca.* pH 1–2) whereas the small intestine is much closer to neutral. pH-responsive polymers can thus be used to target API release to the small intestine. Polymers such as Eudragit L-100 (EL100) or Eudragit L100-55 (EL100-55) have been exploited for such delayed-release delivery of many drugs. The Eudragits are methacrylate based copolymers; they contain myriad COOH groups which are unionized at low pH, rendering the polymer insoluble. As the pH increases the carboxylate groups ionize to COO^-, and the solubility of the polymer increases. Through careful control of the polymer
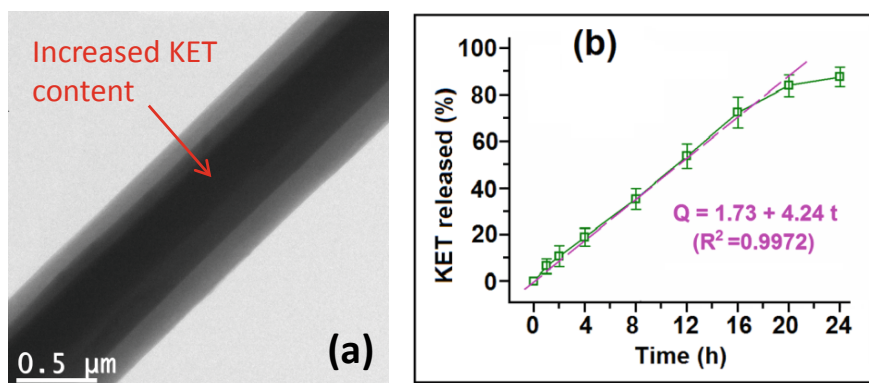
Fig. 7.5 Data on trilayer EC/KET fibers prepared by Yu et al. **a** Transmission electron micrograph showing the three-layer architecture of the fibers. **b** The KET release profile. Reprinted with permission from Yu et al. [63] Copyright 2015 American Chemical Society

chemical structure, systems can be developed with dissolve at certain distinct pHs: thus, EL100-55 is soluble at pH 5.5 or greater, while EL100 becomes soluble at pH 6.0. DDSs composed of Eudragit are insoluble in the stomach and release the drug only when it reaches the small intestine. Sustained release DDSs targeting delivery of mebeverine hydrochloride (MB-HCl) to the colon have been prepared by electrospinning EL100-55 [11]. Diclofenac sodium-loaded EL100 fibers have also been reported [68].

Beyond the Eudragit materials, a range of other polymers such as hydroxypropyl methyl cellulose phthalate and hydroxypropyl methylcellulose acetate succinate have been explored for targeted release, for instance of erythromycin [69] and theophylline [70]. Natural macromolecules can also be applied to give targeted release. Zein and shellac are both naturally occurring polymers with environment-responsive solubility. Shellac is insoluble under acid conditions but soluble in a neutral environment. Yang et al. observed that electrospun fibers with a shellac shell and diclofenac sodium/PVP core could resist acid erosion and thereby potentially deliver the API specifically to the colon [71].

Electrospun fibers have been extensively explored for applications in cancer therapy [72, 73]. Typically, the tumor microenvironment is at a slightly lower pH than the general physiological pH, and this difference can be used to target drug delivery. Electrospun fibers composed of PVA/PCL [74], and poly (N-isopropylacrylamide-co-methacrylic acid-co-vinylpyrrolidone) [P(NIPAAm-MAA-VP) [75] have been studied for delivery of doxorubicin (DOX) and keratin/PLA fibers for 5-fluorouracil [76]. Cellulose nanocrystal-poly[2-(dimethylamino)ethyl methacrylate] reinforced poly(3-hydroxybutyrate-co-3-hydroxy valerate) systems facilitating both pH and temperature sensitive drug release are additionally reported to have potential for cancer treatment [77, 78]. pH-sensitivity can also be imparted to fibers by the inclusion of additional components with polymers which are not themselves stimuli-responsive. For instance, incorporation of sodium bicarbonate has been employed

to generate electrospun systems giving accelerated release under acidic conditions, using polymers such as gelatin/PCL [79] and PLA [80].

7.4.5 Multi-stage Release

Multi-stage drug release can also be of great benefit, and there are a range of examples of ES formulations which have been developed to provide this. The core–shell nanofiber design can be used to obtain biphasic drug release, using a hydrophilic polymer shell to give an initial burst release of the drug and a hydrophobic core to give a sustained maintenance dose. Using this strategy, Qian et al. were able to develop core/shell EC/PVP fibers with biphasic drug release [81]. In other work, pulsatile release (with bursts of "on" and "off" release) has been reported using blend fibers composed of poly(ethylene oxide), sodium alginate and sodium ibuprofen [82]. These fibers give two stage pulsatile release at pH 3, with the extent of release in the "on" phases and the lag time between them tunable by dint of varying the w/w ratio of the ingredients in the formulation.

7.5 Electrospinning of Biologicals

Biological products, or 'biologics' are a potent group of APIs that include vaccines, cell and gene therapy, and recombinant therapeutic proteins [83]. With recent advancements in biotechnology, biological treatments are becoming key in therapeutic protocols for multiple conditions – most notably perhaps in cancer immunotherapy and tissue engineering. In tandem, interest in electrospun biologic formulations has accelerated in the past few years.
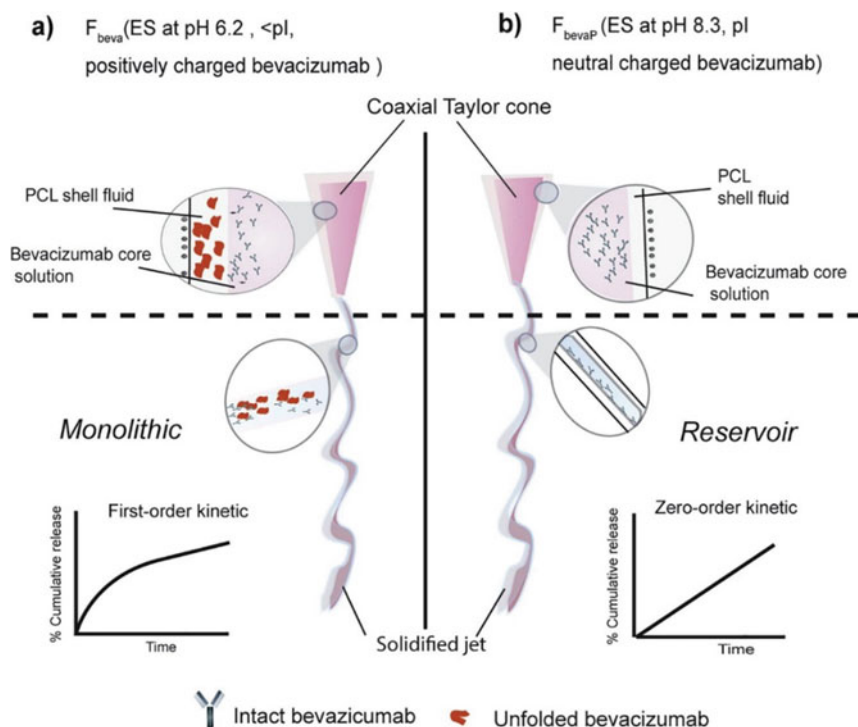
7.5.1 Proteins

The complex and fragile structures of many therapeutic proteins require advanced delivery methods and careful optimization of formulation and manufacturing conditions. Quite often the protein integrity is compromised by the route of administration, leading to denaturation, aggregation or misfolding. For example, the loss of fragile tertiary structures of proteins, defined by non-covalent interactions, may result in reduced biological activity. Currently, parenteral administration of proteins remains the gold standard as other delivery routes are limited or not yet clinically feasible [9, 84, 85].

The field of pharmaceutical technology has long sought possible solutions to protein formulation challenges, leading to the development of multiple inorganic, lipid or polymer-based formulations. Many biomaterial fabrication processes may

negatively impact the stability of the protein being formulated. Typical conventional encapsulation methods, such as spray-drying or hot melt extrusion, require harsh conditions (e.g. application of heat or prolonged contact with solvents) that can potentially cause protein misfolding or aggregation, and consequent loss of activity [9]. Electrospinning could offer a simple route to the fabrication of biocompatible protein-loaded scaffolds that can be easily implanted at the desired site of action. Multiple approaches have been proposed for the incorporation of therapeutic proteins within electrospun materials, including monoaxial and co-axial electrospinning [9]. While monoaxial spinning is attractive in its simplicity, and has been used to develop a number of protein-loaded formulations [86], prolonged exposure to the organic solvent typically required for electrospinning may cause misfolding or aggregation of labile biomolecules like proteins, leading to loss of activity. For this reason, the encapsulation of therapeutic proteins using blend electrospinning is used with caution.

Controlled and sustained protein delivery can be achieved using emulsion electrospinning, where a core–shell structure is formed by electrospinning of a water-in-oil emulsion formed from an aqueous phase (protein) and an organic phase (polymer). When subjected to electric charge, the organic phase (typically containing a volatile solvent) rapidly evaporates. This causes the migration of the aqueous phase (with protein) to the center of the jet, forming core–shell structures with favorable localization of proteins within the center of the fibers/particles, minimizing the risk of the initial burst release of therapeutic cargo. Although the relative simplicity of emulsion electrospinning is attractive from the manufacturability point of view, the protein-polymer blend composition must be carefully optimized to ensure there is no loss of bioactivity resulting from accidental exposure of the biomolecule to the organic solvent. A non-ionic surfactant is often incorporated in the formulation to decrease the contact between protein and organic solvents by forming reverse micelles (emulsions), therefore avoiding denaturation or aggregation [9]. In 2017, Frizzell et al. [2] developed enzyme-loaded electrospun fibers for peroral delivery using surfactant-assisted emulsion electrospinning. Horseradish peroxidase and alkaline phosphatase were blended with EL100 in the presence of the surfactant Tween 20. The nanofibers showed pH-dependent enzyme release patterns, with ~ 5% release at pH 2 and almost 100% at pH 7. Use of EL100 ensured dissolution of the fibers only occurred in neutral and basic pH conditions, leading to protected transit through the stomach and preventing acid- medicated protein degradation.

An alternative to emulsion electrospinning is the co-axial approach. As both solutions are physically separated until the formation of the fiber, protein exposure to organic solvents is limited and therefore accidental degradation can be minimized. The resulting fiber usually holds the protein in the core with a hydrophobic polymeric shell allowing for the gradual release of the cargo at the site of action. A notable example of protein encapsulation within electrospun fibers using this approach has been recently published by Angkawinitwong et al. [87], who explored coaxial electrospinning in the fabrication of bevacizumab-loaded PCL nanofibers for the treatment of age-related macular degeneration in the eye (Fig. 7.6). The study highlighted the importance of the pH of the protein solution. It was found that electrospinning protein

Fig. 7.6 A schematic diagram showing the effect of bevacizumab migration during electrospinning on the fiber properties. **a** When the protein solution is at pH 6.2, the protein carries a net positive charge; this causes it to migrate uncontrollably from the aqueous core to the polymer shell and become unfolded upon exposure to the shell solvent. The resultant distribution of both intact bevacizumab and unfolded bevacizumab within the core and shell leads to first-order release behavior. **b** In contrast, when working at pH 8.3, the pI of bevacizumab, the protein is neutral and does not interact with the electric field. This results in zero-order release of intact bevacizumab. Reprinted with permission from Angkawinitwong et al. [87] Copyright Elsevier 2017 Ltd

solutions at the isoelectric point (pI) of the antibody (where it is uncharged) significantly enhances its in-process stability. Bevacizumab released from the optimal core–shell fibers remained intact and biologically active, confirming the appropriateness of the approach for sustained and localized delivery of antibodies. However, the encapsulation efficiency was negatively affected by electrospinning at the pI of bevacizumab, which was attributed to the lack of electrostatic interactions driving the migration of protein towards the grounded electrode when the antibody is in its uncharged state.

7.5.2   Cells and Extracellular Vesicles

Cell therapies are gaining real momentum in the current landscape of medical innovations, but their clinical translation is often impeded by manufacturing constraints or poor cell survival post-transplantation. Biomaterials are often explored for example to aid stem cell differentiation or trafficking into the desired therapeutic location [88]. Delivering cells directly to the site of action within implantable and biocompatible scaffolds could be an attractive approach for a variety of conditions, such as cardiac repair [89]. Electrospinning has been shown to have significant potential in the generation of such scaffolds.

Cell electrospinning, first introduced by Jayasinghe in 2006 [90], refers to the incorporation of cell suspensions directly into electrospun fibers using a modified co-axial electrospinning apparatus. To ensure sterility, the experiments are often conducted in laminar flow hoods. Probably the most important modification in the setup arises from the fact that cell-containing fiber product cannot be allowed to dehydrate, as this would negatively influence cell viability. For this reason, traditional metal collecting substrates are unsuitable and instead fibers are collected directly into a dish containing cell culture media maintained at 37 °C. Cell electrospinning has now been tested on a variety of cell lines, and in all cases if the operating parameters are optimized it is possible to maintain cell integrity after fiber generation. It seems that exposure to a high voltage at low current (nanoamperes) during electrospinning does not affect the viability [90, 91] and functionality [89] of processed cells.

It is also important to note that the polymers traditionally used for standard electrospinning often require processing in solvents such as tetrahydrofuran, chloroform or acetone. Such solvents, however, are toxic to living organisms and therefore unsuitable for cell electrospinning. Natural polymers such as alginates, collagens and cellulose may appear more appropriate, but are rarely used due to their poor mechanical properties. Instead, water-soluble synthetic polymers such as PVA or poly(dimethylsiloxane) appear to be more effective for the development of cell-loaded mats [92].

Recently, Trindade et al. [93] tackled the unexplored concept of incorporating extracellular vesicles (EVs) into electrospun patches. EVs are cell-derived nano-sized vesicles enclosed within a lipid bilayer [94, 95]. They are less immunogenic and easier to produce and process than stem cells and therefore hold great potential in tissue engineering applications [93]. High encapsulation efficiencies (> 70%) were obtained, and the EVs observed to retain their therapeutic potency after processing. This suggests that electrospinning could be an effective way of preserving EVs for long-term release formulations.

7.6 Translation

This chapter has presented a wide range of electrospun drug delivery systems and sought to highlight some of the key benefits of the approach. However, the vast majority of the work performed to date has been undertaken on the lab scale, and the throughput of such experiments is low: typical yields might be 100 mg per hour [96, 97]. This is clearly insufficient for industrial applications, and for electrospun formulations to make it to the market production on the ton scale is required. Recent years have seen rapid development of large-scale electrospinning, and are discussed elsewhere in this volume. Researchers in the pharmaceutical technology field have been quick to explore such high-throughput systems, and it is encouraging to see that, although increasing the production rate tends to result in more irregular fiber morphologies, the functional performance is unaffected [97, 98].

Most electrospun drug delivery systems have been developed using solution spinning. For translation, great attention must be paid to choosing the solvent system. First, there could be health and safety issues pertaining to the use of volatile solvents in large scale production [99]. Second, it is important to ensure that the final product is solvent free, as certain organic solvents (e.g. dimethylformamide or tetrahydrofuran) may result in harmful toxic effects if any residual solvent remains in the fibers [100–102]. Batch-to-batch consistency must additionally be assured, to ensure therapy is safe and effective.

Work has begun to implement the quality control procedures required for pharmaceutical applications (so called Good Manufacturing Practice, GMP), and industrial facilities now exist where it is possible to prepare large (ton) amounts of materials under GMP conditions. These recent developments auger well for the future translation of electrospun systems from the lab bench to the clinic [97, 103]. It should be noted however that while high-throughput monoaxial electrospinning is now possible, the scale-up of co-axial and other multi-fluid processes lags significantly behind. Thus, the first electrospun formulations to make it to market are likely to be those which exploit the ASD nature of the fibers to accelerate dissolution rates.

7.7 Conclusions

This chapter presents a brief overview of the applications of electrospun fibers in drug delivery. We have shown that it is possible to process both small molecule and biological active ingredients without any loss of functionality. A wide range of release profiles can be obtained. Many reports in the literature explore formulations designed to offer very rapid release of a drug cargo, using a hydrophilic and water soluble polymer to overcome problems of low API solubility and provide rapid relief of symptoms. Others use insoluble or slow-dissolving or degrading polymers to give extended release of an API, meaning there is the potential to reduce dosing frequency and improve patient compliance. Zero-order, targeted, and pulsatile release

can also be achieved through judicious choice of the polymer carrier. The high stability of small molecule drugs makes them relatively straightforward to incorporate into fibers, while there is significantly more challenge with biologics owing to their instability, particularly upon exposure to organic solvents. Nevertheless, a range of potent electrospun formulations containing proteins and even cells have been developed over recent years.

Elecrospinning thus has versatile applications in drug delivery. However, there are a number of challenges still to be addressed. More work is required to develop methods and provide quality control for high-throughput fiber production, particularly when it comes to multi-fluid processing. Maintaining batch-to-batch consistency and putting in place the quality control guidelines needed to comply with regulatory frameworks will be key for clinical applications. There are a number of researchers, both in academia and industry, who are working on these challenges, and at the time of writing several electrospun products have reached clinical trials (e.g. NCT02409628 or NCT03686800). In the authors' view therefore, the future for electrospun formulations is bright, and we confidently expect electrospun medicines to emerge in the market in the next few years.

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