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Nanoparticles and nanofibers for topical drug delivery

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Abstract

This review provides the first comprehensive overview of the use of both *nanoparticles* and *nanofibers* for topical drug delivery. Researchers have explored the use of nanotechnology, specifically nanoparticles and nanofibers, as drug delivery systems for topical and transdermal applications. This approach employs increased drug concentration in the carrier, in order to increase drug flux into and through the skin. Both nanoparticles and nanofibers can be used to deliver hydrophobic and hydrophilic drugs and are capable of controlled release for a prolonged period of time. The examples presented provide significant evidence that this area of research has —and will continue to have — a profound impact on both clinical outcomes and the development of new products.

Keywords

Nanoparticles; Electrospun fiber mats; Nanofibers; Skin; Topical; Drug delivery

1. Introduction

1.1. Skin structure

The skin is the largest organ of the human body and performs several critical functions: It protects the body from the external environment, serving as both a first line of defense against the entry of chemicals and microorganisms as well as providing a barrier to the loss of fluids and salts and helps regulate body temperature. Human skin can vary widely in structure and thickness, but is usually about 1.5 mm thick and consists of three layers (Fig. 1) [1]: (i) The epidermis consists of the stratum corneum and the viable epidermis. The stratum corneum (SC) is the outermost layer of the skin. It is largely responsible for the barrier function of the skin and the poor absorption of drugs. It is comprised of a 10–20 μm thick matrix of dehydrated and dead corneocytes (terminally differentiated keratinocytes) that are embedded in highly ordered lipid layers [2]. The viable epidermis (usually about 0.06–0.8 mm thick) is immediately under the SC and represents the first layer of living cells. It consists of about 4–5 layers of dermal fibroblasts and keratinocytes. (ii) Below the

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Conflict of interest

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epidermis is the dermis, usually a 0.3–5 mm thick layer that contains connective tissue, sweat glands, hair follicles, and a network of capillaries, lymphatic vessels and nerve endings. (iii) The deepest layer of the skin is the subcutaneous tissue or hypodermis, which is composed of loose, white, fibrous connective tissue in which fat provides cushioning [3].

1.2. Drug delivery and the skin

The large surface area of the skin (nearly 20 square feet) makes it a potentially interesting route for drug delivery. *Topical* drug delivery is primarily intended for a *local* effect, where it can (i) potentially eliminate the need for systemically administered drug therapies, (ii) minimize the total dose required to reach the targeted site (skin), and (iii) reduce off-target adverse effects. Some examples of topical dermatologic products include cutaneous anti-fungal treatments, sunscreens, keratolytic agents, local anesthetics, antiseptics and anti-inflammatory agents for skin diseases such as psoriasis. *Transdermal* drug delivery, on the other hand, is intended for a *systemic* drug effect with the skin merely being the drug's entry portal into the body. For example, transdermal patches are used to deliver nicotine for smoking cessation, buprenorphine and fentanyl for chronic pain, and hyoscine (also known as scopolamine) for motion sickness.

In both topical and transdermal drug delivery, drug permeation through the SC is regulated by Fick's second law [4]:

$$J=\frac{DCP}{L} \quad (1)$$

where J is the flux, D is the diffusion coefficient of the drug, C is the drug concentration in the carrier, P is the drug partition coefficient, and L is the thickness of the SC. Beyond the SC, the applied drug must penetrate the various layers of the skin, encountering both lipophilic and hydrophilic domains as it travels toward the dermis. Human skin equivalents with lipid and permeability profiles closer to human skin have been developed as alternatives to human cadaver and animal skin to characterize in vitro drug permeation [5]. Depending on the drug's properties and the method of delivery, the drug may remain local or traverse into the dermis, where, if hydrophilic, it may be rapidly absorbed into the circulation via capillaries. The capillary bed extends into the upper layers of the dermis right underneath the dermato-epidermal junction.

In general, small molecules (both lipophilic and hydrophilic) can penetrate the SC without assistance or traverse the epidermis through shunt pathways created by sweat glands and hair shafts. In contrast, the delivery of larger molecules, such as peptides, proteins, siRNA, or DNA, through the skin continues to be a major research challenge. Therefore, the scientific community has been studying ways to facilitate and enhance the penetration of a wide range of drugs through the SC (for topical delivery) or to assist drug molecules to traverse into the dermis (for transdermal delivery). Some of these strategies are briefly described below.

Chemical enhancers, such as fatty acids, surfactants, esters, alcohols, polyalcohols, pyrrolidones, amines, amides, sulfoxides, terpenes, alkanes and phospholipids [3,6], can be

used to enhance topical drug penetration by: (i) perturbing the highly ordered structure of the SC; (ii) solubilizing and extracting the keratin and/or lipid components of the SC; (iii) fluidizing the crystalline structure and dissolving the lipids of the SC; or (iv) improving the partitioning of a drug, co-enhancer or solvent into the SC [3,6,7]. Unfortunately, chemical penetration enhancers tend to be skin irritants, due to their disruptive effect on the lipid structures of the skin. Usually, the amount of enhancer required to achieve pharmacologically effective drug penetration rates is higher than the concentration tolerated by skin [6]. For this reason, the utility of chemical penetration enhances has so far been limited.

Physical enhancers use physical methods to temporarily compromise the integrity of the skin's barrier function, such as hydrating the skin via occlusion, sonophoresis, laser and or thermal ablation, electroporation, radiofrequency treatment, iontophoresis, magnetophoresis, high pressure jets, and microneedle arrays [6,8]. Although some of these technologies have been translated into FDA-approved products for topical and transdermal drug delivery, physical enhancers are invasive, may cause longer-term damage to the skin's barrier properties, and may produce tingling, irritation and burning sensations [9].

As an alternative, researchers have explored the use of nanotechnology, specifically *nanoparticles* and *nanofibers*, as drug delivery systems for topical and transdermal applications. This approach increases the drug concentration in the vehicle or formulation (C_V), and as a result, increases drug flux (see eq. (1)). Both nanoparticles and nanofibers can be used to deliver hydrophobic and hydrophilic drugs and are capable of controlled release for a prolonged period of time. In this review, we provide an overview of nanoparticles and nanofibers that have been developed for *topical* drug delivery applications. While nanoparticle and nanofibers drug delivery systems have been reviewed before separately [10–12], as far as the authors are aware this is the first comprehensive review that combines nanofiber and nanoparticle systems. Together, these systems have significantly impacted the treatment of many prevalent dermatologic conditions and have collectively generated substantial commercial revenues [8]. The examples of nanoparticles and nanofibers presented herein as topical or transdermal drug delivery systems, provide significant evidence that this area of research has — and will continue to have — a profound impact on both clinical outcomes and the commercialization of these technologies.

2. Nanoparticles for topical therapy

Nanoparticles (also sometimes referred to as nanocarriers) have been investigated for various biomedical applications for over a decade. In general, the use of nano-sized particles offers several advantages over other drug delivery systems. They are used to (i) enhance the solubility of highly hydrophobic drugs; (ii) provide sustained and controlled release of encapsulated drugs; (iii) increase the stability of therapeutic agents by chemical or physical means; (iv) deliver higher concentrations of drugs to target areas due to an *Enhanced Permeation and Retention* (EPR) effect; and (v) provide targeted treatments when modified with cell-specific ligands. Drug-loaded nanoparticles often accumulate in hair follicles and thereby facilitate the penetration of drug molecules through the superficial layers of the SC, followed by drug release into the deeper layers of the skin. The most commonly used

nanoparticles for topical and/or transdermal drug delivery are polymeric nanoparticles, nano-emulsions, lipid-based nanoparticles (liposomes and solid-lipid nanoparticles), metal nanoparticles and dendrimers. The following section discusses the different types of nanoparticles and their potential uses in various topical therapeutic applications (see Table 1 for a summary).

2.1. Natural polymeric nanoparticles

Although a wide range of natural polymers have been used to prepare nanoparticles, chitosan-based nanoparticles have been the most extensively studied for *topical* drug delivery applications [13]. In addition, a few publications report on the use of alginic acid and albumin-derived nanoparticles for topical drug delivery, which are also briefly described in this section. *Chitosan* is a linear polysaccharide derived from chitin, which is found in the exoskeleton of crustaceans. The amino group of chitosan readily undergoes protonation in acidic to neutral conditions, resulting in a net positive charge. This makes chitosan water-soluble and act as a bioadhesive, since the positively-charged chitosan can bind to negatively-charged mucoproteins. This interaction helps prolong the circulation time of chitosan-bound drugs, leading to enhanced drug bioavailability [14]. Chitosan nanoparticles can be prepared using (i) ionic cross-linking, (ii) covalent cross-linking [15], (iii) precipitation [16], (iv) polymerization [17], or (v) self-assembly methods [18], with sizes ranging from 20 to 800 nm dependent on the method of preparation. Chitosan-drug complexes are generally formed via electrostatic interactions between cationic chitosan and anionic drugs [19,20]. For example, Cheng et al. [19] prepared chitosan nanoparticles linked with antisense oligonucleotide to produce particles with a size of 102.6 ± 12.0 nm, zeta potential of 1.45 ± 1.75 mV, and an encapsulation efficiency of 87.6 ± 3.5%. Kim et al. [20] increased the solubility of retinol by more than 1600-fold by encapsulating it into chitosan nanoparticles. Drug delivery via chitosan nanoparticles can be controlled by the degradation of the polymer, which can be tuned by varying the molecular weight and degree of deacetylation of chitosan. As a result, chitosan nanoparticles have been shown to provide sustained release from days to months [21]. In addition, chitosan nanoparticles can be formulated as pulsatile delivery vehicles, where release of the payload is dependent on the physiological needs of the patient; for example, the release of insulin from glucose-sensitive gels in response to varied glucose concentrations has been demonstrated in vitro [22].

Alginate is an anionic polysaccharide derived from algae. Although alginate-derived nanoparticles are not extensively studied as topical drug delivery vehicles, two reports have been recently published in the literature. Ibrahim et al. prepared brimonidine-loaded alginate nanoparticles and showed that they provide a sustained release without an initial burst in vitro and provided an improvement on the intraocular pressure lowering effects when compared to marketed brimonidine tartrate eye drops in vivo [23]. Friedman et al. explored the use of nanoparticles synthesized from chitosan and alginate for the delivery of antimicrobial agents against *Propionibacterium acnes* for the topical treatment of acne and showed superior antimicrobial activity as compared to benzoyl peroxide alone in vitro [24].

Albumin is a non-toxic, biocompatible and biodegradable carrier protein used in drug delivery. Albumin nanoparticles have gained considerable attention as drug delivery vehicles

due to their high binding capacity. Despite this, it is our finding that there is only one report in the literature on the use of albumin nanoparticles for topical drug delivery. Das et al. showed that aspirin-loaded albumin nanoparticles provide prolonged release in vitro for 72 h and hold promise as a topical treatment for diabetic retinopathy [25].

2.2. Synthetic polymeric nanoparticles

Natural polymers sometimes lack batch-to-batch consistency, making it difficult to prepare particles with reproducible characteristics and drug delivery profiles [26]. On the other hand, synthetic polymers can be supplied with high purity and batch-to-batch reproducibility, for preparing nanoparticles with more consistent drug release profiles. Synthetic polymeric nanoparticles are predominantly used to deliver lipophilic, small molecule drugs [26]. Since volatile organic solvents are often used during the preparation of synthetic polymeric nanoparticles, it is challenging to maintain the biological activity of peptides and proteins during the nanoparticle manufacturing process. Tyrosine-derived polymers, aliphatic polyesters, and poly (ε-caprolactone) are examples of biodegradable synthetic polymers that have been extensively explored as nanoparticle drug delivery vehicles for topical applications. These have been described in the following sections.

2.2.1. Tyrosine-derived polymeric nanospheres (TyroSpheres)—Tyrosine-derived polymeric nanospheres (abbreviated TyroSpheres) are synthesized from a family of fully-degradable, ABA-type triblock co-polymers made of poly(ethylene glycol), oligomers of desaminotyrosyltyrosine alkyl esters, and several different, naturally occurring dicarboxylic acids such as succinic acid, adipic acid, suberic acid, or sebacic acid [27]. These tyrosine-derived copolymers spontaneously self-assemble in aqueous media to form nanospheres with a hydrodynamic diameter of approximately 70 nm [27]. These nanospheres form strong complexes with hydrophobic molecules, as demonstrated using the model compound DAF, and clinically used antitumor agent paclitaxel, a powerful chemotherapeutic drug [28]. In contrast, TyroSpheres do not strongly associate with hydrophilic compounds such as fluorescein [29,30]. Batheja et al. demonstrated that a gel formulation of TyroSpheres loaded with Nile red (a hydrophobic model drug) significantly enhanced skin permeation (1.4–1.8 fold) compared to an aqueous dispersion of Nile red-loaded TyroSpheres, both in vitro and in vivo [31]. As these TyroSpheres are suitable only for hydrophobic drugs, they have been extensively studied for the binding and delivery of various therapeutic agents that are hydrophobic and water-insoluble, for example curcumin (unpublished data), cyclosporine A [32], sildenafil [33], rolipram [34] and paclitaxel [30,35,36]. Moreover, these nanospheres are stable for about 6 months, after which time they degrade, most likely through hydrolysis of their ester bonds [28]. Drug release from TyroSpheres is dependent on the properties of the drug, the binding and loading efficiencies, and the pH of the solution [37]. For example, Goyal et al. showed that the release of cyclosporine A was inversely proportional to the amount of drug loaded in the TyroSpheres [32].

In vitro cytotoxicity assays in serum-free media showed no significant decrease in cell metabolic activity at concentrations up to 2 mg/mL, demonstrating that empty TyroSpheres are non-cytotoxic [27]. Further studies have also shown that TyroSpheres can deliver agents into the skin [29,31] and have no detrimental effects on the skin's morphology [31].

Paclitaxel-loaded TyroSpheres have been shown to effectively deliver paclitaxel to tumor cells as determined using an in vitro cell killing assay [37]. In addition, *in vivo* studies were performed to compare the toxicity and anti-tumor efficacy of paclitaxel administered intravenously using TyroSpheres or commercially available Cremophor® EL in two breast cancer murine xenograft models [30]. It was shown that animals treated with paclitaxel-loaded Cremophor® EL lost significant weight and failed to recover following treatment, whereas those treated with paclitaxel-loaded TyroSpheres gained weight normally. Moreover, the anti-tumor efficacy of the two treatments was the same. In addition, a larger volume of distribution and longer half-life were measured for animals treated with paclitaxel-loaded TyroSpheres. These data suggest that TyroSpheres could be used as a more effective delivery vehicle for paclitaxel with fewer side effects for the treatment of breast tumors. Moreover, through modification of the triblock copolymer, ligands could be covalently attached to the TyroSpheres that could target drug-loaded TyroSpheres to specific recipient cells, thereby reducing unwanted side effects to non-targeted cells [35].

TyroSpheres also offer versatility in their storage and handling properties since they can be prepared as a liquid formulation [29], dry formulation [33,34] or incorporated into a gel to prevent runoff when used topically [31]. Tyrosine-derived nanospheres offer a promising tool for the topical skin delivery of lipophilic drugs and personal care agents — as may be desired in the treatment of dermatological conditions such as skin cancer, psoriasis, eczema, microbial infection, sunscreens and cosmetics.

2.2.2. Poly (lactic-co-glycolic acid) nanoparticles—Poly (lactic-co-glycolic acid) (PLGA) has been extensively studied in topical drug delivery applications because it is biocompatible, biodegradable, widely used in medical devices and pharmaceutical formulations approved by the FDA, commercially available with different molecular weights and copolymer ratios, able to encapsulate a wide range of drugs from hydrophobic to lipophilic, and capable of surface modification for site-specific drug delivery. Furthermore, PLGA can be formulated as nanoparticles using several different methods, such as solvent displacement, solvent diffusion, emulsification–evaporation, and phase-inversion; with sizes ranging from 10 to 1000 nm. PLGA nanoparticles have been incorporated into gels using hydroxypropyl methylcellulose (HPMC) or Carbopol® to further enhance the penetration of drugs [38] into the deeper layers of the skin by increasing contact time with the skin and reducing the loss of water from the skin.

2.2.3. Poly(ε-caprolactone) nanoparticles—Poly(ε-caprolactone) (PCL) is another synthetic polymer that is widely employed for the preparation of nanoparticle formulations due to its biocompatibility, biodegradability and favorable rheological properties, including a low glass transition temperature. The degradation of PCL is slower than other polyesters due to its semi-crystalline structure (erosion rates: poly(glycolic acid) > PLGA > poly(L-lactic acid) > PCL) [39]. As a result, PCL is often modified [40] to change its biodegradability to meet specifications of the targeted clinical application (see review by Abedalwafa et al. [41]).

2.3. Lipid-based nanoparticles

2.3.1. Solid-lipid nanoparticles (SLNs)—SLNs are made of solid lipids with an average diameter between 50 and 1,000 nm [42] and prepared using three main components: lipid(s), surfactant(s), and water. The type of lipids used to prepare SLN is very broad, including triglycerides (e.g., tristearin), partial glycerides, fatty acids (e.g., stearic acid), steroids (e.g., cholesterol) and waxes (e.g., cetyl palmitate) [43]. Surfactants are typically required to stabilize the lipid dispersion. SLNs were developed in the early 1990s and are still considered promising drug carrier systems, especially for applications that require sustained release. SLNs can be prepared without organic solvents. In addition, they are biodegradable, biocompatible, physicochemically stable, have low toxicity, and can be produced at large industrial scales at relatively low cost. Jeon et al. prepared surface-modified SLNs containing retinyl palmitate and showed that these negatively-charged SLNs enhanced the cutaneous distribution of retinyl palmitate 4.8-fold as compared to neutral SLNs [44].

2.3.2. Liposomes—Liposomes are spherical vesicles made of lipids, the major component of the cell membrane. Liposomes have at least one bilayered lipid membrane and can be loaded with drugs. The average diameter of liposomes varies from 50 to 300 nm [45]. To date, about 600 clinical trials have involved lipid-derived drug delivery systems [46]. Overall, lipids reduce the interaction of drugs with serum proteins and thereby increase the circulation time of drugs in the body, preventing rapid clearance and providing drug delivery to the targeted site [45]. Liposomes can be prepared using: (i) thin film hydration [47], (ii) reverse-phase evaporation [48], (iii) solvent injection [49], (iv) detergent depletion [50], (v) supercritical fluid [51], (vi) size reduction sonication [52], (vii) high-pressure homogenization [52], and (viii) low-pressure extrusion [53]. Liposomes are able to provide sustained [54] and triggered [55] release of their payload, however the correlation between in vitro and in vivo release kinetics has been poor [56].

2.4. Metallic and silica nanoparticles

A variety of metallic nanoparticles have captured much attention due to their effective application to various areas of science and technology. One example is *silver nanoparticles* (AgNPs), which have been shown to have antiseptic and antimicrobial activity against gram-positive and gram-negative bacteria [57]. AgNPs (ranging in size from ~1–100 nm) can be prepared using a variety of methods: (i) chemical synthesis, (ii) physical dispersion, (iii) photochemical synthesis, and (iv) biological synthesis [58]. Recently, Zhang et al. reported on three multistep methods used to prepare silver nanostructures with well-controlled shapes: (i) double reductant method, (ii) etching technique, and (iii) construction of core-shell nanostructures [59]. These nanoparticles had excellent optical properties. Another example is *gold nanoparticles* (AuNPs), which exhibit a unique combination of physical, chemical, optical, and electronic properties for drug delivery. They are easy to prepare in a range of sizes (1–150 nm), are biocompatible, and can be conjugated to other molecules. AuNPs of ~5 nm diameter have been reported to diffuse though the SC of intact mouse skin [60]. Other examples are the use of metallic nanoparticles, such as *titanium dioxide* (TiO_2) *and zinc oxide* (*ZnO*) *nanoparticles*, in cosmetics and sunscreens for ultraviolet radiation protection [61]. Recently, cerium oxide nanoparticles have also gained attention in wound

healing applications [62]. The sizes of the metallic nanoparticles can be optimized to be large enough to reflect and refract the high energy, very short wavelengths of ultraviolet A and B (~290–400 nm), while being too small to reflect the lower energy, longer wavelengths of visible light (~400–700 nm). In this way they can remain invisible on the skin [63].

2.5. Dendrimers

Dendrimers are a class of highly branched, monodispersed, synthetic macromolecules with a well-defined composition and structure. The most commonly referenced dendrimers used in nanomedicine are polyamidoamines (PAMAM), poly(L-lysine) (PLL) scaffold dendrimers, polyesters (PGLSA-OH), polypropylimines (PPI), poly(2,2-bis (hydroxymethyl)propionic acid) scaffold dendrimers (bis-MPA), and aminobis (methylenephosphonic acid) scaffold dendrimers. Dendrimer-based NPs have been widely studied because of the scientific and technological interest relating to their possible applications in a broad range of areas, such as catalysis, optics, electronics, and biomedical applications [64]. The tunable surface chemistry of dendrimers allows their assembly onto various nanoparticles [65]. For example, magnetic iron oxide nanoparticles have been stabilized using dendrimers [65]. Dendrimer nanoparticles are usually smaller than 5 nm and can be prepared using fast reduction and nucleation chemistry [66]. Perumal et al. [67] showed that dendrimers could be used to enhance the skin permeation of hydrophilic drugs. Dendrimer size, molecular weight, surface charge and hydrophobicity are key parameters guiding topical drug delivery and skin permeation [68].

3. Topical applications of nanoparticles

3.1. Acne

Acne vulgaris is the most common skin disease. It is associated with an elevated rate of sebum secretion, which manifests as mild-severe inflammatory lesions on areas of the body containing large numbers of sebaceous follicles such as the face, back and chest [69]. Acne is classified as mild, moderate, or severe based on the number and type of lesions. Treatment options vary with the stage and intensity of the disease. In general, topical treatment is preferred for mild and moderate acne, whereas systemic therapy is used to treat severe cases [70]. Topical therapy includes the use of antibiotics, retinoids (vitamin A), and combinations thereof. The retinoids often irritate the skin, and can cause dryness, peeling/exfoliation and photosensitivity with resultant hyperpigmentation. The alternative treatment (prolonged use of antibiotics) can lead to bacterial resistance. Because of these complications, nanoparticles are being developed to provide gradual and sustained delivery of these drug(s) into the skin. Comparable or increased effectiveness with concomitantly reduced topical side effects are the key criteria used to evaluate the utility of nanoparticulate formulations of acne drugs [71]. Table 1 lists the drugs used to treat acne by topical application of nanoparticle systems. These new formulations have been shown to provide efficacy, tolerability, compliance, and cosmetic acceptability [72,73].

3.2. Infection

The rate at which infectious diseases and drug-resistant pathogens are emerging is a matter of serious concern. Despite increased knowledge of microbial pathogenesis and a wide

repertoire of antimicrobial therapies, the morbidity and mortality resulting from microbial infections remains high. Therefore, there is a clinical need for novel strategies and new antimicrobial agents to treat infections.

A recent review has reported on the use of nanoparticle systems as antimicrobial and antinfective agents [74]. For example, AgNPs have been studied as antimicrobials, where it has been shown that AgNPs with diameters less than 20 nm can attach to sulfur-containing proteins of bacterial cell membranes. This increases the permeability of the bacterial membrane, causing death to the bacteria [75]. The antibacterial properties are related to the total surface area of the nanoparticles, where smaller particles with larger surface-to-volume ratios have greater antibacterial activity [76]. It has been demonstrated that composites of AgNPs and polymer gels have increased bactericidal activity compared to higher concentrations of AgNPs alone [77].

AuNPs have been used to coat a wide variety of surfaces, such as implants, wound dressings, and glass surfaces for maintaining antimicrobial surfaces [78]. AuNPs have optical absorption in the near-infrared region and can destroy bacteria via photothermal heating [79]. AuNPs generate holes in the cell wall, resulting in the leakage of cell contents and cell death. It is also possible that AuNPs bind to the DNA of bacteria and inhibit the uncoiling and transcription of DNA [80]. Stable conjugates of AuNPs coated with antibiotics have demonstrated bactericidal activity against both Gram-positive and Gram-negative bacteria [81].

Other metal oxide nanoparticles have also been studied for antibacterial activity. For example, halogen-treated *magnesium oxide* (*MgO*) *nanoparticles* have demonstrated antimicrobial activity against bacteria and spores [82]. *Copper oxide* (*CuO*) *nanoparticles* have a high antimicrobial activity against *Bacillus subtilis* [83]. This has been attributed to the greater abundance of amines and carboxyl groups on the cell surface of *B. subtilis* for which Cu has a high affinity. Cu ions may also interact with DNA molecules, intercalate with nucleic acid strands, and/or disrupt biochemical processes [83,84]. *Titanium dioxide* (*TiO_2*) *nanoparticles* have also been explored to fight infection. It has been suggested that UV irradiated nanostructured TiO_2 surfaces can be used as effective disinfectants, eliminating pathogenic microorganisms on food-contacting surfaces [85]. The major disadvantage of using TiO_2 in this way is that UV light is required to activate the photocatalyst, which initiates the killing of bacteria and viruses. *Zinc oxide* (*ZnO*) *nanoparticles* have been shown to generate hydrogen peroxide (H_2O_2) from surfaces and thereby inhibit bacterial growth. It is presumed that by decreasing the particle size, the number of ZnO powder particles per unit volume of powder slurry increases, resulting in an increased surface area with an increased capacity for the generation of H_{2O2}. Another possible mechanism is that released Zn^{2+} ions can directly damage the cell membrane and interact with intracellular contents [86]. Table 1 lists metal-based nanoparticles that have been explored to treat infection.

3.3. Skin cancer

Skin cancer is the most common form of malignancy, although it is not the deadliest [87]. The most common forms of skin cancer are basal cell carcinoma (~2.8 million U.S. cases

annually [88]), and squamous cell carcinoma (~700,000 U.S. cases annually [89]). Malignant melanoma, on the other hand, represents only a very small proportion of skin cancers (~74,000 U.S. cases annually [90]), but accounts for the vast majority of skin cancer deaths. Excision is the current standard treatment for localized skin cancers, and in the case of melanoma this can involve extensive surgeries with deep dissections and wide margins, often requiring soft tissue reconstruction. Furthermore, skin cancers may metastasize to regional lymph nodes and distant sites (particularly in the case of melanoma, and sometimes with squamous cell carcinoma) [91]. Nanoparticles may provide targeted and effective chemotherapeutic delivery to these sites, improving treatment efficacy. Treatments for metastatic malignant melanoma have recently incorporated nanoparticular formulations of cytostatic compounds, as reviewed in 2014 by Berciano-Guerrero et al. [92]. Liposomes, SLNs, polymeric nanospheres and dendrimers are all nanoparticles that have been explored as topical delivery systems for treating skin cancer. Iwamoto et al. recently reviewed the types of drugs and delivery systems used in skin cancer chemotherapy [93]. Table 1 provides a list of nanoparticle-based formulations developed for the treatment of melanoma.

Liposomes exhibit excellent circulation, penetration, and diffusion properties [94]. Early research demonstrated that liposomes are retained in the tumor interstitial fluid in close proximity to tumor vessels [95]. Currently, several liposome-based drug delivery formulations are in clinical use for treating cancer, including melanoma [96]. Several other liposomal carriers for chemotherapeutic drugs are currently in clinical trials [97]. Moreover, major advances with cationic liposomes have led to the successful delivery of small interfering RNA (siRNA) [98]. Finally, theragnostic liposomes offer a new approach for loading a wide variety of diagnostic nanoparticles with anticancer drugs [99].

SLNs can protect drugs against degradation, and provide control over drug release kinetics. SLNs releasing docetaxel have been shown to improve efficacy against colorectal (C-26) and malignant melanoma (A-375) cell lines *in vitro* and *in vivo*. SLNs containing cholesteryl butyrate have been shown to inhibit the ability of human umbilical vein endothelial cells to adhere to cancer cell lines derived from human melanoma, colorectal, breast, and prostate cancers. This approach offers promise by interfering with the vascularity needed for tumors to grow [100].

Polymeric micelles are usually more stable in blood as compared to liposomes and other surfactant micelles. Due to their considerably large size, polymeric micelle systems can be used to co-deliver two or more drugs for combinational treatment modalities, such as radiation agents and anticancer drugs [101]. The use of polymeric micelles was recently investigated for the treatment of mice with melanoma and it was shown that the animals treated with drug-loaded polymeric micelles inhibited tumor growth and increased the survival rate as compared to animals treated with free drug [101].

Dendrimers have also been successfully used in immunotherapy and radio-immunotherapy of various types of tumors [102], including melanoma [103] and cutaneous squamous cell carcinoma [104]. However, the controlled release of drugs from dendrimers remains a significant challenge. New developments in polymer and dendrimer chemistry have provided a new class of molecules called dendronized polymers, which are linear polymers that bear

dendrons at each repeat unit. Dendrons are monodisperse, wedged-shaped sections that make up the structure of dendrimers. Dendrimers and dendrons both possess three key architectural features; 1) an initiator core, 2) interior branching units, and 3) a function of generation (G) level. These molecules have an increased circulation time, and may offer drug delivery advantages such as targeted and sustained delivery.

3.4. Inflammatory diseases

Inflammation is characteristic of many dermatologic disease processes and affects cutaneous physiology, such as the skin's barrier function. This disruption can serve as a portal of entry for microbes, allergens and other pro-inflammatory stimuli, which can cause further inflammation. While many of these disease processes are not fully understood, therapies that modulate inflammation have been shown to significantly decrease morbidity [105]. Inflammatory stimuli are omnipresent in the environment, from microbes that colonize the body, to UV rays, and even commonly ingested foods [106]. These factors can result in cutaneous inflammation with varying degrees of physiological and esthetic impact, such as psoriasis, eczema, atopic dermatitis, rosacea, lichen planus, erythroderma, Stevens–Johnson syndrome and toxic epidermal necrolysis. According to statistics provided by the National Psoriasis Foundation, psoriasis is the most prevalent autoimmune disease in the U.S. with as many as 7.5 million Americans and 125 million people worldwide affected. Nanotechnology has provided an alternative approach for the delivery of drugs that can reduce inflammation and its effects on the skin's barrier function and esthetics. For example, Kilfoyle and co-workers have shown that TyroSpheres are able to provide dose-controlled delivery of paclitaxel, an anti-proliferative agent, and that the paclitaxel is preferentially deposited in the epidermis [36]. These results suggest that paclitaxel-loaded TyroSpheres are a promising approach to the treatment of psoriasis, while minimizing systemic exposure to paclitaxel. Table 1 lists the types of nanoparticle-based formulations used to topically treat inflammatory diseases or conditions of the skin.

3.5. Cosmetics

Many skin conditions, such as dry skin, oily skin, hyper/hypopigmentation, vascular deformities, and photoaging, are major concerns in the field of cosmetic dermatology. A variety of products have been formulated to address these issues [107]. However, there has been much controversy regarding the safety of the topical application of nanoparticles revolving around whether nanoparticles get absorbed systemically, evade immunologic defense mechanisms, form complexes with proteins, and/or induce the formation of free radicals, ultimately damaging healthy skin cells. This controversy is particularly evident with regard to the use of nanoparticles in sunscreens (which are regulated as drugs in the U.S.).

ZnO and TiO_2 nanoparticles have traditionally been used in sunscreens because of their ability to reflect ultraviolet (UV) light [108]. In recent years, nanosized forms of ZnO and TiO_2 have been optimized to be more transparent, less viscous (more spreadable) [109], and easier to blend, while maintaining their potency against UV irradiation [110]. However, their toxicity profiles need to be assessed since smaller sized particles will likely have different chemical, optical, magnetic, and structural properties [111]. Due to the safety concerns

around metal nanoparticles in sunscreens, Cross et al. performed a penetration study using a Franz-cell diffusion setup [112]. ZnO nanoparticles were applied topically to cadaver skin and after 24 h, 0.03% of the applied ZnO nanoparticles were detected in the upper SC, with 0% in the lower SC and epidermis. These data suggest that it is unlikely that ZnO nanoparticles penetrated through the epidermis and into the dermis in this model.

Vitamin A, in various natural and synthetic retinoid forms has been explored for the treatment of skin aging and hyperpigmented lesions [113], however, certain forms *such as retinoic acid* cause irritation, burning, scaling and/or dermatitis, limiting their acceptance by patients. Retinaldehyde and retinol are considerably less irritating. The retinyl palmitate and acetate esters are the least irritating forms of Vitamin A, most probably because they are the natural storage forms of Vitamin A in the skin. In order to improve efficacy and minimize the aforementioned side effects, various novel drug delivery systems, including nanoparticles, have been developed. For example, Yamaguchi et al. [114] observed the effect of nano-scale tretinoin (ali-trans retinoic acid, atRA) on photo-damaged skin and showed reduced irritation and inflammation.

Coenzyme Q10 is a naturally occurring antioxidant used widely in cosmetics [115]. It is a lipid-soluble provitamin with low solubility in aqueous solutions (logP > 10) [116]. Therefore, SLNs, liposomes and other formulations have been explored as drug delivery vehicles for Coenzyme Q10 to facilitate penetration into the deeper layers of skin [117].

Octyl methoxycinnamate (*OMC*), also called *ethylhexyl methoxycinnamate*, is used as an active ingredient in sunscreens [118]. Puglia et al. [119] incorporated two components, OMC and diethyltoluamide, into SLNs and used differential scanning calorimetry to determine the percutaneous absorption. This study provided evidence that the topical application of SLN delivery systems could reduce their systemic absorption, and enhance their safety and efficacy for this application. However, when exposed to sunlight, OMC can change from the primary transform to the cis-form, resulting in a reduced UVB filtering efficiency [120]. Table 1 summarizes the various types of nanoformulations used in cosmetic applications.

3.6. Ophthalmology

The ocular surface epithelium, tear film, and blood-ocular barriers interfere with the penetration of topically applied drugs to the eye. Nanoparticles offer several desirable characteristics when dealing with ocular drug delivery: (i) They can improve the penetration of large, poorly water-soluble molecules, e.g., the delivery of glucocorticoid or immunosuppressive drugs for the treatment of immune-related, vision-threatening diseases, such as uveitis or scleritis [121]. (ii) They can increase the contact time of the administered drug with its target tissue, e.g., brimonidine for the treatment of glaucomaor corticosteroids for autoimmune uveitis [122]. (iii) Nanoparticles can be used to reduce side effects of highly potent drugs. (iv) They can reduce issues with patient non-compliance, e.g., glaucoma requires treatment with daily application of eye drops, which often adversely affects the anterior structure of the eye [123]. Wadhawa et al. reported a significant reduction in the intraocular pressure without irritation of rabbit eyes treated with chitosan-hyaluronic acid nanoparticles loaded with timolol compared to standard timolol eye-drops or empty

nanoparticles [124]. Table 1 lists the various types of nanoparticle formulations studied for the topical treatment of eye diseases.

3.7. Chronic wound healing

In the past, the topical treatment of cutaneous wounds has focused on infection [125], but in more recent years, researchers have developed new multifunctional nanosystems with the potential to provide more comprehensive therapeutic effects [126]. Chronic wounds fail to complete the normal wound healing cascade, resulting in delayed or failed wound closure [127]. These recalcitrant wounds occur most commonly in association with diabetes, peripheral arterial disease and infection. Unlike acute wounds, there is no standard treatment for chronic wounds. Treatment options include gels and occlusive dressings that retain moisture, surgical debridement to remove dead tissue and debris, skin substitutes, vacuum-assisted wound closure, hyperbaric oxygen therapy, compression bandages, and topical drugs [128]. Nanoparticles have been explored to deliver silver and morphine to chronic wounds, to inhibit bacterial colonization, and to reduce pain [129]. In addition, nanoparticles have been used to encapsulate and protect therapeutic agents from degradation in the highly proteolytic wound environment [130]. Vasoactive agents, such as nitric oxide, have also been stabilized and released using nanoparticle technologies to prevent or treat ischemia [131]. Recently, Chigurupati et al. reported on the topical use of cerium oxide nanoparticles for healing full-thickness dermal wounds in mice via a mechanism that enhances the proliferation and migration of various skin cells. The results suggest that cerium nanoparticles penetrated into the wound tissue and reduced oxidative damage to cellular membranes and proteins [62]. Curcumin has also been explored in antimicrobial and wound healing applications [132]. Krausz et al. demonstrated that curcumin-loaded nanoparticles inhibited microbial growth and enhanced wound healing in an in vivo murine wound model [133]. Table 1 lists the various types of nanoparticle formulations explored to treat chronic wounds.

4. Electrospun nanofibers for drug delivery

4.1. Introduction to electrospinning

Electrospinning is a relatively simple, user-friendly and inexpensive process used to fabricate nanofibers. Electrospinning was first patented by Cooley in 1900 [134], and has gained popularity in the last 20 years for use in medical applications, including nanofiber drug delivery systems, tissue engineering scaffolds, filtration membranes, biosensors, and enzyme immobilizers. The typical setup includes at least one syringe pump, a polymer solution with or without drug, a high voltage supply, a source electrode, and a collector electrode (Fig. 2). During the electrospinning process, an electric field is applied to a viscous polymer solution, inducing charge within the polymer and needle. When the charge repulsion force exceeds the surface tension, a jet is initiated from the needle tip (referred to as a “Taylor cone”) that creates extremely thin, elongated droplets with very high surface area. As the solvent rapidly evaporates from these droplets, nanosized fibers are formed that are attracted to an oppositely charged or grounded collector, where a nonwoven, solid, fibrous mat is deposited. The collector may be stationary or rotating and/or translating. Fig. 2 shows a scanning electron micrograph of an electrospun fiber mat. In the electrospinning

process, fiber formation is dependent on a variety of solution and process parameters, as reviewed by Bhardwaj et al. [135]. These include polymer concentration (Fig. 3), polymer molecular weight, solution viscosity, surface tension, conductivity of the polymer, solvent, field strength/voltage, flow rate of the feed, type of collector, and distance between the needle tip and the collector. This process can produce fibers with a diameter ranging from 2 nm to greater than 5 μm, but most commonly fiber diameters from about 10 to several hundreds of nanometers are reported in the literature [136]. Through the optimization of these parameters and atmospheric conditions (e.g., humidity and temperature), electrospinning can be used to produce nanofibers with a desired diameter and morphology for a targeted clinical application.

Fig. 2 represents the standard electrospinning process used to produce drug delivery systems. The drug is either co-dissolved or finely dispersed in the polymer solution. Variations of this setup include coaxial spinning, emulsion electrospinning, and the use of dual spinnerets. Coaxial spinning is a modified electrospinning setup where two different solutions (e.g., one containing polymer and the other containing drug) are fed through a co-axial capillary channel to produce nanofibers with a core-shell structure (drug in the core and polymer in the shell) [138]. Emulsion electrospinning uses a surfactant to separate the distinct phases (e.g., organic vs. acqueous) and produce nanofibers with a core-shell structure [139]. Coaxial and emulsion spinning provide alternative approaches to electrospinning materials that are not able to be electrospun via standard setups. Co-axial electrospinning can also be used to protect therapeutic molecules from denaturation or degradation. An alternative approach, using dual spinnerets, allows the user to simultaneously electrospin two polymer solutions onto a single collector [140]. The distance between the spinnerets is an additional process parameter that could be optimized by the user.

4.2. Electrospun nanofibers as topical drug delivery systems

Electrospun fiber mats offer several desirable features as drug delivery systems. (i) The electrospinning process can be used to fabricate nanofibers from a wide variety of solutions of both natural polymers (e.g., chitosan, fibronectin, gelatin, collagen, silk, ethyl cellulose) and synthetic polymers (e.g., PLA, PGA, PLGA, tyrosine-derived polycarbonates, polycaprolactone, polyurethane, poly(vinyl pyrrolidone), poly(vinyl alcohol)), or combinations thereof as reviewed by Bhardwaj et al. [135]. (ii) Fiber mats have high surface area-to-volume ratios that provide efficient delivery of both hydrophilic and hydrophobic drugs [141]. (iii) The drug release profile can be tuned to meet the specific clinical application by modulating a variety of parameters, such as the drug to polymer ratio, fiber diameter, morphology, and/or porosity [142]. Functionalization of the nanofibers (e.g., surface graft polymerization) is another approach used to modulate drug release, as reviewed by Yoo et al. [12]. (iv) Electrospun fiber mats can provide sustained release, which reduces the frequency of topical application to increase patient compliance. (v) Electrospun fiber mats have high porosity with interconnectivity, which can play a critical role in mass transport [143,144]. (vi) Nanofiber meshes are malleable, making them suitable for topical drug delivery applications. (vii) Fiber mats can be incorporated into wound dressings, as part of a drug-releasing wound treatment technology.

Although electrospinning has been developed into an industrial scale process for the manufacture of HEPA filters and insulating materials, the exact reproducibility required for the production medical devices is still a challenge. Modifications, such as bubble electrospinning [145] and porous hollow tubes [146], have been explored to scale up the electrospinning process.

5. Areas of potential clinical use for the topical application of electrospun nanofiber drug delivery systems

5.1. Infected or highly contaminated wounds

Infection of cutaneous wounds can lead to delayed healing time, longer hospital stay, and death in some cases. The local delivery of antibiotics can be beneficial in the treatment of infection. Various antibiotic agents have been impregnated into electrospun fibers and shown to have bactericidal activity in vitro. Some examples are described below and summarized in Table 2.

Katti et al. showed that cefazolin, an antibiotic, can be loaded into PLGA nanofibers using a standard electrospinning setup [147]. Verrek et al. used nonbiodegradable polyurethane-based nanofibers as a topical delivery system for itraconazole, a hydrophobic anti-fungal agent. This system provided ultrafast release (<24 h) of the payload, with a linear relationship to the square root of time, indicating diffusional release [141]. Kim et al. demonstrated the sustained release of cefoxitin sodium, a hydrophilic antibiotic, for up to one week, from electrospun copolymers of PLGA and polyethylene glycol (PEG), and confirmed the bioactivity of the released drug in an *in vitro Staphylococcus aureus* inhibition assay [148]. Huang et al. used co-axial electrospinning to incorporate gentamycin sulfate, an antibacterial agent, into polyurethane fibers, where the *in vitro* release followed zero-order kinetics for up to 7 days [149]. Mupirocin is an antibiotic commonly used to treat cutaneous infections, and typically formulated as a 2% cream or ointment that requires application three times a day for up to 10 days. Thakur et al. fabricated poly(L-lactic acid) (PLLA) fiber mats containing mupirocin and lidocaine hydrochloride (an anesthetic) using both a single and a dual spinneret setup, and showed that the setup significantly affected that the burst release profile of mupirocin [140]. In addition, the presence of both mupirocin and lidocaine hydrochloride in a single fiber mat changed the release kinetics of at least one of the drugs. This study demonstrated that the dual spinneret setup was preferred over the single spinneret to produce prototype dressings to treat infected wounds. Ciprofloxacin, a fluoroquinolone antibiotic, is effective against both Gram-positive *Staphylococcus* (*S*) and Gram-negative *Pseudomonas* (*P*) bacteria that cause cutaneous infections. Jannesari et al. demonstrated that the release of ciprofloxacin ranged from a few days from poly (vinyl alcohol) fibers to over 80 days from poly (vinyl acetate) fibers. The release profile could be tuned by blending poly (vinyl alcohol) and poly(vinyl acetate) [150]. Said et al. demonstrated the release of fusidic acid, an antimicrobial agent, from PLGA nanofibers over 9–15 days, which proved efficacious against *Pseudomonas aureus, Pseudomonas aeruginosa*, and methicillin-resistant *S. aureus* (MRSA) [151]. This group also incorporated a bioburden-triggered release mechanism [152]. Linezolid is a synthetic antimicrobial that was shown to inhibit *S. aureus* when released from PCL fiber mats [153]. Alhusein et al. reported on the controlled release

of tetracycline hydrochloride from triple-layered electrospun fiber mats, where the two outer layers consisted of PCL and the inner layer consisted of poly(ethyleneco-vinyl acetate). It was shown that the nanofibers were effective at killing biofilms formed by *S. aureus* [154]. Poly (vinyl pyrrolidone) – iodine complexes are known to have broad-spectrum antimicrobial activity and as a result, have been explored as a treatment for various cutaneous injuries. Ignatova et al. showed that photo-crosslinked poly(vinyl pyrrolidone) or poly(vinyl pyrrolidone)/poly(ethylene oxide) fiber mats containing iodine had biocidal activity against *S. aureus, Escherichia coli* (*E. coli*), and *Candida albicans* (a type of fungus) [155].

The incorporation of metals into electrospun fiber mats has also been used to kill microbes, target bacterial colonization, and inhibit contamination. Thomas et al. incorporated biosynthesized AgNPs into PCL nanofibers via electrospinning and demonstrated their antimicrobial effects against *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* [156]. Similarly, Dashdorj et al. incorporated AgNPs into zein (a corn protein) nanofibers and showed bactericidal activity against *S. aureus* and *E. coli* [157]. GhavamiNejad et al. used electrospinning to form AgNPs on the surface of poly(dopamine methacrylamide-*co*-methyl methacrylate) (MADO) fibers [158]. The fibers released ~13% of the Ag payload within 1 day, followed by a slower release for the next 6 days. In addition, the fiber mats had bactericidal activity against *E. coli, S. aureus, and P. auregenosa*. An in vivo rat study confirmed the effectiveness of AgNPs-MADO fiber mats, where full thickness wounds treated for 15 days showed higher wound healing rates (92%) compared to controls (51%) and MADO-alone fiber mats (65%). Similarly, Woo et al. developed a bilayered construct with an upper layer consisting of TiO_2-loaded chitosan nanofibers and a lower layer consisting of human adipose-derived extracellular matrix [159]. The bilayered construct was shown to have *in vitro* bactericidal activity against *E. coli* and *S. aureus* and inhibit bacterial penetration and accelerate wound healing *in vivo* in a rat model.

5.2. Chronic wounds/wound healing

The treatment of cutaneous wounds, such as burns, traumatic cutaneous injuries, and chronic wounds is currently a significant clinical challenge. Generally, normal cutaneous wound healing is categorized into three time-dependent phases: (i) inflammation, starts immediately after injury; (ii) new tissue formation, overlaps with the first stage; and (iii) tissue reorganization, where scar tissue is formed and may remodel for a year or more [160]. Typically, in cases of deep burns, the normal wound healing is not possible, as there is no source of cells remaining for regeneration. In chronic wounds, the inflammation stage often proceeds far too long, resulting in wounds that remain open for months to years. In these types of wounds, dressings play an important role to (i) protect the wound; (ii) maintain a moist wound environment; (iii) protect the wound from contamination with exogenous microorganisms; and (iv) accelerate wound closure. The ideal wound dressing should serve as a physical barrier between the wound and the external environment, but be permeable to oxygen. Electrospun fiber mats have properties that are suitable for wound healing applications, such as (i) a highly porous membrane structure that facilitates the exchange of liquids and gases with the environment; (ii) well-interconnected pores that are required to protect the wound from bacterial penetration; (iii) high surface area; and (iv) can provide the

local release of drugs into the skin. The electrospun fiber mats can be used as drug delivery vehicles that aid in wound healing.

Many groups have reported on the use of electrospun fiber mats as matrices for wound healing (summarized in Table 2). For example, Wang et al. reported on electrospun core-shell fibers made of PCL/hyaluronic acid containing epidermal growth factor (EGF). This formulation accelerated wound closure *in vivo* [161]. Several other groups have also reported on the impregnation of EGF [162–164], basic fibroblast growth factor (bFGF) [165,166], vascular endothelial growth factor (VEGF) [167], and platelet-derived growth factor-BB (PDGF-BB) [167] into electrospun fiber mats as a strategy for accelerating wound closure. Systemic and topical administration of ketanserin, a selective S2-serotonin antagonist, accelerated wound healing of diabetic foot ulcers [168,169]. Macri et al. incorporated a fibronectin-derived peptide (P12) that holds promise in the treatment of burns [170] into tyrosine-derived polycarbonates using a standard electrospinning setup. It was shown that both polymer composition and drug loading significantly affected *in vitro* drug release [142]. Recently, Peh et al. impregnated a cocktail of compounds (Vitamin C, hydrocortisone, insulin, triiodothyronine, EGF, and Vitamin D3) into electrospun PLGA/collagen fiber mats and tested their potential utility in wound healing applications. These researchers also confirmed the bioactivity of the released molecules *in vitro* [171].

5.3. Cosmetics/skin care

Electrospun fiber mats have been developed as cosmetic skin care masks due to their ability to be molded to the topography of the skin [135]. For skin care and renewal applications, various therapeutic molecules could be incorporated into the nanofibers (summarized in Table 2). For example, Sheng et al. impregnated silk fibroin nanofibers with Vitamin E, an antioxidant and stabilizer of biological membranes [172]. All formulations exhibited a burst release for the first 30 min followed by slow release for the next 72 h. *In vitro* studies also showed that Vitamin E-loaded silk fibroin fiber mats enhanced mouse skin fibroblast (L929 cells) viability under oxidative stress. In addition, Taepaiboon et al. demonstrated the potential use of electrospun Vitamin A (retinoic acid)-loaded fibers in cosmetic applications [173].

5.4. Anesthetics

Local anesthetics, such as lidocaine hydrochloride or bupivacaine, are commonly used for pain management during surgical procedures. Most commonly, these require multiple injections to infiltrate a region. Weldon et al. developed electrospun fibers that provided sustained local analgesia using bupivacaine [174]. Efficacy was demonstrated in a rat model where local analgesia was reported in 9 of 10 animals treated with bupivacaine-loaded fibers, with an onset of effect at day 1 and the maximum noted at day 3, followed by loss of the effect between 7 and 9 days. Chen et al. developed a sandwich-structure electrospun fiber mat (two outer layers were made of PLGA/collagen fibers, and the inner layer consisted of PLGA fibers containing three drugs), which released gentamycin and vancomycin (antibiotics) and lidocaine (anesthetic) for more than 3 weeks and demonstrated promising repair of infected wounds, in an *in vivo* rat model [175]. Table 2 summarizes examples of fiber mats used as topical drug delivery vehicles for anesthetics.

5.5. Keloids

A keloid is an excessive and abnormal type of scar tissue, which is firm, fibrous and extends beyond the normal boundaries of the healing cutaneous wound. It results from an overgrowth of granulation tissue produced by fibroblasts, but unlike a hypertrophic scar, a keloid grows beyond the margins of the original injury. Dexamethasone (DEX) has been shown to induce keloid regression by suppressing endogenous (not exogenous) VEGF expression and the proliferation of fibroblasts [176]. Li et al. impregnated DEX into PLGA fibers using a standard electrospinning setup and showed ~40% release of the payload within 10 days, followed by very slow release for another 15 days (t = 25 days) [177]. Keloids treated with DEX-loaded PLGA fiber mats, in a mouse model, were significantly reduced in size compared to silicon gel sheet-treated controls. To further enhance this reduction in size, green tea polyphenols (GTP)were co-spun with DEX and PLGA to fabricate DEX/GTP-loaded PLGA fibermats. It was shown that the addition of hydrophilic GTP into the PLGA fiber mat enhanced the release of hydrophobic DEX from the fiber mats. Further, the addition of GTP significantly enhanced the disappearance of distinguishing keloid characteristics in the mouse model, as noted by histological analyses [177]. Table 2 summarizes examples of fiber mats used as topical drug delivery vehicles for keloids.

5.6. Electrospun sutures

Sutures can provoke pain, inflammatory reactions, or infection. Therefore, researchers have explored the use of electrospinning to produce drug-loaded ultrafine fibers as sutures, aiming to reduce these side effects (Table 2). He et al. incorporated an antibiotic, tetracycline hydrochloride (tetracycline-HCl), into PLLA fibrous sutures to minimize bacterial colonization [178]. It was shown that tetracycline HCl-loaded PLLA fibers electrospun from a standard setup released 30% of its payload within the first 8 h, followed by very slow release kinetics. On the other hand, core-shell tetracycline HCl-loaded PLLA exhibited a slight burst within the first 2 h, followed by sustained release for at least 5 days. Although the breaking strength of these fibers was three times less than a commercial suture, electrospinning is a promising approach for the production of drug-loaded, fibrous sutures. Hu et al. developed braided PLLA nanofiber sutures as a drug delivery system for cefotaxime sodium, a semisynthetic third-generation antibiotic, and showed effective bactericidal activity against *E. coli* and *S. aureus* [179].

6. Formulation of nanoparticles and nanofibers for topical application in the clinic

Topical drug delivery vehicles (e.g., nanoparticles and nanofibers) can provide therapeutic action directly to the targeted site, potentially reducing unwanted systemic side effects. There is a variety of ways that nanoparticles can be formulated for topical use in the clinic, for example, as solution/liquid formulations, dry formulations, or viscous formulations (i.e., creams, lotions, gels, ointments). The medium used to suspend the nanoparticles is typically selected with a specific clinical application in mind. This medium should be biocompatible and used to facilitate percutaneous absorption. The suspending medium may also alter the

release kinetics of the drug from the nanoparticles [32]. A recent review highlights the considerations employed for the development of topical dermatologic formulations [180].

Fiber mats can be applied directly onto a wound as drug-eluting dressings due to their malleable handling properties. The fiber mats may be covered with other clinically used, non-adherent bandages to maintain a moist wound environment. A recent review focuses on the design of electrospun fiber mats for tissue engineering, drug delivery and wound healing applications [181].

7. Conclusion

From the plethora of research involving nanoparticles in the past two decades, it is clear that nanoparticles have the potential to effectively deliver drugs across the skin barrier. Solid lipid nanoparticles and liposomes offer potential value as topical drug delivery systems in addition to polymeric and metal-based nanoparticles. Electrospun nanofibers have also shown great promise in the area of wound healing and as antimicrobial dressings. However, as demonstrated by the small number of advanced clinical studies, the clinical impact of nanoparticles and fibermats as topical or transdermal drug delivery systems has been limited. It seems that the translation of a very extensive global research effort into clinically used products has been slow. Although nanotechnology has proven promise in topical applications, a greater emphasis is needed on quantitative studies that can relate the dose and exposure of nanoparticle to nanoparticle penetration and therapeutic efficacy. More quantitative studies are warranted in the area of nanoparticle toxicity. Also, comparisons are lacking between healthy skin versus diseased skin in the context of nanoparticle penetration efficiency. Little is known about the mechanisms of nanoparticle transport through the three main skin layers. Another interesting observation is that very few studies use commercially relevant controls, e.g., the effect of a nanoparticular drug formulation is often compared against no treatment or drug-free formulation instead of using the current clinical “gold standard” as a point of reference. Consequently, there are many interesting unanswered questions and technical challenges that provide significant opportunity for further investigative studies.

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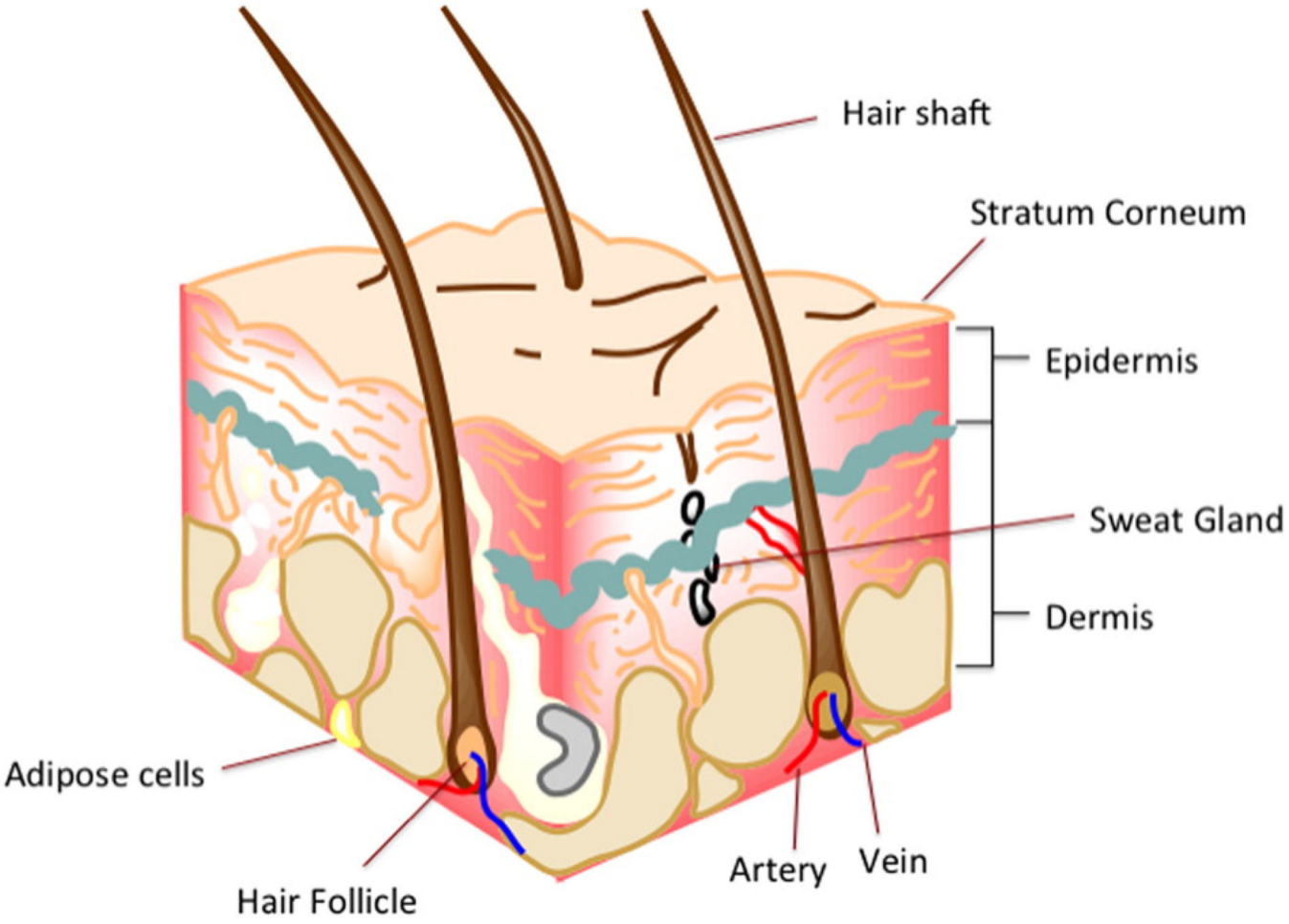

Fig. 1.

A schematic of the structure of the skin illustrating the stratum corneum, the epidermis and the dermis. The hypodermis is not included in this diagram. Image created using Chem Bio Draw Ultra version 14.

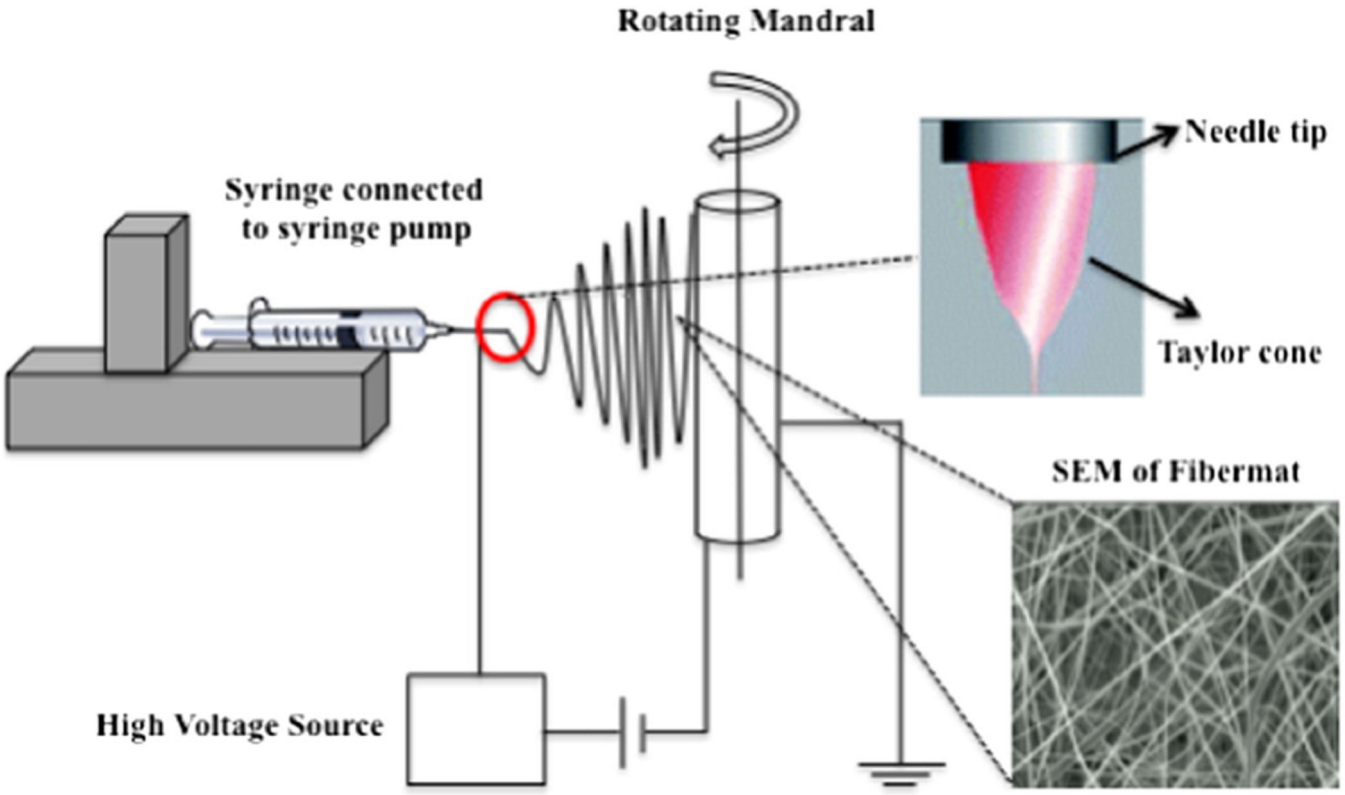

Fig. 2.

Schematic of a standard horizontal electrospinning setup including at least one syringe pump, a polymer solution with or without drug, a high voltage supply, a source electrode, and a collector electrode. (Note, Taylor cone adapted from ref.: [137]).

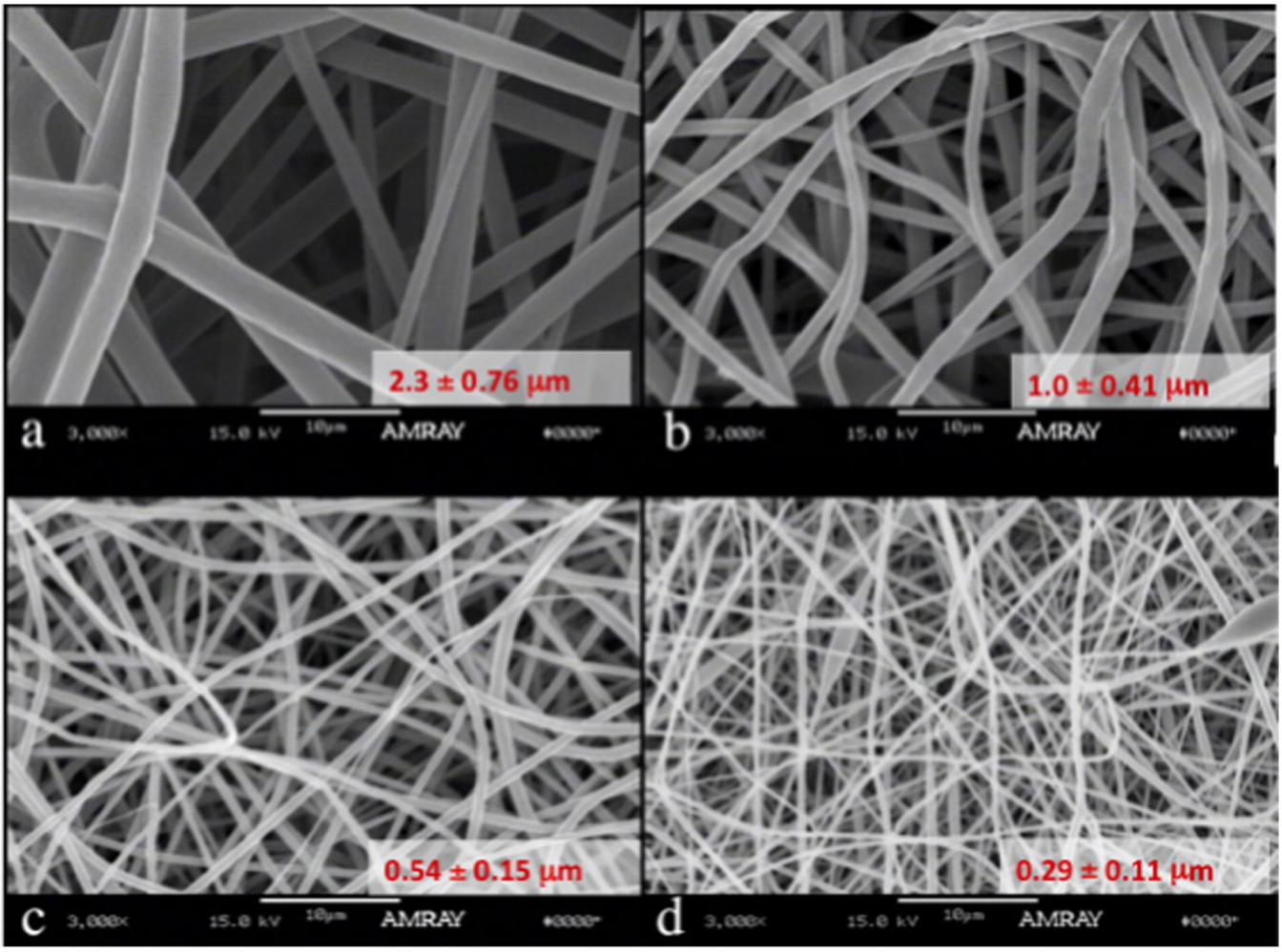

Fig. 3.

Tyrosine-derived polycarbonate fiber mats were electrospun using a standard setup and glacial acetic acid as the solvent. The fiber diameter, morphology and overall porosity were affected by changes in the solution parameters, in this case, polymer concentration in the feed. Images are courtesy of the New Jersey Center for Biomaterials and were obtained by Charles Florek.

Table 1

Types of nanoparticles and their clinical uses as topical drug delivery vehicles.

Application	Drug	Type of nanoparticle	Reference
Acne	Azelaic acid	PLGA	[71]
	Adapalene	SLN, Eudragit® EPO	[182,183]
	Isotretinoin	SLN, Niosome, liposome	[184–186]
	Tretinoin	Chitosan-SLN, Lipid-core-polymeric nanocapsules, lipid based	[187,188,189]
	Benzoyl peroxide	SLN, Niosome, liposome	[190,191]
	Retinoic acid	SLN	[192]
	Cyproterone acetate	Lipid, SLN	[193]
	Triclosan	Eudragit® E 100	[194]
	Clindamycin	Liposome	[195]
	Salicylic acid	Liposome	[196]
	Lauric acid	Liposome	[197]
	Finasteride	Liposome	[198]
	Tea oil	Liposome	[199]
	Erythromycin	Niosome	[200]
	Sphingosome	SLN	[201]
	Target Microorganism	**Type of nanoparticle**	**Reference**
Antibacterial	*E. coli, B. subtilis, S. aureus*, methicillin-resistant coagulase-negative staphylococci, vancomycin-resistant *Enterococcus faecium*, ESBL-positive *K. pneumonia, S. typhi, Vibri cholera*	Silver	[76,202,203]
	MRSA, VRE, *E. coli, Pseudomonas aeruginosa*	Gold	[204,205]
	E. coli, B. subtilis, B. megaterium	Magnesium oxide	[82]
	E. coli, S. aureus, Listeria monocytogenes	Titanium dioxide	[206]
	E. coli 0157:H7, *B. subtilis, Pseudomonas fluorescens*, *L. monocytogenes, Salmonella enteritidis, S. aureus, S. typhimurium*	Zinc oxide	[207]
	B. subtilis	Copper oxide	[83]
Antiviral	HIV-1, Influenza virus, Herpes Simplex virus, Respiratory syncytial virus, Monkey pox virus	Silver	[208–211]
	HIV and several strains of influenza virus	Gold	[208,212]
Antifungal	*Trichophyton mentagrophytes* and Candida species	Silver	[213,214]
	Candida albicans Biofilms	Titanium dioxide	[215]
	Drug	**Type of nanoparticle**	**Reference**
Skin cancer	Cisplatin	Lipids	[216]
		Hyaluronic acid nanoparticles	[217]
		Hexadentate-poly (DL-lactic-co-glycolic acid) nanoparticles	[218]
		PAMAM dendrimer	[219]

Application	Drug	Type of nanoparticle	Reference
		Human ferritin	[220]
	Vincristine	Lipids	[221]
	Doxorubicin	Lipids	[222]
		SLN	[223]
		Hyaluronic acid nanoparticles	[224]
		Poly-L-lysine dendrimer	[225]
	Paclitaxel	N-isopropylacrylamide/vinyl pyrrolidone based nanoparticles	[226]
	Disease	**Type of nanoparticle**	**Reference**
Skin inflammation	Eczema/psoriasis	SLN	[227]
		Lipid nanoparticles	[228]
		Polymeric nanospheres	[31]
	Dermatitis	Zinc oxide	[229]
		Hydrocortisone-loaded chitosan nanoparticles	[230]
		Hydrocortisone-loaded poly(ε-caprolactone)	[231]
	Stevens–Johnson syndrome/Toxic epidermal necrolysis	Nanocrytalline silver dressing	[232]
	Chronic skin inflammation	Polymer-lipid	[233]
		Ammonium glycyrrhizinate-loaded niosomes	[234]
		Curcumin	[235]
	Intended therapeutic effect	**Type of nanoparticle**	**Reference**
	Sunscreen	Zinc oxide	[236]
		Magnesium oxide	[237]
		Titanium dioxide	[238]
Cosmetics		Octyl or ethylhexyl methoxycinnamate (OMC) with SLN and PLGA	[118,239]
	Skin care, wounds, antioxidants	Vitamin E with polymer	[172]
	Antioxidants/anti-aging	Coenzyme Q10 with liposome	[117]
	Intended therapeutic effect	**Type of nanoparticle**	**Reference**
Ocular	Glaucoma	Nano-emulsion	[240]
		Liposomes	[241]
		SLN	[242]
		Polymeric nanoparticles	[243]
		Dendrimers	[243]
	Ocular inflammation	Liposomes	[244]
		SLN	[244]
		Polymeric nanoparticles	[245]
	Chronic dry eye	Nano-emulsion	[244]
		Liposomes	[246]
		SLN	[247]
	Eye cancer	Polymeric nanoparticles	[248]
	Intraocular infections	SLN	[249]
	Corneal neovascularization	Nanoparticles	[250]

Application	Drug	Type of nanoparticle	Reference
Wound healing		Gold nanoparticle	[251]
		Copper oxide nanoparticle	[252]
		Cerium oxide nanoparticles	[62]
		Polymeric nanoparticles	[253]
		Liposomes	[254]

Table 2

Types of polymeric fiber mats and their clinical uses as topical drug delivery vehicles.

Therapeutic molecule class	Example molecules	Polymer delivery system	Solvent	Electrospinning setup	Fiber diameter^	In vitro drug release	Refs
Antimicrobial	Fusidic acid	Poly(lactide-co-glycolide)	Dichloromethane	Standard	200 nm–2 μm	9–15 days	[151,152]
	Linezolid	Poly(ε-caprolactone)	Acetone	Standard	450–800 nm	1–14 days	[153]
		Poly(L-lactic acid)	Hexafluoroisopropanol	Standard, co-axial	260 nm–2 μm	1 — at least 5 days	[178]
	Tetracycline hydrochloride	Poly(ethylene-co-vinyl acetate), poly(lactic acid), and their blends	Chloroform/methanol	Standard	1–6 μm	Hours to at least 5 days	[255]
	Iodine	Poly(vinyl pyrrolidone) (PVP) and poly(ethylene oxide)/PVP	Water	Standard *	230–730 nm	Data not available	[155]
	Cefazolin	Poly(lactide-co-glycolide)	Tetrahydrofuran/dimethylformamide	Standard	450–500 nm	Data not available	[147]
	Mupirocin	Poly(L-lactic acid)	Hexafluoroisopropanol	Standard, dual	Data not available	At least 3 days	[140]
	Silver nanoparticles	Poly(ε-caprolactone)	Acetone	Standard	2–4.3 μm	Data not available	[156]
		Zein	Citric acid in ethanol	Standard	350–500 nm	Data not available	[157]
		Poly(dopamine methacrylamide-co-methyl methacrylate)	Dimethylformamide	Standard	800 nm	At least 7 days	[158]
	Gentamycin sulfate	Polycaprolactone	Chloroform (shell)/distilled water (core)	Coaxial	153 nm–1.7 μm	7 days	[149]
	Cefoxitin sodium	Poly(lactic-co-glycolic acid) (PLGA)	Dimethylformamide/water	Standard	260 nm	7 days	[148]
Antifungal	Itraconazole	Polyurethane	Dimethylformamide	Standard	300 nm–2 μm	24 h	[141]
Antioxidant	Vitamin E	Silk fibroin	Water	Standard	380–723 nm	3 days	[172]
	Green tea polyphenols	Poly(lactide-co-glycolide)	Acetone/dimethylformamide	Standard	780 nm	10–14 days	[177]
	Vitamin A	Cellulose acetate	Acetone/dimethylacetamide	Standard	250 nm	6 days	[173]
	Resveratrol	Polycaprolactone	Chloroform (shell)/ethanol(core)	Coaxial	147 nm–1.6 μm	7 days	[149]
Anti-proliferative	Dexamethasone	Poly(lactide-co-glycolide)	Acetone/dimethylformamide	Standard	780 nm	At least 25 days	[177]
Local anesthetic	Bupivacaine	Poly(lactide-co-glycolide)	Hexafluoroisopropanol	Standard	800 nm–1 μm	12 days	[174]
	Vancomycin Gentamicin	Poly(lactide-co-glycolide)/collagen	Hexafluoroisopropanol	Standard, multiple	55–314 nm	At least 21 days	[175]
	Lidocaine	Poly(L-lactic acid)	Hexafluoroisopropanol	Standard, dual	Data not available	15 days 1 h–3 days	[140]
Wound healing	Epidermal growth factor	Poly(ε-caprolactone)/hyaluronic acid	Chloroform/formic acid/water	Standard	150 nm	At least 30 days	[161]
	Basic fibroblast growth factor	Poly(ethylene glycol)-Poly(DL-lactide)	Chloroform/PBS	Standard	780 nm	25 days	[165]
		Hyaluronic acid	Sodium hydroxide/dimethylformamide	Dual	486 nm	5 days	[167]

Therapeutic molecule class	Example molecules	Polymer delivery system	Solvent	Electrospinning setup	Fiber diameter^	In vitro drug release	Refs
	Ketanserin	Polyurethane	Dimethylacetamide	Standard	500 nm–2 μm	24 h	[141]
	Vascular endothelial growth factor	Gelatin nanoparticles in hyaluronic acid	Sodium hydroxide/dimethylformamide	Dual	486–534 nm	28 days	[167]
		Platelet-derived growth factor	Gelatin nanoparticles in collagen	Acetic acid		28 days	
		Endothelial growth factor	Collagen	Acetic acid		21 days	

* Polymer was electrospun using a standard electrospinning setup, however, therapeutic molecule was loaded after.

^ Fiber diameter is reported as a range if the authors investigated the effects of electrospinning parameters on fiber morphology.