Expert Opinion

Enhanced composite electrospun nanofiber scaffolds for use in drug delivery

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The utility of nanofibrous electrospun composite scaffolds has greatly expanded over the last decade, so that they now serve as viable drug delivery vehicles for a host of different biomedical applications. The material properties of electrospun scaffolds are extremely advantageous for drug delivery, in which site-specificity and lower overall medicinal dosages lead to a potential industry-altering mechanism of delivering therapeutics. Different drugs used to predominantly treat infections and cancers can easily be incorporated and released at therapeutic dosages. Further, the inherent high porosity of these electrospun scaffolds allows for a more precisely controlled degradation which is tunable by polymer composition and fiber morphology, leading to sustained drug release. This review examines the current research and breakthrough discoveries that have elevated electrospun scaffolds to a cutting-edge technology that will dramatically alter the landscape of drug delivery.

Keywords: drug delivery, electrospinning, nanofibers, scaffolds

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1. Introduction

The original process of electrostatic processing, or electrospinning, was first described by Zeleny in the early part of the 20th century [1], and its use in developing polymeric fibers was first patented by Formhals in 1934. Initial research in electrospinning focused on understanding the fundamentals of the process, i.e., how the jet is formed under certain electrostatic field strengths, fluid viscosity, molecular weight of polymers in solution, etc, especially with the work of Taylor [2] and Baumgarten [3] laying the groundwork for the current technology. Today, electrospinning is a well-utilized technology for the fabrication of biodegradable scaffolds that are composed of fibers that can range from nanometers to microns in diameter, an attribute that is, otherwise, intrinsically difficult to obtain from other fiber fabrication processes [4]. In particular, these nanoscale fibers account for the extremely high surface area-to-volume ratio that is characteristic of electrospun scaffolds, which also exhibit a tremendously high porosity that is extremely advantageous for a plethora of biomedical applications. Furthermore, the polymer compositions of these electrospun scaffolds can be adjusted to various concentrations to achieve maximum biocompatibility and biofunctionality for any intended application, including chemical and optical sensors [5-10], electrodes [11-14], filters [15-17], tissue engineering scaffolds [18-34] and drug delivery systems [35-58].

As mentioned above, the actual process of electrospinning has long been practiced and is well characterized. Briefly, a charged polymer solution is pumped through a spinneret to which an electric field, powered by a high voltage power supply, is applied. A droplet is formed at the tip of the spinneret and develops into a cone, while the surface tension of the droplet is counterbalanced by the applied external electrostatic forces. Once the applied voltage is strong

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enough to overcome the droplet's surface tension, a fiber jet is emitted from the cone and captured on a grounded collecting substrate (e.g., a collecting plate or spinning drum). The distance between the spinneret and the collecting substrate is where the solvent within the ejected jet stream evaporates, resulting in a collection of non-woven small micron or submicron-sized fibers that form a highly porous scaffold. The resulting scaffold thickness, fiber morphology and average fiber diameter are all properties stemming from the effects of the polymer solution's viscosity, conductivity and surface tension, as well as the electrospinning parameters such as electric field strength, temperature, distance between spinneret and collecting substrate, and humidity, all of which have been summarized in detail in recent reviews [59,60].

Drug delivery via electrospun scaffolds affords ample flexibility in creating an optimal delivery vehicle for therapeutic treatment. While drug delivery is classically regarded as delivering medication (e.g., antibiotics or anticancer pharmaceuticals), proteins [61-81], polysaccharides [82-88] and DNA [89-91] can also be incorporated into the electrospun fibers and released through different pathways (e.g., diffusion, desorption, scaffold degradation) that are dependent upon the scaffold's polymer/fiber composition. Differing modes of scaffold fabrication such as emulsion electrospinning [92-95] and coaxial electrospinning [96-106] have also been employed to better fine-tune and optimize the kinetics of drug release. This review will examine the latest research conducted in the fabrication of electrospun scaffolds designed specifically for drug delivery and speculate on their feasibility and potential for clinical applications and commercial development.

2. Polymers used for electrospun scaffolds

The materials utilized as base polymers for generating electrospun scaffolds must be carefully chosen, for their inherent chemical properties principally dictate the stability and functionality of the scaffolds. Both synthetic and natural base polymers, as well as blends of the two, have been thoroughly studied and are also extensively reviewed by Sill and von Recum [38] and Liang *et al.* [107].

2.1 Natural polymers

Natural polymers, when compared to synthetic polymers, clearly demonstrate lower toxicity, immunogenicity and improved biocompatibility. For example, proteins, such as collagen, have been successfully used as the base composition of electrospun fibers. Collagen is the most prevalent protein in the extracellular matrix (ECM) of soft and hard tissues, and collagen types I, II and III have all been utilized as the principal polymer component of electrospun scaffolds [29,69-73]. Matthews and his colleagues produced fibers of calfskin collagen type I with an average fiber diameter of 100 nm that, even after the electrospinning process, still exhibited the 67 nm banding pattern that is characteristic of native collagen [69]. The authors determined that the structural properties of electrospun collagen varied with the tissue of origin (e.g., type I from skin versus type I from placenta), the isotype (collagen type I versus collagen type III) and the concentration of the collagen solution.

Similarly, Shields *et al.* generated collagen type II electrospun scaffolds and evaluated their material properties, especially between uncrosslinked or crosslinked [71]. Uncrosslinked scaffolds exhibited a minimum and average fiber diameter of 70 and 496 nm, respectively, while crosslinked collagen type II scaffolds exhibited diameters of 140 and 1.46 µm, respectively. The average thickness of the uncrosslinked scaffolds was 0.20 ± 0.02 mm and 0.52 ± 0.07 mm for crosslinked scaffolds. Further, uniaxial tensile tests of the uncrosslinked scaffolds revealed an average tangent modulus of 172.5 ± 36.1 MPa, an ultimate tensile strength of 3.3 ± 0.3 MPa and an ultimate strain of 0.026 ± 0.005 mm/mm. Clearly, modification and post-processing treatment of fibers can alter the material properties of the electrospun scaffolds, expanding the spectrum of applications for which these scaffolds can be utilized.

Elastin is another example of a natural polymer that has been extensively utilized as a polymer for fabricating electrospun scaffolds, especially for vascular tissue engineering [74-81]. For example, Boland *et al.* electrospun pure bovine elastin at concentrations of 20 and 30% (w/v) but only the 30% elastin showed optimal fiber formation properties with an average fiber diameter of 1.1 ± 0.7 µm [74]. The authors reasoned that a blend of 80:20 collagen type I : elastin would be more suitable then elastin or collagen I alone for mimicking the physiological protein distribution of a small diameter blood vessel ECM. To this end they used this approach to generate an electrospun scaffold which they populated sequentially with smooth muscle, dermal fibroblasts and endothelial cells. The resulting 3D scaffold was then processed for histology and results showed the formation of a three-layer construct with complete cellular infiltration. Specifically, the cell distribution was equal but a dense layer of smooth muscle cells formed beneath the basal lamina and had begun to align circumferentially around the construct. In contrast, the fibroblasts and smooth muscle cells formed a dense cellular population on the outer scaffolding. Thus, this study clearly demonstrates the feasibility of using electrospun collagen and elastin scaffolds for developing a multi-layer vascular graft.

Subsequently, a number of other studies were conducted using blends of elastin with either natural or synthetic polymers for the development of vascular grafts. One study in particular combined collagen type I, elastin and poly(lactide-co-glycolide) (PLGA) to create an electrospun vascular graft that exhibited tissue composition and mechanical properties similar to native vessels and was also biocompatible and non-toxic when it was implanted *in vivo* [79]. Recently, Heydarkhan-Hagvall *et al.* also used blends of collagen, elastin, gelatin and poly(ε-caprolactone) (PCL) to generate electrospun scaffolds whose morphology, porosity, fiber

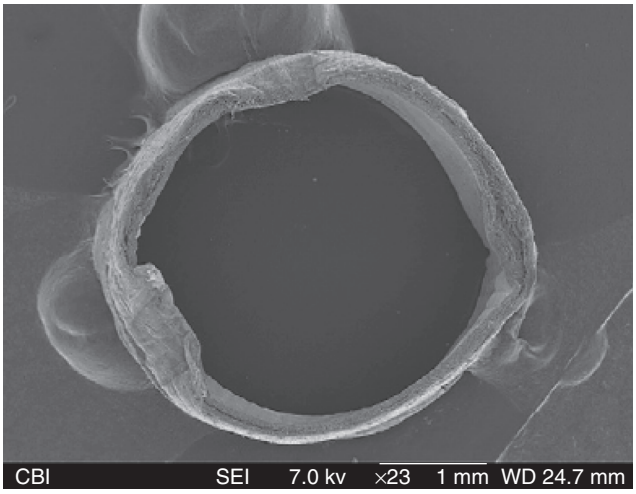

Figure 1. A low magnification SEM image of the PIJV segment with the electrospun polymer deposited onto its adventitial surface.

Reprinted from El Kurdi MS, Hong Y, Stankus JJ, et al. Transient elastic support for vein grafts using a constricting microfi brillar polymer wrap. Biomaterials 2008;29:3213-20 [81], Copyright (2008), with permission from Elsevier.

diameter, material properties and interactions with cells were all investigated [80]. Based on their data, the authors suggest that a gelatin 10%/PCL 10% electrospun scaffold may be optimal for cardiovascular tissue engineering. Similarly, El-Kurdi *et al.* used a mixture of poly(ester urethane)urea, collagen and elastin that was electrospun onto a freshly excised porcine vein segment (**Figure 1**) [81]. Using tissue viability assays as well as biofunctionality and perfusion tests, the authors showed that the electrospinning process did not affect tissue viability and that the composition and degradation of the electrospun wrap can determine the mid-wall circumferential wall stress versus time profile, potentially leading to the engineering of an improved arterial vein graft.

Another naturally occurring polymer, chitin, a polysaccharide that is found in the cell walls of fungi or exoskeletons of arthropods, and along with chitosan, which is commercially produced by the deacetylation of chitin, has also been successfully electrospun into nanofibrous based scaffolds [82-88]. Noh *et al.* contrasted the *in vitro* characteristics of chitin nanofibers (Chi-N) to commercially available chitin microfibers (Chi-M) that had average diameters of 163 nm and 8.77 µm, respectively, and found that the degradation rate for Chi-N was higher over 15 days [82]. This is likely due to its significantly higher surface area when compared to that of Chi-M. Another study by Desai *et al.* noted that electrospinning for pure chitosan was hindered by its limited solubility in aqueous acids and high degree of inter- and intra-chain hydrogen bonding. The authors circumvented the problem by electrospinning high molecular weight chitosan/poly(ethylene oxide) (PEO) blends (95:5) that exhibited fiber diameters as low as 80 ± 35 nm and had smooth fiber surfaces [83].

2.2 Synthetic polymers

Numerous studies have incorporated synthetic polymers instead of natural polymers in order to enhance various characteristics such as degradation time, mechanical properties and cell affinity [60]. Because synthetic polymers can be specifically tailored to give a wider range of properties such as hydrophilicity and hydrophobicity and represent a more fiscally reasonable source of raw, biocompatible and biodegradable materials, many researchers used them as base components for electrospun scaffolds.

The most commonly used synthetic polymers (individually or in blends) for the fabrication of electrospun scaffolds are the hydrophobic, biocompatible and biodegradable polyesters such as poly(glycolide) (PGA) [108], poly(lactide) (PLA) [29,51,93,94,109-111], PLGA [30,43,45,57,62,66,88,90,112-117] and PCL [21,22,33,39,53,86,98,99,101,105,115,118-122]. In addition, hydrophilic polymers, such as poly(vinyl alcohol) [65,85,86,123-125], poly(urethane) [126,127], poly(ethylene glycol) [57,119,128] and poly(ethylene oxide) [115,129], have also been successfully electrospun for a variety of biomedical applications. The vast array of viable synthetic polymers used to generate non-woven, nanofibrous scaffolds provides a tremendous source of materials for the specific design of scaffolds to address any particular clinical need. The ability to also blend combinations of natural polymers, synthetic polymers, random copolymers and block copolymers together to more precisely fine-tune the material properties of scaffolds was recently and comprehensively reviewed by others [39,105]. It is this wide-ranging flexibility of polymer compositions that gives electrospun scaffolds such huge promise and explosive potential in medical treatments, causing the huge spike of research we have witnessed in the last decade. As polymers themselves form the basis of the electrospun scaffold, how the drugs are embedded within the scaffolds is another important feature that must be considered. As this review intends to explore drug delivery, examples of such medicated electrospun scaffolds are discussed in the next section.

3. Drug delivery and other potential clinical applications

Research into drug delivery using electrospun scaffolds has mainly focused on two predominant classes of drugs: antibiotics for the treatment of infections and the prevention of abdominal adhesions and anticancer agents. In addition, numerous studies have incorporated different types of drugs for other uses, which will be covered in the third subsection.

3.1 Antibiotic medicated electrospun scaffolds

Approximately 93% of all abdominal surgical procedures result in pathological fibrotic bands that develop in the peritoneal cavity and are commonly referred as abdominal adhesions [124]. Adhesions can result in not

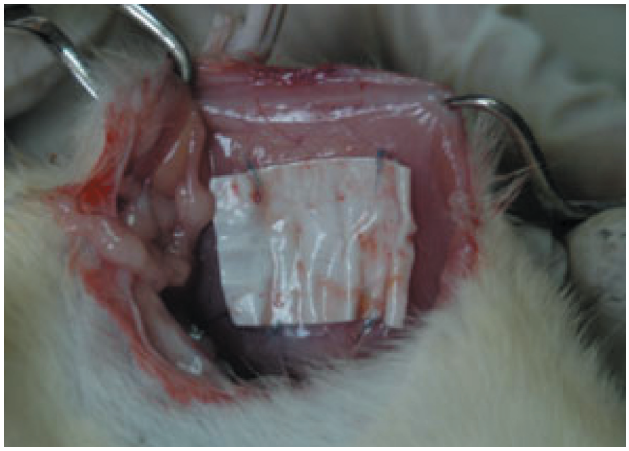

Figure 2. Representative image of site of membrane implantation indicating no adhesions.

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only subsequent operations to remove the excessive tissue, but also small bowel obstruction, female infertility and chronic debilitating pain [130]. To combat this problem, physical barriers are used to prevent tissue formation by placing them between the injured sites and the surrounding tissue. These barriers can also be used in conjunction with antibiotics, anticoagulants and anti-inflammatory agents as possible factors to prevent post-operative surgical adhesions [131-136].

From this perspective, antibiotic-containing electrospun scaffolds can serve a dual functionality: a physical barrier as well as a drug delivery system that can prevent abdominal adhesions [43,53]. To this end, Zong *et al.* examined the efficacy of a drug-loaded, PLGA-based electrospun scaffold in a rat model of cecum abrasion [43]. Scaffolds were generated with only PLGA or a blend of PLGA and PEG–PLA diblock copolymer alone or with the antibiotic drug, Cefoxitin sodium (Mefoxin®, Merck, NJ, USA) at 5 wt%, which is approximately 1/20 of the typical post-operative dosage for patients. To investigate the *in vivo* performance of these scaffolds, they were used in an animal model in which rat cecums were abraded until serosal bleeding was evident, and then a 1 × 1 cm^2 area of abdominal wall muscle was excised directly across from the cecal wound. After four weeks, the incidence of adhesions was 78% for the control group (abrasion only), 40% for the PLGA scaffold group, 22% for the PLGA/PEG-PLA scaffold group and 0% with Mefoxin-containing PLGA/PEG-PLA scaffolds. The authors noted that the relatively poor performance of the PLGA scaffolds was perhaps due to substantial shrinkage when immersed in a fluid environment. In contrast, the PLGA/PEG-PLA scaffolds retained their original conformation. The authors also reported that these results confirm that site-specific delivery of antibiotics, in conjunction with the physical presence of the electrospun scaffold, is a highly efficacious approach in preventing post-operative abdominal adhesions.

Similarly, Bölgen *et al.* investigated the efficacy of electrospun poly(ε-caprolactone) (PCL) scaffolds in preventing post-operative abdominal adhesions in a rat model of abdominal wall defects [53]. PCL solutions (13 g/100 ml) were mixed with chloroform and dimethylformamide (DMF) and the resulting electrospun PCL scaffold (~ 25 µm thick) was then loaded with drugs by adding droplets of the commercially available antibiotic, Biteral® (Roche, France), resulting in a total of 25 mg of medication. From this technique, the antibiotic would be entirely on the surface of the fibers and be prone to a burst release upon immersion into a fluid environment. The authors note that a burst release of drug was indeed evident by 3 h, in which 80% of the absorbed Biteral® in the PCL scaffold was released; the remaining drug was completely released by 18 h. As for prevention of adhesions, 2 × 3 cm^2 plain PCL scaffolds reduced the extent of adhesions by 14.3%. In contrast, PCL scaffolds loaded with Biteral® were even more effective in reducing adhesions (~ 46.1%) (**Figure 2**), leading the authors to contend that the antibiotic, most of which was released (diffused out) within several hours, not only possessed a therapeutic capability by eradicating micro-organisms that could have contaminated the injury sites, but also facilitated the physical presence of the barrier in preventing adhesion formation, an observation that was also confirmed by Zong *et al.* [43].

Aside from these *in vivo* studies, which suggest that these antibiotic-medicated electrospun scaffolds can serve a dual function, a larger number of *in vitro* studies were conducted to study more fundamental properties of the scaffolds. For example, one of the earliest studies to report on the incorporation of an antibiotic was carried out by Kenawy *et al.* [48]. The antibody tetracycline hydrochloride was electrospun in fibers made from either PLA or poly(ethylene-co-vinyl acetate) (PEVA), or from a 50:50 blend of the two. Drug release assays revealed that 65% of the drug was released from electrospun PEVA scaffolds within 120 h, whereas ~ 50% was released by the 50/50 scaffold over the same time. The release kinetics also showed an initial burst of drug, probably as a result of the presence of tetracycline hydrochloride on the fiber surfaces. Also, after 50 h, the drug release from both was negligible.

A study that focused on optimizing parameters for fabricating PLGA-based electrospun scaffolds also investigated the incorporation and release of the broad spectrum antibiotic, cefazolin [44]. The authors found an increase in nanofiber average diameter (from 340 to 490 nm) that was associated with the presence of cefazolin. Similarly, Verreck and colleagues explore the possibility of designing an electrospun scaffold capable of topically delivering drugs for infections and wound healing [47]. In this study, water insoluble drugs such as itraconazole (treatment for fungal infections) and ketanserin (selective S2-serotonin antagonist shown to accelerate wound healing) were incorporated into a polyurethane-based

electrospun scaffold. Results showed that at low drug loading, itraconazole release was linear without an initial burst. In contrast, a biphasic release was obtained for ketanserin. Based on these data, the authors concluded that these release profile phases may be temporally correlated with drug diffusion either through the polymer or through formed aqueous pores.

Cui and colleagues focused on the different diameters and drug content as factors to control drug release and polymer fiber degradation of electrospun scaffolds [51]. The study utilized poly-DL-lactide (PDLLA) as the base polymer and paracetamol, an analgesic drug, to generate their electrospun scaffolds. Specifically, the authors generated a number of electrospun scaffolds that had different fiber diameters and drug loading amounts, such as 5.0% and diameters of 212, 551 and 1.31 μm and a drug content of 2.0, 5.0 and 8.0% with ~ 400 nm fibers. Release experiments revealed a typical biphasic pattern with an initial burst of paracetamol release followed by a plateau or a gradual release. Specifically, during the first 24, 48 and 96 h the total amount of release was 80, 50 and 80% for fibers with a size of 212, 551 and 1.31 μm, respectively. In the case of the 400 nm fibers but with drug content of 2.0, 5.0 and 8.0%, the results showed that there was ~ 50% paracetamol release in the initial 4 h (from the 8.0%). The release from the 5% drug-containing fibers exhibited a better sustained release. Lastly, the 2.0% fibers showed a slower and continuous release within the first 16 h but with a decreased release for the next 2 weeks. This study suggests that fiber size and drug concentration are factors that influence the drug release profile from electrospun-medicated scaffolds.

A more recent study described the use of two-stream electrospinning to fabricate scaffolds consisting of biodegradable poly(ester urethane) urea (PEUU) and PLGA that was loaded with tetracycline and investigated the relationship between material properties and drug concentration [58]. Results revealed that the initial modulus and tensile strength of PLGA–tetracycline scaffolds decreased as the tetracycline concentration increased. Specifically, PEUU had a tensile strength of 12 ± 1 MPa and breaking strain of 191 ± 15%, where as the initial moduli of the blend PEUU/PLGA-tetracycline scaffold it was ~ 8 – 11 MPa and the breaking strain was ~ 200%; for PLGA-tetracycline scaffolds it ranged from 21 – 61%. The tensile strength values of the PEUU/PLGA-tetracycline scaffold were also significantly lower than the 14 – 55 MPa obtained with the PLGA-tetracycline scaffold and higher than the 6 MPa for PEUU.

Although the aforementioned studies focused on the incorporation and release kinetics of various drugs, they did not investigate the bioactivity of the released compounds (with the exception of Hong *et al.* [58]). In contrast, Kim *et al.* investigated the release of Mefoxin from PLGA-based electrospun scaffolds and quantified both drug release and efficacy of bacterial growth inhibition [45]. PLGA scaffolds were electrospun with an amphiphilic diblock copolymer, poly(ethylene glycol)-b-poly(lactide) (PEG-b-PLA). The amount of Mefoxin in each scaffold was 5 wt%, which represented 1/20th the typical daily post-operative patient dosage. The authors discovered that increasing Mefoxin within the scaffolds altered fiber morphologies from a bead-and-string structure to a completely fibrous one. Furthermore, the average fiber diameter and fiber diameter distribution decreased from 360 ± 200 nm (with no drugs) to 260 ± 90 nm (with Mefoxin). Finally, the average density of the scaffolds with no embedded drugs decreased from 0.41 to 0.20 g/cm^3 for those with Mefoxin. The authors speculate that this phenomenon can be attributed to the salt effect of Mefoxin, in which the drug molecules increased the conductivity of the drug solution prior to electrospinning; the charge density of the ejected polymer jet increases, resulting in fibrous morphology. The authors additionally demonstrated that PLGA electrospun scaffolds experience a burst release within a few hours. However, the authors also noted that the initial amount of released drug varied with regards to drug concentration and polymer composition – that is, scaffolds with lower drug concentrations experienced a smaller amount of initial drug release. Further, to determine the bioactivity of the released drugs, the authors introduced scaffolds – with and without drug – into liquid (dynamic) and agar (static) cultures of *Staphylococcus aureus*, a Gram-positive spherical bacterium that is the most common cause of surgical site infections. In liquid cultures, the authors report that the mere presence of the scaffold inhibited some bacterial growth (13 ± 10%), whereas medicated scaffolds completely eradicated the bacteria. In the static cultures, the inhibition of bacterial growth was visually detected to assess the viability of the Mefoxin-loaded electrospun scaffolds (**Figure 3**). It was clearly seen that the medicated scaffolds greatly inhibited bacterial growth after 24 h of incubation. What is of interest, as the authors describe, is that bacteria cells begin to proliferate at time periods longer than 24 h – an occurrence that the authors speculate is due to the structural breakdown of the diffused Mefoxin.

While not incorporating a true antibiotic, a study by Ignatova *et al.* [85] reported on the incorporation of quaternized chitosan (QCh) mixed with poly(vinyl alcohol) (PVA) to generate a medicated electrospun scaffold. QCh derivatives are know to be potent (broader spectrum and higher killing rate) against micro-organisms as compared to those of chitosan. The authors initially generated electrospun scaffolds composed of mixed solutions of various rations of QCh/PVA that resulted in different fiber diameter (range of 60 – 200 nm), as well as including a triethylene glycol diacrylate as crosslinking agent (stabilizes the nanofibers against degradation in water). More importantly, the authors tested the bioactivity of these electrospun scaffolds against two types of micro-organisms, *S. aureus* and *Escherichia coli*, and showed that the photo-crosslinked scaffolds inhibited 100%

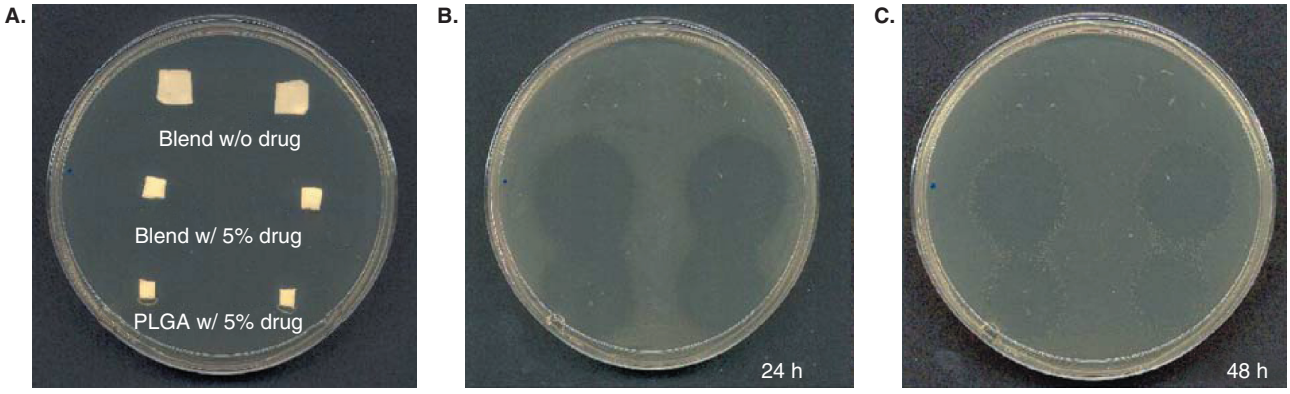

Figure 3. Bacteria growth inhibition on agar plates with scaffold sections of 1 × 1 cm (A). Scaffolds were incubated at 37°C for 4 h and then removed. *S. aureus* was plated and slowed to proliferate overnight. The areas surrounding the drug-containing scaffolds did not exhibit any bacteria growth after 24 h (**B**) or 48 h (**C**).

Reprinted from Kim K, Luu YK, Chang C, et al. Incorporation and controlled release of a hydrophilic antibiotic using poly(lactide-co-glycolide)-based electrospun nanofi brous scaffolds. J Control Release 2004;98:47-56 [45], Copyright (2004), with permission from Elsevier.

S. aureus growth within 60 min. In contrast, the electrospun photo-crosslinked PVA scaffold (control) had no effect on the bacteria. With *E. coli*, the results were not as potent; the photo-crosslinked scaffolds inhibited 30 – 40% bacterial growth within 60 min, but by 120 min their inhibitory effect reached 100%, whereas the electrospun photo-crosslinked PVA scaffold (control) had no effect on either micro-organism. Based on these data, it was concluded that the antibacterial activity their electrospun QCh/PVA scaffolds possessed could contribute to the prevention of secondary wound infections by *S. aureus*, further resulting in limited scar formation.

Using coaxial electrospinning, a study reported the incorporation of two drugs, the antioxidant, Resveratrol, and the antibiotic, Gentamycin Sulfate, into the inner layers of the fiber cores and polycaprolactone (PCL) as the outer layer or shell [52]. Aside from the structural and material properties measured, the release revealed a smooth and controlled release with both drug-loaded scaffolds and no initial burst release, suggesting an ideal interaction of both drugs within the scaffold's individual fibers. Lastly, a recent study reported on a mechanism of release from such electrospun fibers and suggests that solid-state diffusion may not be the primary process [137]. Specifically, release from electrospun nanofibers was previously demonstrated by many of the aforementioned studies to be saturated at various levels (~ 30 – 90 wt%) and typically the release rates at the highest saturation values (80 – 90 wt%) were achieved as a result of fiber degradation during the release process. Instead, according to this new study, the release rate of the incorporated compounds from either the nanopores in the fibers or the surface in contact with the water can be explained by desorption. The authors further state that the two important parameters controlling the desorption process and thus release rate are variations of polymer molecular weight and concentration in the electrospun solutions [137].

Thus, it is clear from these various studies that antibiotic-releasing electrospun scaffolds exhibit potential to be used as biomedical devices that can be easily implanted into specific surgical sites and effectively reduce the possibility of infection with minimal drug concentration, resulting in a shorter duration and improved quality of post-operative patient care.

3.2 Anticancer medicated electrospun scaffolds

In addition to the incorporation of antibiotics for the prevention and treatment of infections and post-surgical abdominal adhesions, a number of studies have begun exploring the utilization of electrospun scaffolds for the delivery of anticancer pharmaceuticals. Similar to the treatment of infections, post-surgical chemotherapy treatment for cancer is often systemic, it has to be administered in high concentrations and generates unwanted side effects. Thus, to bypass these major disadvantages, medicated electrospun scaffolds are generated and can provide local, controlled and sustained anticancer drug delivery: the results of such studies are reviewed below.

For example, Xie *et al.* investigated the efficacy of PLA/PLGA (30/70 blend) electrospun fibers embedded with the anticancer agent, Cisplatin, and compared the results with microparticles of the same formulation [54]. Cisplatin-loaded biodegradable microparticles with an approximate particle size of 5 mm and electrospun scaffolds with fibers exhibiting diameters of 0.5 – 1.7 mm were tested for encapsulation efficiency and drug release *in vitro*. The microparticles possessed encapsulation efficiencies ranging from 33 – 72%, while those of the electrospun fibrous scaffolds were greater than 90%. In the drug release experiments, Cisplatin-loaded microparticles resulted in a large initial burst of approximately 70% followed by a slow sustained release over 35 days to, ultimately, a 90% overall release of the drug. In contrast, the fibrous scaffolds achieved a sustained release of 75 days with an ultimate release of approximately 70% without experiencing a large initial burst. Further, the authors tested the efficacy of the released

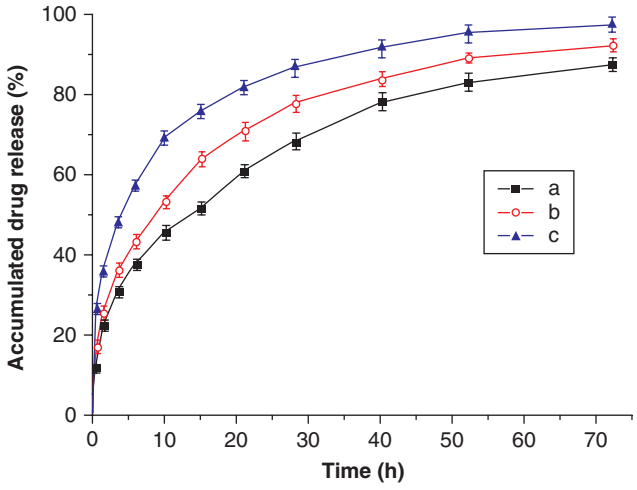

Figure 4. Temporal release profile of BCNU from PLLA-based electrospun fibers at 5 wt%, 10 wt% and 20 wt%.
Reprinted from Xu X, Chen X, Xu X, et al. BCNU-loaded PEG-PLLA ultrafine fibers and their in vitro antitumor activity against Glioma C6 cells. J Control Release 2006;114:307-16 [55], Copyright (2006), with permission from Elsevier.

drugs by quantifying the cytotoxicity of the different formulations against C6 glioma cells. Results showed that both microparticles and electrospun scaffolds had a higher cytotoxic effect than that of the free (unincorporated) drug. Specifically, the microparticle formulations had only slightly higher cytotoxicity (1.6 – 2.0 times) than the free drug, whereas that of the electrospun fibrous scaffolds was approximately four times higher in comparison. Thus, the longer, sustained release without an initial burst from the electrospun scaffolds provides substantial evidence that they can release therapeutics in a much more controlled manner, resulting in increased drug potency that could translate into substantial clinical improvements.

A study by Xu *et al.* investigated the development of an implantable BCNU-loaded poly(ethylene glycol)–poly(L-lactic acid) (PEG–PLLA) diblock copolymer scaffold containing 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) [55]. BCNU is a widely used anticancer pharmaceutical for the treatment of malignant gliomas because it is capable of penetrating the blood–brain barrier (it is lipid soluble and has low molecular weight). Specifically, the authors investigated the release rate and bioactivity of BCNU from a number of different scaffolds (containing 5, 10 and 20 wt% of drug) and their ability to kill rat Glioma C6 cells and reported that the release rates from these BCNU-loaded scaffolds were 45.5, 53.1 and 68.6% at 10 h, respectively (**Figure** 4). An initial burst release was also observed (due to the diffusion of BCNU near the fiber surfaces) at 0.5 h, which is desirable because it is required for an antineoplastic to achieve enough initial dosage [55]. Results from cytotoxic assays with the C6 cells showed cell growth inhibition rates of 52, 78 and 89% (48 h) and 59, 85 and 93% (at 72 h) for the 5, 10 and 20% BCNU-loaded scaffolds, respectively. The control scaffolds containing no drug did not induce any cytotoxicity at 72 h. When cytotoxicity was compared to unincorporated (pristine) BCNU at the same concentration, the pristine drug appeared to lose its anticancer activity after 48 h, presumably due to structural breakdown under the experimental conditions. Based on these data, the authors concluded that the medicated electrospun scaffolds may serve as useful implantable devices for malignant glioma.

A more recent study reported on the formulation of PEG–PLA diblock copolymer emulsion electrospun scaffolds containing the small water-soluble anticancer drug, Doxorubicin hydrochloride (Dox) [49]. Dox was selected as the model drug in this study because it is used clinically to treat many different types of human cancers as a chemotherapy agent. By generating a number of different scaffolds containing various concentrations of Dox (0.5, 1, 2 and 3wt%), the authors showed that there was no difference in the morphological appearance and average diameter of the nanofibers and that the release rates varied based on the incorporated drug concentration. Specifically, there was a fast release for the first 6 – 15 h followed by a plateau (**Figure** 5). Also, as expected, the release rate of Dox was proportional to the concentration (e.g., 73.1, 60.5, 47.7 and 36.8% at 10 h, for 0.5, 1, 2, and 3 wt% scaffolds, respectively).

Lastly, Ranganath and Wang conducted both *in vitro* and *in vivo* studies using PLGA (85:15 and 50:50) nano and microfiber discs and scaffolds with incorporated Paclitaxel, a mitotic inhibitor and radiosensitizing cancer-treating drug [56]. The *in vitro* release study of paclitaxel from both micro and nanofiber discs and scaffolds revealed sustained release over the course of the 80-day experiment. Initially, the discs and scaffolds showed a slight burst, 6 and 16% after 9 days, respectively. Further, the microfiber-based discs displayed an almost linear release and the total amount of paclitaxel released after day 80 was 26%. For the nano-based discs, around 35% of total paclitaxel was released for the same time. Similarly, the micro- and nano-based fiber scaffolds showed release rates of ~ 26 and 46%, respectively, at the end of the 80 days. Next, the authors investigated the effects of the electrospun discs and scaffolds on C6 glioma cells by monitoring the level of apoptosis (via caspase 3 activity) in comparison to Taxol® (Bristol-Myers Squibb, NY, USA; positive control) after days 4, 8 and 12. For the Taxol group, large apoptotic activity was observed on day 4 but when it was washed off, the cells recovered and began to proliferate especially at days 8 and 12, indicating decreased apoptotic activity. In contrast with the fiber-treated groups, on day 4 there was a slightly higher rate of cellular apoptosis than the negative controls (blank discs or scaffolds) but the cells' apoptotic activity continued to increase on both day 8 and 12, especially for those treated with the nano-based fiber scaffolds.

The authors also performed an *in vivo* study to evaluate the efficacy of both electrospun micro and nano-based

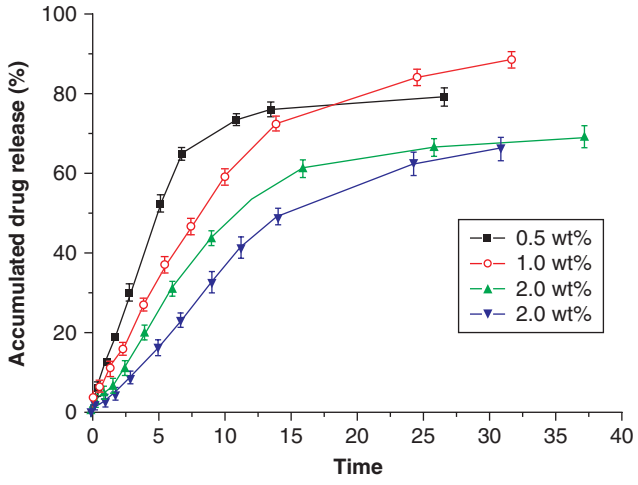

Figure 5. Temporal release profiles of Dox from Dox-containing PEG–PLA electrospun fibers.
Reprinted from Xu X, Chen X, Ma P, et al. The release behavior of doxorubicin hydrochloride from medicated fibers prepared by emulsion-electrospinning. Eur J Pharm Biopharm 2008;70:165-70 [49], Copyright (2008), with permission from Elsevier.

discs and scaffolds in inhibiting subcutaneous C6 glioma tumor in nude mice [56]. As controls, placebo fiber discs and commercial Taxol were also used. Results from this study showed that after surgical implantation, for animals with placebo discs, the tumor grew continuously to more than 2000 mm^3 at the day of killing (day 24). In particular, both micro and nanofiber disc treated groups had ~ 75 and ~ 78% smaller tumors on day 24 as compared to placebo control, respectively. Similarly, in comparison to tumors treated with Taxol control, both micro and nanofiber disc treated groups had ~ 38 and ~ 44% smaller tumors on day 24, respectively. For the same time duration, micro and nanofiber scaffolds treated groups had ~ 69 and ~ 71% smaller tumors in comparison to placebo control and ~ 21 and ~ 26% smaller tumors in comparison to Taxol control, respectively, on day 24. These results suggest that the electrospun PLGA microfiber discs/scaffolds could be utilized as paclitaxel delivery implants for chemotherapy treatment, especially for post-surgical malignant brain tumors. The authors also caution that further *in vivo* experimentation is necessary, especially those using intracranial experiments (e.g., drug biodistribution and tumor regression studies) through non-invasive bio-imaging.

3.3 Other types of medicated electrospun scaffolds

A number of other studies incorporating drugs in electrospun scaffolds have been reported for numerous biomedical applications. For example, in a study focusing on possible treatment for post-surgical atrial fibrillation, Jiang *et al.* incorporated the anti-inflammatory agent ibuprofen into a composite scaffold composed of PLGA and poly(ethylene glycol)-*g*-chitosan (PEG-*g*-CHN) [57]. The authors described two different ways of preparing such scaffolds, one where the ibuprofen was directly incorporated into the fibers by blending; and the second by covalently conjugated to the PEG-g-CHN prior to electrospinning. The rate of ibuprofen release rates from three different types of electrospun scaffolds: i) PLGA containing 5% ibuprofen; ii) PLGA/PEG-g-CHN (70:30) containing 5% ibuprofen; and iii) PLGA/PEG-g-CHN-ibuprofen conjugate containing 4.4% ibuprofen were investigated. The results from these experiments show an initial burst release for the PLGA scaffold and a total of more than 85% of ibuprofen released after 4 days. In contrast, ibuprofen release from the PEG-g-CHN scaffold was slower, with a total of ~ 70% total release over 16 days. Lastly, over the same time period, release from the last type of scaffold (a blend of PLGA with PEG-g-CHN-ibuprofen) followed pseudo-linear kinetics, with less than 40% of ibuprofen being released. The authors conclude that the compliant and stable mechanical properties of PLGA/PEG-g-CHN ibuprofen composite scaffolds, together with their sustained release capacity, makes them ideal for the treatment of post-surgical atrial fibrillation.

Another drug delivery approach intended for tissue engineering or wound repair applications utilized poly(ethylene glycol) functionalized with low molecular weight heparin (PEG-LMWH) and electrospun into a nanofibrous scaffold [41]. The authors evaluated surface morphology and fiber diameters and found that the diameters ranged from approximately 100 – 400 nm. In addition, it was determined that 3.5 – 85 µg of heparin/mg of electrospun fibers can be incorporated into the electrospun scaffold and that the incorporation of PEG-LMWH enables the retention of the heparin for at least 14 days. The ability of the electrospun fibers functionalized with PEG-LMWH to bind basic fibroblast growth factor was also investigated and found to be 32 and 56% greater than those functionalized with LMWH alone or with just PLGA, respectively.

Further, a number of other studies have also incorporated proteins, especially growth factors, as potent 'drugs' for the possible treatment of various medical conditions. Specifically, electrospun scaffolds using synthetic polymers were functionalized with platelet-derived growth factor-bb (PDGF-bb) for various regenerative medicine applications [61], bone morphogenetic protein (BMP-2) for stimulating bone formation [62,64,67], epidermal growth factor (EGF) for the treatment of wound healing of diabetic ulcers [68] and nerve growth factor (NGF) for stimulating nerve regeneration [69]. Undoubtedly, much more exciting research will be reported in the next decade to augment these findings by incorporating drugs, proteins and even DNA in multi-layered electrospun structures composed of solid fibers or core/shell fibers that can be utilized for a seemingly limitless number of medical applications. These future studies will undoubtedly improve the delivery mechanisms and subsequently the feasibility of medicated electrospun scaffolds in the clinic. Some of the existing hurdles that we need to overcome in order to be able to reap the benefits of this technology are described below.

4. Expert opinion

Electrospinning, utilized as a core technology to manufacture micro and nanofibrous scaffolds, has paved the way for a new class of drug delivery vehicles whose multiple biofunctionalities can serve an array of therapeutic applications. The ability to create non-woven composite scaffolds with optimal physical and material properties allows for the incorporation of not only drugs but also cells, DNA and proteins that can be delivered site-specifically and in a controlled and sustained manner over periods of time that can span hours, days, weeks and even months. The versatility of the electrospinning process to produce these types of scaffolds results in an enormous surface area-to-volume ratio, as well as uniform fiber degradation, which are advantageous for the direct release of incorporated medications. Collectively, these properties have garnered electrospun scaffolds much excitement within the past few years for their tremendous potential to be used as therapeutic tools for specific medical applications.

Widespread research exploring the many different methods through which electrospun scaffolds can be manufactured has been ongoing, with many exciting breakthroughs and accomplishments. The inclusion of drugs, ranging from those treating various types of cancers, to heart disease, to bacterial infections, provides a platform upon which scaffolds of various thicknesses, compositions and surface topographies can be generated, each custom-made for the intended application. Site-specific controlled and sustained drug release from electrospun scaffolds over long periods of time would eliminate the prevalence of drug administration errors in hospitals today, as well as their systemic side effects due to the relatively large dosages of infused medications that usually extend the patient's hospital stay.

Although most of the current research is still at the experimental, preclinical trial stage, extensive knowledge of these electrospun scaffolds has been attained. The requisite equipment and various processing parameters are well known to generate fibers of specific diameters that can range from tens of nanometers up to microns. Biomedical applications have been targeted for which drug-containing electrospun scaffolds can be used either as preventative or therapeutic devices. The multidisciplinary studies requisite for comprehensively characterizing these scaffolds are ongoing and quickly moving forward. For example, in the realm of engineering, the focus is to build various electrospinning set ups, each designed for a specific application; in chemistry, the goal is to study drug–polymer interactions so that drug release profiles can be more readily controlled and understood; in biology, the aim is to study the safety and efficacy of the released drugs in preventing infections/adhesions or killing cancerous cells in an *in vivo* setting in order to compile pertinent data to use for applying and ultimately receiving FDA approval to launch Phase I clinical trials. Clearly, among the biggest hurdles to developing commercially these electrospun scaffolds for clinical use is the confidence with which investigators can translate their *in vitro* and *in vivo* data to human efficacy. Will the scaling up of medicated electrospun scaffolds to human needs impose other factors on their potency? Will a combination of multiple ailments affecting an individual patient affect the performance of the medicated scaffold? From a technical point, can we be certain that 100% of the solvents used to manufacture medicated scaffolds are completely evaporated, or will traces induce toxicity or inflammation? Will physicians/surgeons embrace this new technology? And, for clinical trials, will patients consent to undergo a first surgical procedure to implant the scaffold and then a second to examine the results?

In order for us to be in a position to conduct clinical trials, this burgeoning field of research needs to be enhanced by the development of new animal models that represent some of the major existing clinical issues (e.g., pain management, prevention of abdominal adhesions, treating and preventing infections, cancer therapy, cardiovascular disease, etc). With these medical conditions representing a significant portion of the healthcare industry, the enormous work done already, both *in vitro* and *in vivo*, will accelerate the application of these medicated electrospun scaffolds into the clinical setting to meet the need. Specifically, to expound upon the knowledge that has already been acquired in broadening the acceptance and ultimately the clinical applicability of these medical devices, we need: i) a more precise spatial and temporal control of drug release (pharmacokinetics); ii) improved control and fine-tuning of fiber/scaffold degradation for efficient and effective localized release (pharmacodynamics); iii) better understanding of scaffold behavior and effectiveness *in vivo*; iv) controlling inflammation and immune response to the scaffolds *in vivo*; v) reducing toxicity; and vi) possibly, the sequential release of multiple drugs contained within a single scaffold. Finally, for generating viable clinical drug delivery products, we need to implement manufacturing or scale-up, especially in the context of cheap automated mass production, cost-effective and efficient manufacturing processes, quality control, safe long-term storage, easy transport and handling and ultimately safe implantation.

The market is certainly ready for the introduction of new drug delivery devices, and the growing number of published data contributing to this field is a clear indication that nanofibrous composite scaffolds hold immense promise in offering an improved mode of patient treatment. Successful therapeutic implementation of medicated electrospun scaffolds will inevitably aid the healthcare sector in reducing needless expenditure and lost productivity. With additional federal, state and private foundation funds, as well as developing partnerships with prominent industrial companies that already have in place the resources for mass production, many scientific queries surrounding the robust biomedical potential of

these nanofibrous scaffolds will be determined and will bring their applicability in the clinic as prescribed mode of treatment one step closer to reality. Indeed, with a plethora of academic laboratories, as well as several companies in the private sector conducting fascinating and cutting edge research using the latest biomedical and biotechnological technologies, the future of drug delivery – and the overall healthcare industry – could very well be profoundly affected by these innovative and versatile medicated electrospun scaffolds.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Zeleny J. The electrical discharge from liquid points, and a hydrostatic method of measuring the electric intensity at their surface. Phys Rev 1914;3:69-91

• **This groundbreaking paper established the core physical principles of electrospinning and laid the foundation upon which all future electrospinning research is based.**

2. Taylor GI. Electrically driven jets. Proc Natl Acad Sci London 1969;A313:453e75
3. Baumgarten P. Electrostatic spinning of acrylic microfibers. J Colloid Interface Sci 1971;36:71e9
4. Li D, Xia YN. Electrospinning of nanofibers: reinventing the wheel? Adv Mater 2004;16:1151-70
5. Wannatong L, Sirivat A. Electrospun fibers of polypyrrole/polystyrene blend for gas sensing applications. PMSE Preprints 2004;91:692-3
6. Wang XY, Kim YG, Drew C, et al. Electrostatic assembly of conjugated polymer thin layers on electrospun nanofibrous membranes for biosensors. Nano Lett 2004;4:331-4
7. Ding B, Kim J, Miyazaki Y, Shiratori S. Electrospun nanofibrous membranes coated quartz crystal microbalance as gas sensor for NH3 detection. Sensors Actuators B Chemical 2004;B101:373-80
8. Ding B, Kim J, Fujimoto K, Shiratori S. Electrospun nanofibrous polyelectrolyte membranes for advanced chemical sensors. Chem Sensors 2004;20:264-5
9. Wang XY, Drew C, Lee SH, et al. Electrospun nanofibrous membranes for highly sensitive optical sensors. Nano Lett 2002;2:1273-5
10. Liu HQ, Kameoka J, Czaplewski DA, Craighead HG. Polymeric nanowire chemical sensor. Nano Lett 2004;4:671-5
11. Kim C, Park SH, Lee WJ, Yang KS. Characteristics of supercapacitor electrodes of PBI-based carbon nanofiber web prepared by electrospinning. Electrochimica Acta 2004;50:877-81
12. Kim C, Choi YO, Lee WJ, Yang KS. Supercapacitor performances of activated carbon fiber webs prepared by electrospinning of PMDA-ODA poly(amic acid) solutions. Electrochimica Acta 2004;50:883-7
13. Kim C, Yang KS. Electrochemical properties of carbon nanofiber web as an electrode for supercapacitor prepared by electrospinning. Appl Phys Lett 2003;83:1216-8
14. Kim C, Yang KS, Lee WJ. The use of carbon nanofiber electrodes prepared by electrospinning for electrochemical supercapacitors. Electrochem Solid State Lett 2004;7:A397-9
15. Schreuder Gibson H, Gibson P, Wadsworth L, et al. Effect of filter deformation on the filtration and air flow for elastomeric nonwoven media. Adv Filtration Sep Technol 2002;15:525-37
16. Schreuder Gibson HL, Gibson P, Tsai P, et al. Cooperative charging effects of fibers from electrospinning of electrically dissimilar polymers. Int Nonwovens J 2004;13:39-45
17. Schiffman JD, Schauer CL. One-step electrospinning of cross-linked chitosan fibers. Biomacromolecules 2007;8:2665-7
18. Venugopal JR, Low S, Choon AT, et al. Nanobioengineered electrospun composite nanofibers and osteoblasts for bone regeneration. Artif Organs 2008;32:388-97
19. Kim GH. Electrospun PCL nanofibers with anisotropic mechanical properties as a biomedical scaffold. Biomed Mater 2008;3(2):25010. Epub ahead of print
20. Li WJ, Jiang YJ, Tuan RS. Cell-Nanofiber-Based Cartilage Tissue Engineering Using Improved Cell Seeding, Growth Factor, and Bioreactor Technologies. Tissue Eng Part A [Epub 2008 Apr 17]
21. Choi JS, Lee SJ, Christ GJ, et al. The influence of electrospun aligned poly(varepsilon-caprolactone)/collagen nanofiber meshes on the formation of self-aligned skeletal muscle myotubes. Biomaterials 2008;29:2899-906
22. Jeong SI, Lee AY, Lee YM, Shin H. Electrospun gelatin/poly(L-lactide-co-epsilon-caprolactone) nanofibers for mechanically functional tissue-engineering scaffolds. J Biomater Sci Polym Ed 2008;19:339-57
23. Janjanin S, Li WJ, Morgan MT, et al. Mold-Shaped, Nanofiber Scaffold-Based Cartilage Engineering Using Human Mesenchymal Stem Cells and Bioreactor. J Surg Res [Epub 2008 Jan 25]
24. Ma K, Chan CK, Liao S, et al. Electrospun nanofiber scaffolds for rapid and rich capture of bone marrow-derived hematopoietic stem cells. Biomaterials 2008;29:2096-103
25. Zhang YZ, Su B, Venugopal J, et al. Biomimetic and bioactive nanofibrous scaffolds from electrospun composite nanofibers. Int J Nanomed 2007;2:623-38
26. Barnes CP, Sell SA, Boland ED, et al. Nanofiber technology: designing the next generation of tissue engineering scaffolds. Adv Drug Deliv Rev 2007;59:1413-33
27. Ashammakhi N, Ndreu A, Yang Y, et al. Tissue engineering: a new take-off using nanofiber-based scaffolds. J Craniofac Surg 2007;18:3-17
28. Li WJ, Mauck RL, Cooper JA, et al. Engineering controllable anisotropy in electrospun biodegradable nanofibrous scaffolds for musculoskeletal tissue engineering. J Biomech 2007;40:1686-93
29. Chiu JB, Liu C, Hsiao BS, et al. Functionalization of poly(L-lactide) nanofibrous scaffolds with bioactive collagen molecules. J Biomed Mater Res A 2007;83:1117-27
30. Inanc B, Arslan YE, Seker S, et al. Periodontal ligament cellular structures engineered with electrospun poly(DL-lactide-co-glycolide) nanofibrous membrane scaffolds. J Biomed Mater Res A [Epub 2008 May 19]
31. Patel S, Kurpinski K, Quigley R, et al. Bioactive nanofibers: synergistic effects of

nanotopography and chemical signaling on cell guidance. Nano Lett 2007;7:2122-8

32. Park K, Ju YM, Son JS, et al. Surface modification of biodegradable electrospun nanofiber scaffolds and their interaction with fibroblasts. J Biomater Sci Polym Ed 2007;18:369-82
33. Chen M, Patra PK, Warner SB, Bhowmick S. Role of fiber diameter in adhesion and proliferation of NIH 3T3 fibroblast on electrospun polycaprolactone scaffolds. Tissue Eng 2007;13:579-87
34. Hosseinkhani H, Hosseinkhani M, Tian F, et al. Bone regeneration on a collagen sponge self-assembled peptide-amphiphile nanofiber hybrid scaffold. Tissue Eng 2007;13:11-9
35. Zeng J, Xu X, Chen X, et al. Biodegradable electrospun fibers for drug delivery. J Control Release 2003;92:227-31
36. Xie J, Tan JC, Wang CH. Biodegradable films developed by electrospray deposition for sustained drug delivery. J Pharm Sci [Epub 2007 Oct 8]
37. Xie J, Tan RS, Wang CH. Biodegradable microparticles and fiber fabrics for sustained delivery of cisplatin to treat C6 glioma in vitro J Biomed Mater Res A 2008;85:897-908
38. Sill TJ, Von Recum HA. Electrospinning: applications in drug delivery and tissue engineering. Biomaterials 2008;29:1989-2006

•• **This reference provides a very comprehensive listing of viable biodegradable and biocompatible polymers for electrospinning and their respective utilities in biomedical engineering.**

39. Luong Van E, Grondahl L, Chua KN, et al. Controlled release of heparin from poly(epsilon-caprolactone) electrospun fibers. Biomaterials 2006;27:2042-50
40. Xu X, Yang L, Xu X, et al. Ultrafine medicated fibers electrospun from W/O emulsions. J Control Release 2005;108:33-42
41. Casper CL, Yamaguchi N, Kiick KL, Rabolt JF. Functionalizing electrospun fibers with biologically relevant macromolecules. Biomacromolecules 2005;6:1998-2007
42. Zeng J, Yang L, Liang Q, et al. Influence of the drug compatibility with polymer solution on the release kinetics of electrospun fiber formulation. J Control Release 2005;105:43-51
43. Zong X, Li S, Chen E, et al. Prevention of postsurgery-induced abdominal adhesions by electrospun bioabsorbable nanofibrous poly(lactide-co-glycolide)-based membranes. Ann Surg 2004;240:910-5

• **This is the first manuscript to report on the *in vivo* efficacy of drug-containing electrospun membranes for the prevention of abdominal adhesions.**

44. Katti DS, Robinson KW, Ko FK, Laurencin CT. Bioresorbable nanofiber-based systems for wound healing and drug delivery: optimization of fabrication parameters. J Biomed Mater Res B Appl Biomater 2004;70:286-96
45. Kim K, Luu YK, Chang C, et al. Incorporation and controlled release of a hydrophilic antibiotic using poly(lactide-co-glycolide)-based electrospun nanofibrous scaffolds. J Control Release 2004;98:47-56

•• **Although this is not the initial manuscript to report on the incorporation of an antibiotic into an electrospun scaffold, this study was the first to demonstrate the structural integrity and bioactivity of the released antibiotics to inhibit bacterial growth.**

46. Brewster ME, Verreck G, Chun I, et al. The use of polymer-based electrospun nanofibers containing amorphous drug dispersions for the delivery of poorly water-soluble pharmaceuticals. Pharmazie 2004;59:387-91
47. Verreck G, Chun I, Rosenblatt J, et al. Incorporation of drugs in an amorphous state into electrospun nanofibers composed of a water-insoluble, nonbiodegradable polymer. J Control Release 2003;92:349-60
48. Kenawy el-R, Bowlin GL, Mansfield K, et al. Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend. J Control Release 2002;81:57-64

• **This manuscript represents the earliest study on the incorporation of an antibiotic into electrospun polymeric fibers.**

49. Xu X, Chen X, Ma P, et al. The release behavior of doxorubicin hydrochloride from medicated fibers prepared by emulsion-electrospinning. Eur J Pharm Biopharm 2008;70:165-70
50. Chunder A, Sarkar S, Yu Y, Zhai L. Fabrication of ultrathin polyelectrolyte fibers and their controlled release properties. Colloids Surf B Biointerfaces 2007;58:172-9
51. Cui W, Li X, Zhu X, et al. Investigation of drug release and matrix degradation of electrospun poly(DL-lactide) fibers with paracetamol inoculation. Biomacromolecules 2006;7:1623-9
52. Huang ZM, He CL, Yang A, et al. Encapsulating drugs in biodegradable ultrafine fibers through co-axial electrospinning. J Biomed Mater Res A 2006;77:169-79
53. Bolgen N, Vargel I, Korkusuz P, et al. In vivo performance of antibiotic embedded electrospun PCL membranes for prevention of abdominal adhesions. J Biomed Mater Res B Appl Biomater 2007;81:530-43
54. Xie J, Tan RS, Wang CH. Biodegradable microparticles and fiber fabrics for sustained delivery of cisplatin to treat C6 glioma in vitro J Biomed Mater Res A 2008;85:897-908
55. Xu X, Chen X, Xu X, et al. BCNU-loaded PEG-PLLA ultrafine fibers and their in vitro antitumor activity against Glioma C6 cells. J Control Release 2006;114:307-16

• **An excellent manuscript that clearly demonstrates the efficacy of drug-loaded electrospun scaffolds to fight glioma cells.**

56. Ranganath SH, Wang CH. Biodegradable microfiber implants delivering paclitaxel for post-surgical chemotherapy against malignant glioma. Biomaterials 2008;29:2996-3003

•• **This manuscript reports a combination of both *in vitro* and *in vivo* data on the efficacy of drug-loaded electrospun scaffolds to inhibit glioma tumors.**

57. Jiang H, Fang D, Hsiao B, et al. Preparation and characterization of ibuprofen-loaded poly(lactide-co-glycolide)/poly(ethylene glycol)-g-chitosan electrospun membranes. J Biomater Sci Polym Ed 2004;15:279-96
58. Hong Y, Fujimoto K, Hashizume R, et al. Generating elastic, biodegradable polyurethane/poly(lactide-co-glycolide) fibrous sheets with controlled antibiotic release via two-stream electrospinning. Biomacromolecules 2008;9:1200-7
59. Huang ZM, Zhang YZ, Kotaki M, Ramakrishna S. Areviewon polymer nanofibers by electrospinning and their applications in nanocomposites. Composites Sci Technol 2003;63:2223-53
60. Chiu J, Luu YK, Fang D, et al. Electrospun nanofibrous scaffolds for biomedical

applications. J Biomed Nanotech 2005;1:115-32

• **This review thoroughly examines the tissue engineering applications of electrospun scaffolds with regards to cell delivery, protein delivery and gene delivery.**

61. Liao IC, Chew SY, Leong KW. Aligned core-shell nanofibers delivering bioactive proteins. Nanomedicine 2006;1:465-71
62. Nie H, Soh BW, Fu YC, Wang CH. Three-dimensional fibrous PLGA/HAp composite scaffold for BMP-2 delivery. Biotechnol Bioeng 2008;99:223-34
63. Goldberg M, Langer R, Jia X. Nanostructured materials for applications in drug delivery and tissue engineering. J Biomater Sci Polym Ed 2007;18:241-68
64. Li C, Vepari C, Jin HJ, et al. Electrospun silk-BMP-2 scaffolds for bone tissue engineering. Biomaterials 2006;27:3115-24
65. Zeng J, Aigner A, Czubayko F, et al. Poly(vinyl alcohol) nanofibers by electrospinning as a protein delivery system and the retardation of enzyme release by additional polymer coatings. Biomacromolecules 2005;6:1484-8
66. Fu YC, Nie H, Ho ML, et al. Optimized bone regeneration based on sustained release from three-dimensional fibrous PLGA/HAp composite scaffolds loaded with BMP-2. Biotechnol Bioeng 2008;99:996-1006
67. Choi JS, Leong KW, Yoo HS. In vivo wound healing of diabetic ulcers using electrospun nanofibers immobilized with human epidermal growth factor (EGF). Biomaterials 2008;29:587-96
68. Chew SY, Wen J, Yim EK, Leong KW. Sustained release of proteins from electrospun biodegradable fibers. Biomacromolecules 2005;6:2017-24
69. Matthews JA, Boland ED, Wnek GE, et al. Electrospinning of collagen type II: a feasibility study. J Bioactive Compatible Polymers 2003;18:125-34
70. Matthews JA, Wnek GE, Simpson DG, Bowlin GL. Electrospinning of collagen nanofibers. Biomacromolecules 2002;3:232-8
71. Shields KJ, Beckman MJ, Bowlin GL, Wayne JS. Mechanical properties and cellular proliferation of electrospun collagen type II. Tissue Eng 2004;10:1510-7

• **This study was among the first to examine the mechanical properties of electrospun membranes and their potential uses in various hard and soft tissues.**

72. Rho KS, Jeong L, Lee G, et al. Electrospinning of collagen nanofibers: effects on the behavior of normal human keratinocytes and early-stage wound healing. Biomaterials 2006;27:1452-61
73. Li M, Mondrinos MJ, Gandhi MR, et al. Electrospun protein fibers as matrices for tissue engineering. Biomaterials 2005;26:5999-6008
74. Boland ED, Matthews JA, Pawlowski KJ, et al. Electrospinning collagen and elastin: preliminary vascular tissue engineering. Front Biosci 2004;9:1422-32
75. Buttafoco L, Kolkman NG, Engbers Buijtenhuijs P, et al. Electrospinning of collagen and elastin for tissue engineering applications. Biomaterials 2006;27:724-34
76. Sell SA, McClure MJ, Barnes CP, et al. Electrospun polydioxanone-elastin blends: potential for bioresorbable vascular grafts. Biomed Mater 2006;1:72-80
77. Lee SJ, Yoo JJ, Lim GJ, et al. In vitro evaluation of electrospun nanofiber scaffolds for vascular graft application. J Biomed Mater Res A 2007;83:999-1008
78. Thomas V, Zhang X, Catledge SA, Vohra YK. Functionally graded electrospun scaffolds with tunable mechanical properties for vascular tissue regeneration. Biomed Mater 2007;2:224-32
79. Stitzel J, Liu J, Lee SJ, et al. Controlled fabrication of a biological vascular substitute. Biomaterials 2006;27:1088-94
80. Heydarkhan Hagvall S, Schenke Layland K, Dhanasopon AP, et al. Three-dimensional electrospun ECM-based hybrid scaffolds for cardiovascular tissue engineering. Biomaterials 2008;29:2907-14
81. El Kurdi MS, Hong Y, Stankus JJ, et al. Transient elastic support for vein grafts using a constricting microfibrillar polymer wrap. Biomaterials 2008;29:3213-20
82. Noh HK, Lee SW, Kim JM, et al. Electrospinning of chitin nanofibers: degradation behavior and cellular response to normal human keratinocytes and fibroblasts. Biomaterials 2006;27:3934-44
83. Desai K, Kit K, Li J, Zivanovic S. Morphological and surface properties of electrospun chitosan nanofibers. Biomacromolecules 2008;9:1000-6
84. Zhang YZ, Su B, Ramakrishna S, Lim CT. Chitosan nanofibers from an easily electrospinnable UHMWPEO-doped chitosan solution system. Biomacromolecules 2008;9:136-41
85. Ignatova M, Starbova K, Markova N, et al. Electrospun nano-fibre mats with antibacterial properties from quaternised chitosan and poly(vinyl alcohol). Carbohydr Res 2006;341:2098-107
86. Mohammadi Y, Soleimani M, Fallahi Sichani M, et al. Nanofibrous poly(epsilon-caprolactone)/poly(vinyl alcohol)/chitosan hybrid scaffolds for bone tissue engineering using mesenchymal stem cells. Int J Artif Organs 2007;30:204-11
87. Ye P, Xu ZK, Wu J, Innocent C, Seta P. Nanofibrous poly(acrylonitrile-co-maleic acid) membranes functionalized with gelatin and chitosan for lipase immobilization. Biomaterials 2006;27:4169-76
88. Park K, Ju YM, Son JS, et al. Surface modification of biodegradable electrospun nanofiber scaffolds and their interaction with fibroblasts. J Biomater Sci Polym Ed 2007;18:369-82
89. Luu YK, Kim K, Hsiao BS, et al. Development of a nanostructured DNA delivery scaffold via electrospinning of PLGA and PLA-PEG block copolymers. J Control Release 2003;89:341-53

•• **This manuscript represents the first study to report on the incorporation, release and bioactivity of DNA from electrospun scaffolds.**

90. Nie H, Wang CH. Fabrication and characterization of PLGA/HAp composite scaffolds for delivery of BMP-2 plasmid DNA. J Control Release 2007;120;111-21
91. Liang D, Luu YK, Kim K, et al. In vitro non-viral gene delivery with nanofibrous scaffolds. Nucleic Acids Res 2005;33:170
92. Maretschek S, Greiner A, Kissel T. Electrospun biodegradable nanofiber nonwovens for controlled release of proteins. J Control Release 2008;127:180-7
93. Yang Y, Li X, Qi M, et al. Release pattern and structural integrity of lysozyme encapsulated in core-sheath structured poly(dl-lactide) ultrafine fibers prepared by emulsion electrospinning. Eur J Pharm Biopharm 2008;69:106-16
94. Yang Y, Li X, Cui W, et al. Structural stability and release profiles of proteins from core-shell poly (DL-lactide) ultrafine fibers prepared by emulsion electrospinning. J Biomed Mater Res A [Epub 2007 Oct 29]
95. Qi H, Hu P, Xu J, Wang A. Encapsulation of drug reservoirs in fibers by emulsion electrospinning: morphology characterization

and preliminary release assessment. Biomacromolecules 2006;7:2327-30

96. Arumuganathar S, Jayasinghe SN. A novel direct fibre generation technique for preparing functionalized and compound scaffolds and membranes for applications within the life sciences. Biomed Mater 2007;2:189-95

97. He CL, Huang ZM, Han XJ. Fabrication of drug-loaded electrospun aligned fibrous threads for suture applications. J Biomed Mater Res A [Epub 2008 Apr 21]

98. Kim GH, Min T, Park SA, Kim WD. Coaxially electrospun micro/nanofibrous poly(epsilon-caprolactone)/eggshell-protein scaffold. Bioinspir Biomim 2008;3:16006

99. Li S, Sun B, Li X, Yuan X. Characterization of electrospun core/shell poly(vinyl pyrrolidone)/poly(L-lactide-co-epsilon-caprolactone) fibrous membranes and their cytocompatibility in vitro. J Biomater Sci Polym Ed 2008;19:245-58

100. Li XH, Shao CL, Liu YC. A simple method for controllable preparation of polymer nanotubes via a single capillary electrospinning. Langmuir 2007;23:10920-3

101. Zhao P, Jiang H, Pan H, et al. Biodegradable fibrous scaffolds composed of gelatin coated poly(epsilon-caprolactone) prepared by coaxial electrospinning. J Biomed Mater Res A 2007;83:372-82

102. Ma M, Krikorian V, Yu JH, et al. Electrospun polymer nanofibers with internal periodic structure obtained by microphase separation of cylindrically confined block copolymers. Nano Lett 2006;6:2969-72

103. McCann JT, Marquez M, Xia Y. Melt coaxial electrospinning: a versatile method for the encapsulation of solid materials and fabrication of phase change nanofibers. Nano Lett 2006;6;2868-72

104. Dong H, Jones WE JR. Preparation of submicron polypyrrole/poly(methyl methacrylate) coaxial fibers and conversion to polypyrrole tubes and carbon tubes. Langmuir 2006;22;11384-87

105. Zhang YZ, Wang X, Feng Y, et al. Coaxial electrospinning of (fluorescein isothiocyanate-conjugated bovine serum albumin)-encapsulated poly(epsilon-caprolactone) nanofibers for sustained release. Biomacromolecules 2006;7:1049-57

106. Jiang H, Hu Y, Zhao P, et al. Modulation of protein release from biodegradable core-shell structured fibers prepared by coaxial electrospinning. J Biomed Mater Res B Appl Biomater 2006;79:50-7

107. Liang D, Hsiao BS, Chu B. Functional electrospun nanofibrous scaffolds for biomedical applications. Adv Drug Deliv Rev 2007;59:1392-412

• **This review thoroughly examines the fundamental principles of electrospinning and addresses more basic issues regarding the polymer chemistry and physical chemistry regarding electrospinning.**

108. Park KE, Kang HK, Lee SJ, et al. Biomimetic nanofibrous scaffolds: preparation and characterization of PGA/chitin blend nanofibers. Biomacromolecules 2006;7:635-43

109. Kim K, Yu M, Zong X, et al. Control of degradation rate and hydrophilicity in electrospun non-woven poly(D,L-lactide) nanofiber scaffolds for biomedical applications. Biomaterials 2003;24:4977-85

110. Cui W, Li X, Zhou S, Weng J. In situ growth of hydroxyapatite within electrospun poly(DL-lactide) fibers. J Biomed Mater Res A 2007;82:831-41

111. Corey JM, Gertz CC, Wang BS, et al. The design of electrospun PLLA nanofiber scaffolds compatible with serum-free growth of primary motor and sensory neurons. Acta Biomater 2008;4:863-75

112. Inanc B, Arslan YE, Seker S, et al. Periodontal ligament cellular structures engineered with electrospun poly(DL-lactide-co-glycolide) nanofibrous membrane scaffolds. J Biomed Mater Res A [Epub 2008 May 19]

113. Zhao L, He C, Gao Y, et al. Preparation and cytocompatibility of PLGA scaffolds with controllable fiber morphology and diameter using electrospinning method. J Biomed Mater Res B Appl Biomater [Epub 2008 Apr 2]

114. Pan H, Jiang H, Chen W. The biodegradability of electrospun Dextran/PLGA scaffold in a fibroblast/macrophage co-culture. Biomaterials 2008;29:1583-92

115. Kim TG, Lee DS, Park TG. Controlled protein release from electrospun biodegradable fiber mesh composed of poly(epsilon-caprolactone) and poly(ethylene oxide). Int J Pharm 2007;338:276-83

116. Bashur CA, Dahlgren LA, Goldstein AS. Effect of fiber diameter and orientation on fibroblast morphology and proliferation on electrospun poly(D,L-lactic-co-glycolic acid) meshes. Biomaterials 2006;27:5681-8

117. Kim GH. Electrospun PCL nanofibers with anisotropic mechanical properties as a biomedical scaffold. Biomed Mater 2008;3(2):25010. Epub ahead of print

118. Zhao P, Jiang H, Pan H, et al. Biodegradable fibrous scaffolds composed of gelatin coated poly(epsilon-caprolactone) prepared by coaxial electrospinning. J Biomed Mater Res A 2007;83:372-82

119. Dalton PD, Lleixa Calvet J, Mourran A, et al. Melt electrospinning of poly-(ethylene glycol-block-epsilon-caprolactone). Biotechnol J 2006;1:998-1006

120. Zhang YZ, Wang X, Feng Y, et al. Coaxial electrospinning of (fluorescein isothiocyanate-conjugated bovine serum albumin)-encapsulated poly(epsilon-caprolactone) nanofibers for sustained release. Biomacromolecules 2006;7:1049-57

121. Bolgen N, Menceloglu YZ, Acatay K, et al. In vitro and in vivo degradation of non-woven materials made of poly(epsilon-caprolactone) nanofibers prepared by electrospinning under different conditions. J Biomater Sci Polym Ed 2005;16:1537-55

122. Jiang H, Hu Y, Li Y, et al. A facile technique to prepare biodegradable coaxial electrospun nanofibers for controlled release of bioactive agents. J Control Release 2005;108:237-43

123. Dong C, Yuan X, He M, Yao K. Preparation of PVA/PEI ultra-fine fibers and their composite membrane with PLA by electrospinning. J Biomater Sci Polym Ed 2006;17:631-43

124. Chuangchote S, Supaphol P. Fabrication of aligned poly (vinyl alcohol) nanofibers by electrospinning. J Nanosci Nanotechnol 2006;6:125-9

125. Zeng J, Aigner A, Czubayko F, et al. Poly(vinyl alcohol) nanofibers by electrospinning as a protein delivery system and the retardation of enzyme release by additional polymer coatings. Biomacromolecules 2005;6:1484-8

126. Kidoaki S, Kwon IK, Matsuda T. Structural features and mechanical properties of in situ-bonded meshes of segmented polyurethane electrospun

from mixed solvents. J Biomed Mater Res B Appl Biomater 2006;76:219-29

127. Hong Y, Fujimoto K, Hashizume R, et al. Generating elastic, biodegradable polyurethane/poly(lactide-co-glycolide) fibrous sheets with controlled antibiotic release via two-stream electrospinning. Biomacromolecules 2008;9:1200-7

128. Spasova M, Paneva D, Manolova N, et al. Electrospun chitosan-coated fibers of poly(L-lactide) and poly(L-lactide)/poly(ethylene glycol): preparation and characterization. Macromol Biosci 2008;8:153-62

129. Duan B, Dong C, Yuan X, Yao K. Electrospinning of chitosan solutions in acetic acid with poly(ethylene oxide). J Biomater Sci Polym Ed 2004;15:797-811

130. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating health care-associated infections and deaths in US hospitals, 2002. Public Health Rep 2007;22:160-6

131. Weinstein RA. Nosocomial infection update. Emerg Infect Dis 1998;4:416-20

132. Menzies D. Postoperative adhesions: their treatment and relevance in clinical practise. Ann R Coll Surg Engl 1993;75:147-53

133. Menzies D. Peritoneal adhesions: incidence, cause and prevention. Surg Annu 1992;24:27-45

134. Di Zerega GS. Contemporary adhesion prevention. Fertil Steril 1994;61:219-35

135. Pijlman BM, Dorr PJ, Brommer EJP, Vemer HM. Prevention of adhesions. Eur J Obstet Gynecol Reprod Biol 1994;53:155-63

136. Bakkum EA, Trimbos JB, Trimbos Kemper TCM. Postsurgical adhesion formation and prevention – recent developments. Reprod Med Rev 1996;5:1-13

137. Srikar R, Yarin AL, Megaridis CM, et al. Desorption-limited mechanism of release from polymer nanofibers. Langmuir 2008;24:965-74

• **This study closely examines the incorporation and kinetics of release as well as defining the mechanism.**

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