On-Demand Drug Delivery Systems Using Nanofibers

Subjects: Nanoscience & Nanotechnology | Medicine, Research & Experimental | Chemistry, Medicinal
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On-demand drug-delivery systems using nanofibers are extensively applicable for customized drug release based on target location and timing to achieve the desired therapeutic effects. A nanofiber formulation is typically created for a certain medication and changing the drug may have a significant impact on the release kinetics from the same delivery system. Nanofibers have several distinguishing features and properties, including the ease with which they may be manufactured, the variety of materials appropriate for processing into fibers, a large surface area, and a complex pore structure. Nanofibers with effective drug-loading capabilities, controllable release, and high stability have gained the interest of researchers owing to their potential applications in on-demand drug delivery systems.

on-demand drug release | nanofibers | drug administration

1. Introduction

The development of on-demand drug delivery systems (DDSs) has received significant attention owing to the high demand for controlled delivery of various drugs to organs and cell tissues [1][2]. The aim of advanced and smart DDSs is to achieve high therapeutic effects while avoiding adverse side effects on human health [3][4]. Most conventional DDSs are administered via enteral routes, such as tablets, capsules, and granules, while others are administered via parenteral routes, such as intravenous, intra-arterial, intramuscular, or subcutaneous routes [5][6]. There are various drawbacks to the routes and methods of administration, such as first-pass metabolism and discomfort [7][8].

The drugs that reach the market have potential side effects; for example, anticancer chemotherapeutics are a source of concern for both therapists and patients because of their inherent toxicity [9][10]. Although their efficacy and target selectivity have increased over time, significant side effects, such as infections, vomiting, tiredness, loss of taste, anemia, and immune system damage, still exist. The mode of administration affects the therapeutic benefit of a medication by influencing various aspects, such as pharmacokinetics, distribution, pharmacodynamics, metabolism, and toxicity [11][12]. With the discovery of nanomaterials, novel methods have been developed for preparing DDSs [13][14]. Using passive or active targeting techniques depending on the final formulation, nanomaterials can be utilized as carriers to wrap and distribute drugs that are extremely toxic, insoluble, rapidly cleared, or unstable as free molecules [15][16][17][18][19][20][21][22].

Among several alternatives, nanofibers (NFs) have attracted much attention because of their immense potential for smart DDSs (**Figure 1**) [23][24]. NFs offer unique qualities, such as a microstructure that is comparable to that of an

extracellular matrix; a large surface area; high porosity with interconnectivity, which enhances cell adhesion, proliferation, drug delivery, and mass transport capabilities; and a variety of matrix materials [25][26]. Furthermore, the advancement of specialized electrospinning methods has provided new possibilities for the loading and release of insoluble drugs [27][28]. Excellent stability, improved targeting, low toxicity, high drug-loading capacity, remarkable mechanical characteristics, encapsulation of a wide range of medicines, and compatibility with thermolabile medications are all benefits of NF scaffold formulations. Delivering drugs to patients in the most appropriate manner has long been a challenge [29][30]. As delivery matrices, a wide range of biocompatible, biodegradable, and nonbiodegradable polymeric materials can be employed [31].

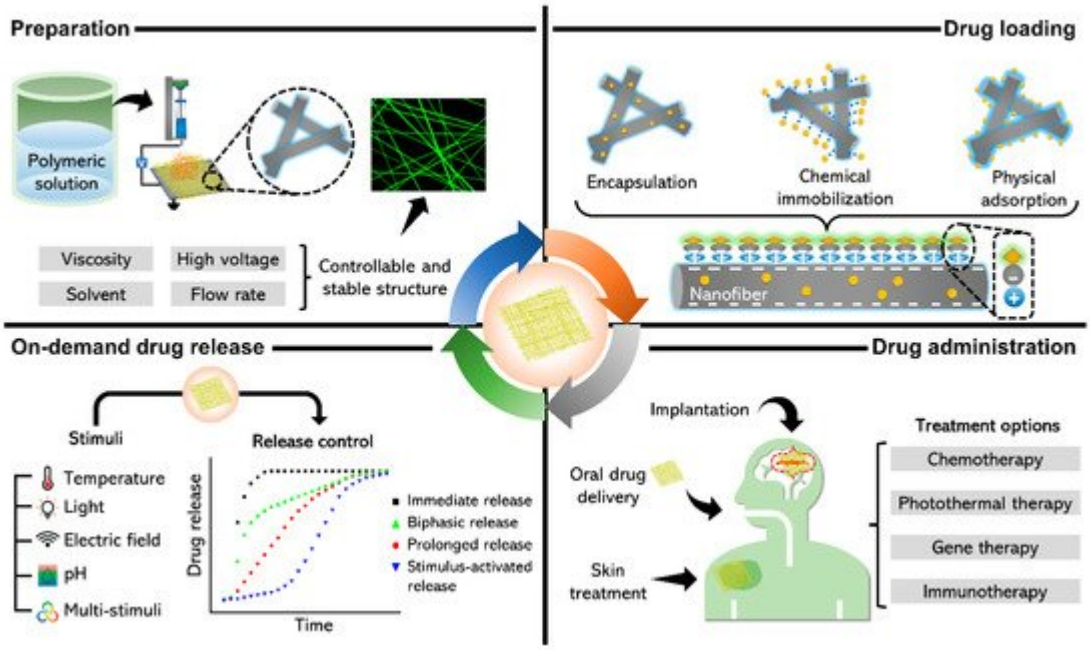

Figure 1. Schematic of on-demand drug delivery systems using stimuli-responsive NFs.

NFs for therapeutic applications follow several basic designs. Homogeneous architectures, in which the drug is spread throughout the polymer matrix, and core-shell NFs, in which the drug-carrying matrix is purified by polymers, are the most common designs. NFs stabilize with active molecules on their surface [32][33][34]. Because of their benefits, such as improving drug solubility and bioavailability or regulating the pace and location of administration, rapid dissolution and controlled release have become crucial for creating innovative drug delivery methods [35]. NFs have several properties, such as protection of drugs from systematic decomposition in the blood circulation, controlled release of the drug at a constant rate over a longer period of time, drug release only at the targeted body area, and permeation of certain membranes or barriers [36].

2. Stimuli-Responsive on-Demand Drug Release

It is generally acknowledged that medications must be delivered in a regulated manner to target areas to increase therapeutic efficacy while reducing or avoiding unwanted effects [37]. Stimuli-based DDSs have demonstrated tremendous potential for the effective targeting of active pharmacological moieties [24]. Combining electrospinning

methods with stimuli-sensitive materials to create stimuli-responsive drug-loaded NFs is an intriguingly growing topic [28]. A few stimuli-responsive systems have been integrated into electrospun nanofibrous delivery vehicles by direct co-electrospinning or post-modification via chemical or supramolecular linkages, such as crosslinkers, or on the polymer backbone [38]. Stimulation causes a volume change or disassembly of the delivery vehicles, which results in pulsatile drug release [30].

2.1. Temperature

Temperature-responsive drug-loaded electrospun NFs are produced from polymers with abruptly varying solubilities [39][40]. This is based on the competition between hydrophilic and hydrophobic molecules on the polymer chain [41][42]. The human body temperature has a restricted range and fluctuates during the day. Fever, hyperthermia, and hypothermia are all examples of deviations from normothermia [43][44]. Fever is a sign of a variety of medical conditions, including infectious diseases, immunological diseases, cancer, and metabolic imbalances [37][45][46]. External sources can be used to either heat or cool tissues, resulting in localized hyperthermia or hypothermia. This implies that temperature may be controlled and utilized as a trigger to modify drug release [38][47]. Tran et al. [48] reported a study on controllable and switchable drug delivery of IBU from temperature-responsive NFs. Electrospun NFs of PNIPAM and hydrophobic PCL polymers were used without burst effects at both room temperature and at temperatures beyond its lower critical solution temperature (LCST) for controlled and variable IBU release. These NFs may be used for transdermal drug administration, which greatly improves the effectiveness of drug dependence and drug misuse. Temperature has a negligible impact on the IBU diffusion rates from PCL/IBU NFs. For PNIPAM/IBU NFs, a considerable burst effect is achieved at 22 °C, but at higher temperatures, the rate of diffusion and the burst effect are significantly decreased. The explosive impact is considerably decreased at both 22 °C and 34 °C for the PNIPAM/IBU/PCL NFs. At 22 °C, the diffusion rate is 75% higher than that at 34 °C. Of course, there are several practical applications in the pharmaceutical and medical sciences, and such a controlled and switchable delivery system can readily be found.

T_g-modulated NFs were activated for greater antibacterial release at a physiological temperature of 37 °C (**Figure 2**a). It has not been used to achieve thermo-activated drug release from NFs to prevent bacterial infections during wound healing. The authors initially created electrospun NFs from ERS and bioinert PMMA blended polymers to produce a tailored wet T_g, or thermal stimulation. A model drug, octenidine (OCT), was then used and integrated into the mixed polymer. By adjusting the ERS/PMMA ratio, regulated OCT release at physiological temperature was achieved at an optimal wet T_g of the NFs (**Figure 2**b). Because of the controlled OCT release regulated by the thermal switch, the produced nanofibrous membrane demonstrated excellent antibacterial activity against both Gram-positive and Gram-negative microorganisms at physiological temperatures. The observations and conclusions presented here are not only scientifically intriguing but can serve as bases for noninvasive self-stimulated release of antimicrobials for the treatment of skin wound infections, hence reducing antibiotic misuse. T_g-based drug release aims to prevent antibiotic misuse by providing regulated release at or above the physiological temperature.

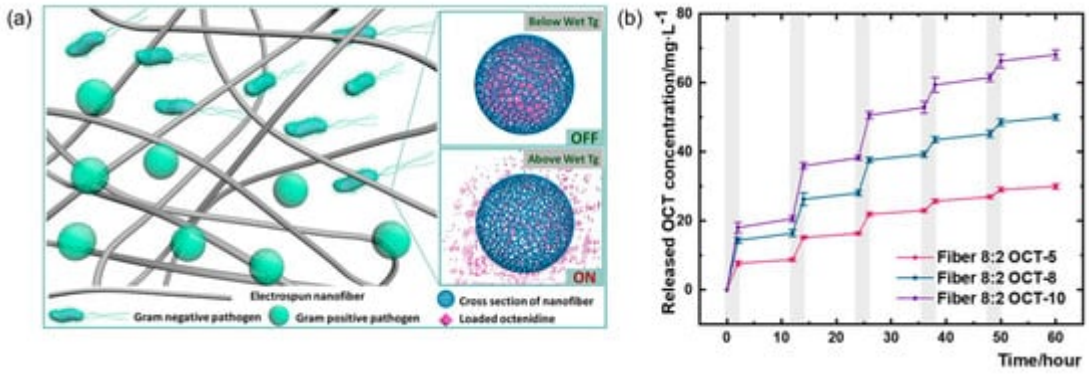

Figure 2. (**a**) Schematic hypothesis of T_g−triggered OCT release from NFs. (**b**) In vitro pulsewise drug release from NFs. Reproduced with permission from [49], CC BY−NC−ND license, Copyright © 2021 The Authors, Published by American Chemical Society.

2.2. Light

Light-responsive materials manifest great potential for providing distant and precise operation that may be readily directed into specific regions of therapeutic applications [38]. The photoresponsivity of these materials is frequently based on photoisomerization of component molecules, which undergo substantial conformational shifts between two states in response to light absorption at two distinct wavelengths [37].

A versatile platform based on electrospun NFs for NIR light-driven biomedical use was reported by Nakielski et al. [50]. The authors successfully manufactured a platform with biomimetic structural characteristics for the on-demand distribution of medicines. This platform consists of electrospun PLLA NFs loaded with a drug model RhB encapsulating P(NIPAAm-co-NIPMAAm)/GNR plasmonic hydrogel. The study outlines the discovery of a simple technique to substantially increase the medication supply to a specified tissue. Cascades, such as NIR light, absorbed by GNRs into heat, are used to regulate the release. These stimuli, in turn, induce hydrogel structural changes and accelerate the kinetics of drug release. Analysis at different temperatures were performed to examine the reactivity of the cushion platform. The same method may be used for non-healing infected wounds when a laser pillow can release antimicrobial products locally, while the heat generated can lessen bacterial colonies. Because the platform effectively satisfies the biocompatibility and stability requirements for thermoresponsive nanomaterials, the PLLA/P(NIPAAm-co-NipmaAm)/GNR system is a good choice for achieving the on-demand release of medications in conjunction with photothermal processing. In another study presented by our group, PNIPAM NFs containing GNRs and drugs that can be controlled by NIR light irradiation were prepared (**Figure 3**) [38]. Stable PNIPAM NFs were generated by a crosslinking process with OpePOSS to prevent them from dissolving in water below the LCST. The thermal/optical responsiveness of PNIPAM NFs containing GNRs and the drugs produced by electrospinning was high. The results demonstrated that the NFs were structurally stable and had a very large surface-area-to-volume ratio for successful on-demand drug delivery. The introduction of GNRs into NFs resulted in a substantial photothermal impact. Because of the thermal sensitivity of PNIPAM, the heat generated by the GNRs during NIR light irradiation might govern the swelling and deswelling behavior of the NFs, resulting in

drug release. The biocompatibility of the NFs was validated through cell studies using camptothecin (CPT) as an anticancer drug.

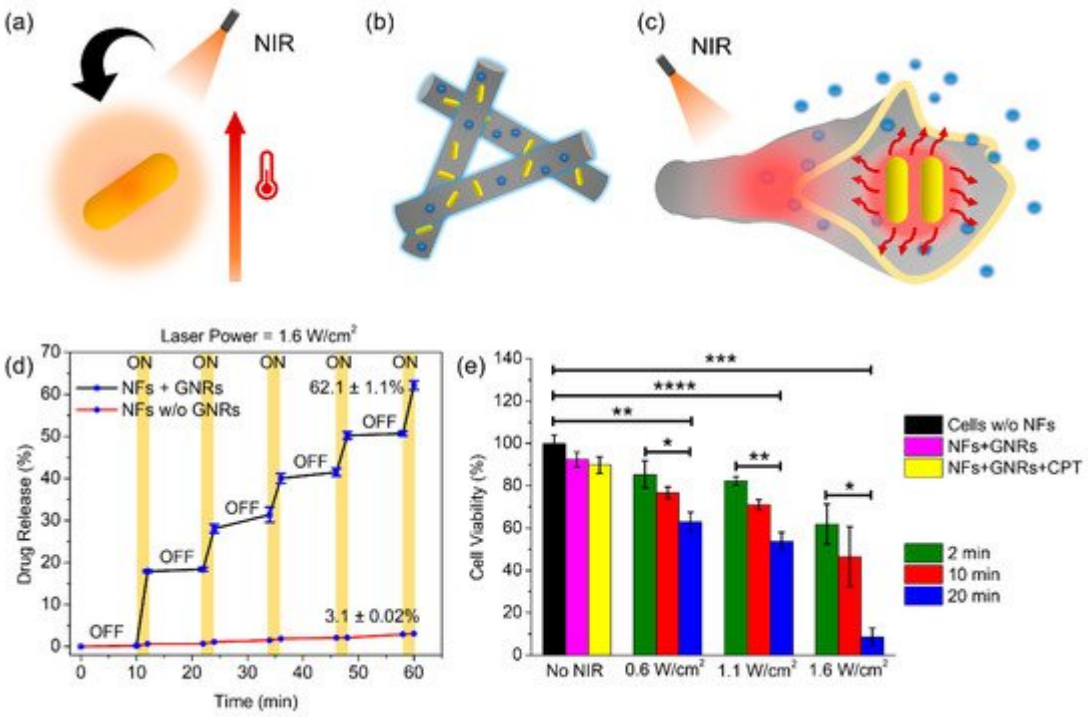

Figure 3. Schematic of (**a**) heat generated by GNRs upon NIR irradiation, (**b**) NFs encapsulating drug and GNRs after electrospinning, and (**c**) drug release due to shrinkage of NFs upon NIR irradiation. (**d**) Pulsatile drug release from NFs through the cyclic on–off of NIR light irradiation at different time intervals. (**e**) Cell viability of U87 cells due to CPT release from the NFs upon NIR irradiation at different time intervals. Reproduced with permission from [38], CC BY license, Copyright © 2021 The Authors, Published by MDPI. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$.

Crosslinked hydrophilic NFs produced by electrospinning a combination of PAA and rGO exhibited excellent aqueous stability (**Figure 4**a). Two antibiotics, ampicillin and cefepime, were loaded onto the rGO-embedded hydrophilic NFs fabricated by electrospinning. The PAA NFs showed relatively little photothermal heating; however, PAA@rGO NFs with continuous NIR irradiation resulted in a temperature increase of approximately 67 ± 2 °C. Even reducing the laser power density resulted in a significant increase in the surface temperature of the PAA@rGO NFs in a moist environment, reaching saturation at approximately 51 ± 2 °C within 5 min. Exposure to NIR radiation leads to a release of adequate quantities of Gram-positive and Gram-negative bacteria, whereas negligible antibiotic release is detected under physiological conditions (**Figure 4**b). There is a strong connection between the antibiotic release caused by the NIR and bactericidal action. The easy manufacturing and modular characteristics of the platform is anticipated to be modified to supply numerous medicines on request for treating various diseases.

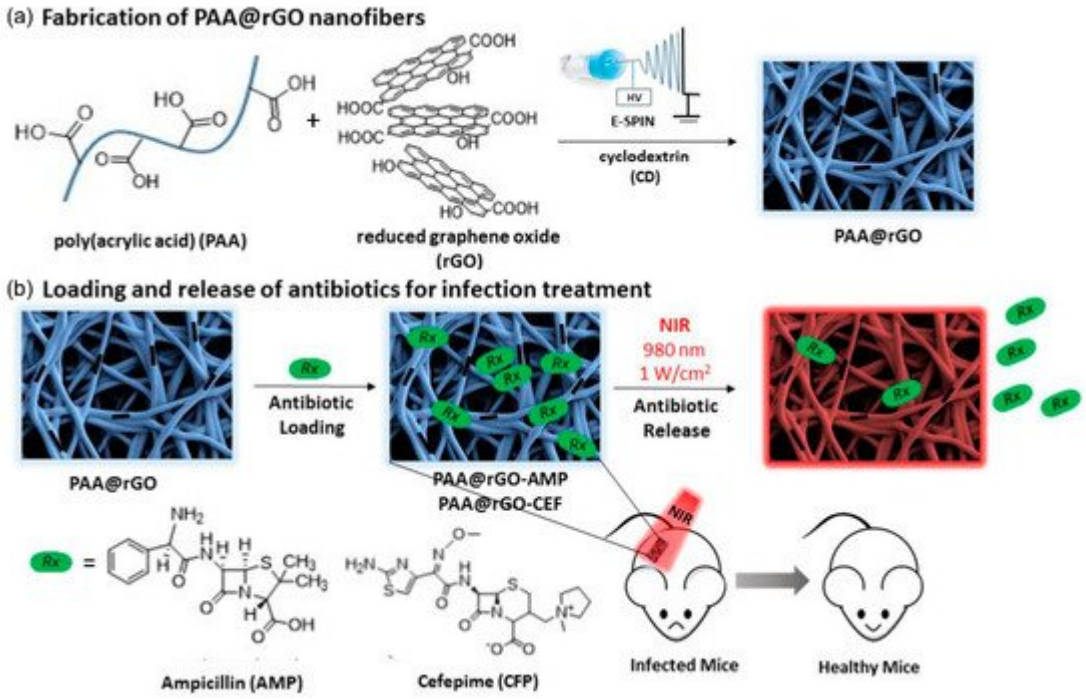

Figure 4. Schematic of (**a**) electrospinning of rGO-loaded PAA NF mats followed by (**b**) loading with different antibiotics and photothermal triggered antibiotic release. Reproduced with permission from [51], Copyright © 2021, American Chemical Society.

2.3. pH

Acid-base homeostasis regulates the pH of the human body, maintaining the arterial blood pH between 7.38 and 7.42. On the other hand, many tissues or cell compartments have their own specific pH conditions for optimal functioning [37]. The acidic environment prevalent in tumor tissues can be used to selectively focus the release of anticancer medications at the tumor in response to pH variations via the use of pH-sensitive nano-formulations [52]. Treatment can begin when NFs adorned with targeting modules are manufactured using the electrospinning technique and filled with anticancer medication [53]. When the therapy is initiated, an internal stimulation, such as a low pH in tumor tissues, induces the release of the medication at the exact site of the tumor, allowing the treatment to be applied to tumor cells [54].

A quantitative color change analysis of nanofibrous mats in simulated wound settings demonstrates that there is sufficient color change to identify distinct wound states. Ciprofloxacin is released on demand in several simulated wound situations. Owing to the repulsion of negative -COO- ions, the proportion of ciprofloxacin released nearly doubled after a few hours under simulated wound conditions (high pH release medium). At pH 7 and 8.5, the swelling ratio of the nanofibrous mats increased to 1378 and 1565%, respectively. A high swelling ratio may be beneficial for absorbing wound exudates. An antibacterial study of the samples provided sufficient evidence that the fabricated NFs were efficiently active against both Gram-positive and Gram-negative bacteria (**Figure 5**). From the successful pH-responsive color change and drug delivery, it can be anticipated that the developed dual-functional pH-responsive electrospun NFs are potential candidates for various wound dressing applications.

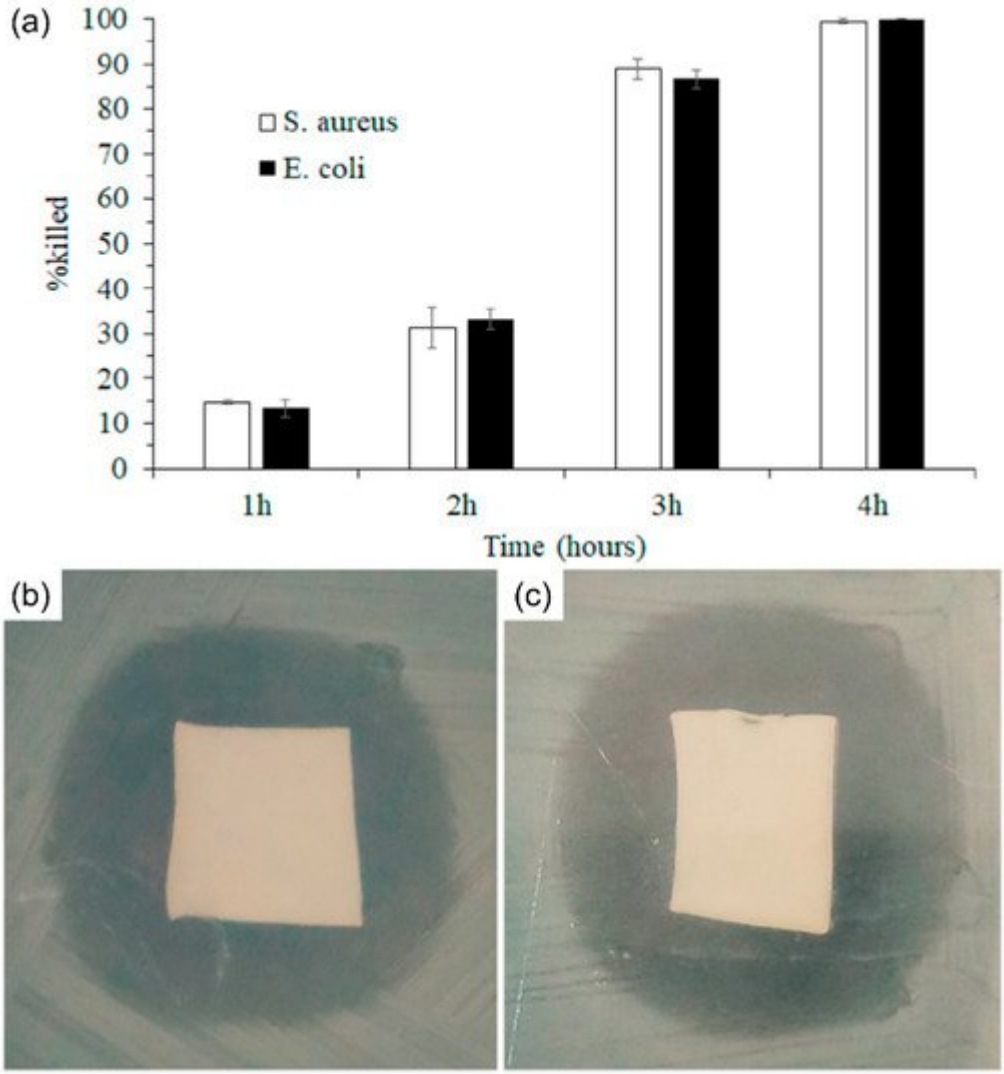

Figure 5. (**a**) Antibacterial activity of PVA/PAA10*-C samples against *S. aureus* and *E. coli* and inhibition zone of PVA/PAA10*-C samples against (**b**) *E. coli* and (**c**) *S. aureus*. Reproduced with permission from [52], Copyright © 2021, Elsevier.

Demirci et al. [55] explored pH-responsive NFs with regulated drug release characteristics. pH-responsive poly(4-vinylbenzoic acid-co-(ar-vinylbenzyl)trimethylammonium chloride) (poly(VBA-co-VBTAC)) NFs encapsulating ciprofloxacin were effectively produced in their study using electrospinning procedures for controlled drug release systems. Poly(VBA-co-VBTAC) contains cationic VBTAC units and pH-responsive VBA units. The observed drug release was mostly attributable to drug diffusion or penetration via the polymer matrix because the duration of the experiment (720 min) was insufficient to show polymer degradation. Ciprofloxacin was homogeneously distributed throughout the poly(VBA-co-VBTAC) NFs without producing phase-separated crystalline aggregates. The investigation revealed that the poly(VBA-co-VBTAC)/ciprofloxacin NFs were capable of releasing ciprofloxacin in a regulated manner over an extended period depending on the pH. Because of the increased intermolecular and/or intramolecular contacts, the first burst release increased with increasing pH levels. However, the overall amount of ciprofloxacin released from NFs was greater in the acetate buffer solution than at higher pH levels. These pH-

sensitive poly(VBA-co-VBTAC) NFs may lead to the development of novel responsive materials for a variety of biomedical applications.

Composite pH-sensitive NFs were produced via electrospinning. PVP-superparamagnetic iron oxide NPs (SPIONs) (a negative MRI contrast agent) and carmofur (a model drug) were mixed into pH-responsive and biocompatible Eudragit polymer fibers (**Figure 6**). Fibers with smooth cylindrical morphologies were produced with an amorphous dispersion of carmofur. SPION encapsulation in fibers resulted in excellent digestion protection in the acidic environment of the stomach, and in vitro drug release tests indicated fast release of carmofur at pH levels characteristic of the small intestine and colon. Based on these findings, this platform appears to be a promising oral delivery method for colonic cancer. The fibers also show pH-responsive relaxation behavior in the physiological pH range, making them ideal candidates for the development of ultra-sensitive reporters to detect aberrant microenvironments in the small intestine and colon. Chemotherapeutic release and absorption can be significantly influenced by changing the local environment and colonic residence time, making it difficult to provide effective and safe doses. The dynamic process of matrix dissolution/swelling allows water molecules to access the SPIONs, increasing diffusive water access, and thus improving their relaxation rates and relaxivities. The obtained r_2 relaxivity profiles can be used to determine whether an MRI signal is suitable for monitoring NF dissolution/swelling, and thus the release of carmofur and SPIONs. Because most chemotherapeutic drugs are cytotoxic and nonspecific, their safety remains a major concern, and these formulations may pave the way for a novel approach to significantly reduce off-target adverse effects in chemotherapy.

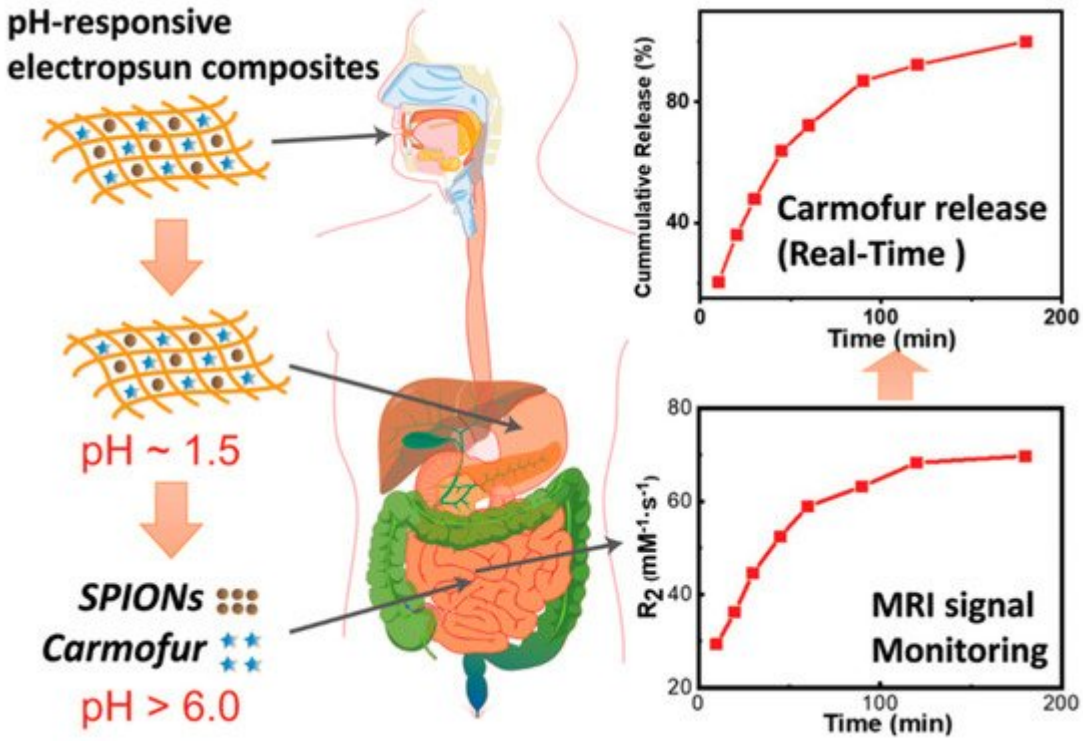

Figure 6. Strategic underpinning nanoplatform design of pH-responsive NFs allowing MRI monitoring of drug release. Reproduced with permission from [56], CC BY license, Copyright © 2021, The Royal Society of Chemistry.

2.4. Electric and Magnetic Field

Electrical fields can cause redox reactions and, in some circumstances, ionization, which can lead to swelling, shrinking, or bending of polymeric drug carriers [39]. Yun et al. [57] created an electro-responsive drug carrier by electrospinning PVA/PAA/multiwalled carbon nanotubes (PVA/PAA/MWCNTs) (**Figure 7**). MWCNTs were used to enhance the conductivity of the DDS. The swelling ratio of the electrospun NFs increased with the increase in electric voltage. The carboxylic acid groups in the polymer were ionized because of the applied electric voltage. The ionization of carboxylic acid groups caused electrostatic repulsion, which resulted in fiber swelling. Therefore, increasing the applied electric voltage leads to quicker drug release from the electrospun scaffold.

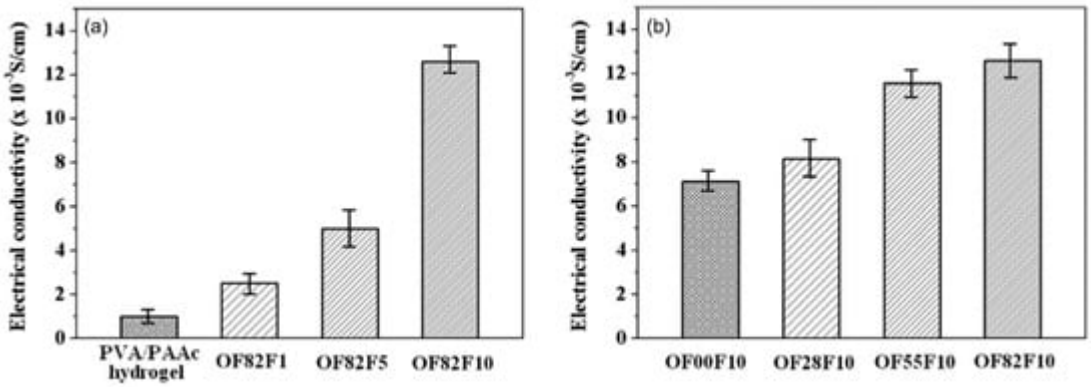

Figure 7. Variations in electrical conductivity of nanofibers depending on (**a**) content of oxyfluorinated MWCNTs and (**b**) oxyfluorination condition for MWCNTs. Reproduced with permission from [57], Copyright © 2021, Elsevier.

The switchable drug release achieved switchable changes in the swelling ratio of NFs in response to alternating on–off switches of the AMF because the self-generated heat from the incorporated MNPs induces deswelling of polymer networks in the NFs. The reported integration of intelligent characteristics into the NFs is attributed to their exceptional surface area and porosity and should be an easy platform for drug administration. Samadzadeh et al. [58] discovered that all magnetic NFs (MNFs) had heat production properties and on–off switchable heating capabilities (**Figure 8**).

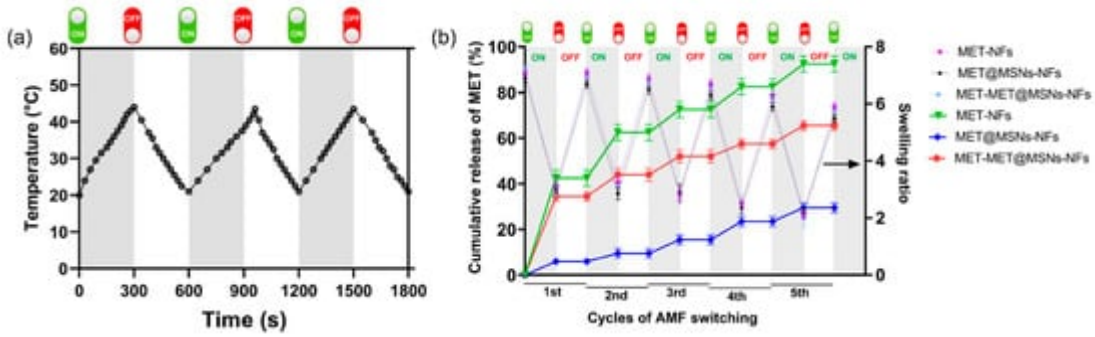

Figure 8. (**a**) Heating and cooling profile of the MET-MET@MSNs-MNFs in response to alternating switching of AMF (**b**) 'ON-OFF' switchable and reversible heat profile and swelling ratio of the MNFs with increasing 'ON-OFF' switching cycle of AMF, and MET release pattern corresponding to reversible swell-shrink property in response to temperature changes. Reproduced with permission from [58], Copyright © 2021, Elsevier.

The swelling ratio with reversible changes and the matching drug discharge in response to AMF application with on–off switching were also exhibited. The NFs were fabricated by electrospinning a temperature-responsive copolymer of NIPAAm and N-hydroxymethylacrylamide (HMAAm) [poly(NIPAAm-coHMAAm)] blended with MNPs and metformin (MET)-loaded mesoporous silica NPs (MSNs). The MNPs act as heating sources in response to the AMF. The MNPs in combination with NFs caused local hyperthermia, which increased the drug release. Furthermore, MSNs can release large amounts of a drug gradually, consistently, and precisely because of their large pore volume and surface engineering properties.

2.5. Multistimuli

To increase the broad tunability over drug administration, multistimuli-responsive electrospun NFs that respond to a combination of two or more signals have been produced [37][59]. These integrated reactions may occur either concurrently or sequentially. Dual stimuli-responsive drug-loaded electrospun NFs, for example, can trigger the release of medications to an infection site anytime the local pH or temperature deviates from normal [60][61]. Multistimuli-responsive electrospun NFs can be composed of a few single stimuli-responsive electrospun fibers or of macromolecules, polymer mixtures/blends, or surface coatings that respond to several stimuli [62].

Tiwari et al. [63] present a significant step forward in the development of a therapeutic model for cancer treatment by utilizing the pH and NIR dual responsive property of PDA alone in a fibrous mat (**Figure 9**). PDA coated PCL-DOX mats demonstrated pH and NIR dual responsive behavior in their study, exhibiting improved drug release in an acidic medium compared to physiological pH conditions (pH 7.4), which is further increased by NIR exposure.

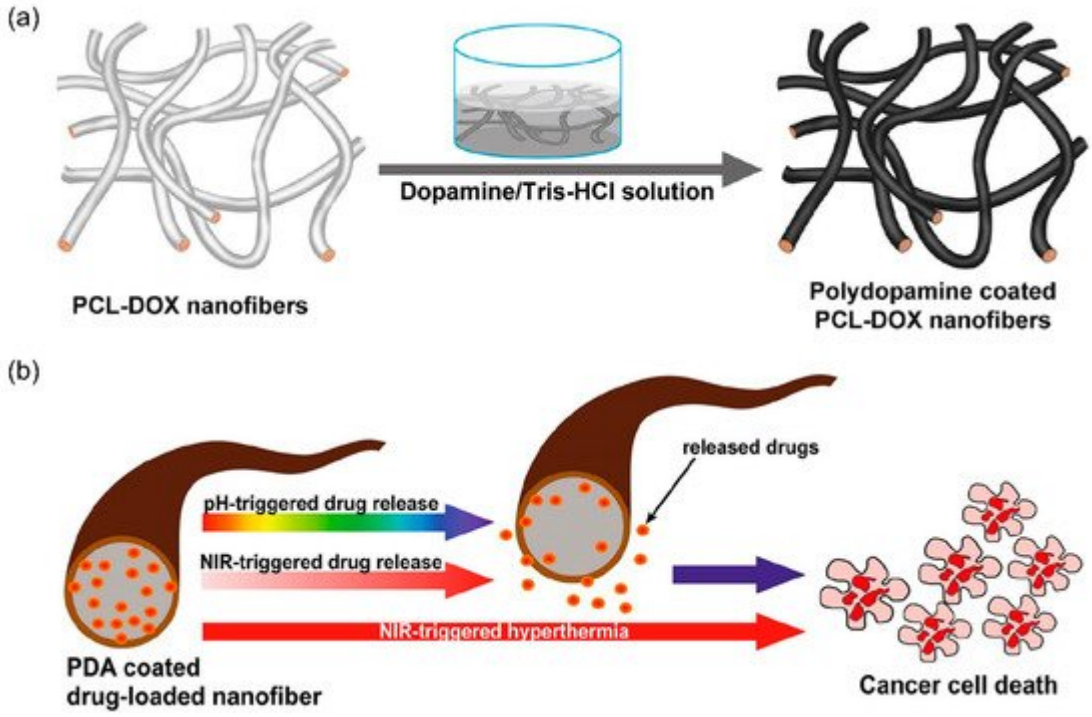

Figure 9. (**a**) Schematic of the fabrication procedure of the PDA modified PCL-DOX nanofibrous mat. (**b**) Schematic of cell death mechanism. Reproduced with permission from [63], CC BY license, Copyright © 2021 The Authors, Published by Springer Nature.

3. Modes of Drug Administration

The potential of NFs in providing different administration routes, as well as the accompanying obstacles, has been discussed, including NF commercial goods for biomedical purposes. Here, we discuss the capacity of NFs to transport therapies through multiple pathways and their potential to deliver a wide range of treatments for treating diverse illnesses [64][65][66].

3.1. Oral Drug Delivery

Because of its noninvasive nature, convenience of use, and increased patient compliance, oral drug delivery is one of the favored methods for drug administration [67]. Furthermore, oral formulations can be developed in a variety of ways, and they can be manufactured inexpensively. In comparison to other methods, the orally administered dose form requires no skill, and is, thus, helpful for chronic conditions requiring regular dosage consumption [64]. NFs can be administered using fast-dissolving drug delivery methods because they can dissolve/disintegrate quickly, allowing the desired drug to be delivered without the need for swallowing or water. Orodispersible medicines dissolve or disintegrate quickly in the mouth without the need for water to facilitate swallowing [68]. Celebioglu et al. [67] described a quick dissolving oral DDS based on electrospinning of cyclodextrin/IBU inclusion complex NFs. The authors used the electrospinning approach to create rapidly dissolving nanofibrous webs from hydroxypropyl-beta-cyclodextrin (HPβCyD)/IBU inclusion complexes without the need for any polymeric additive (**Figure 10**).

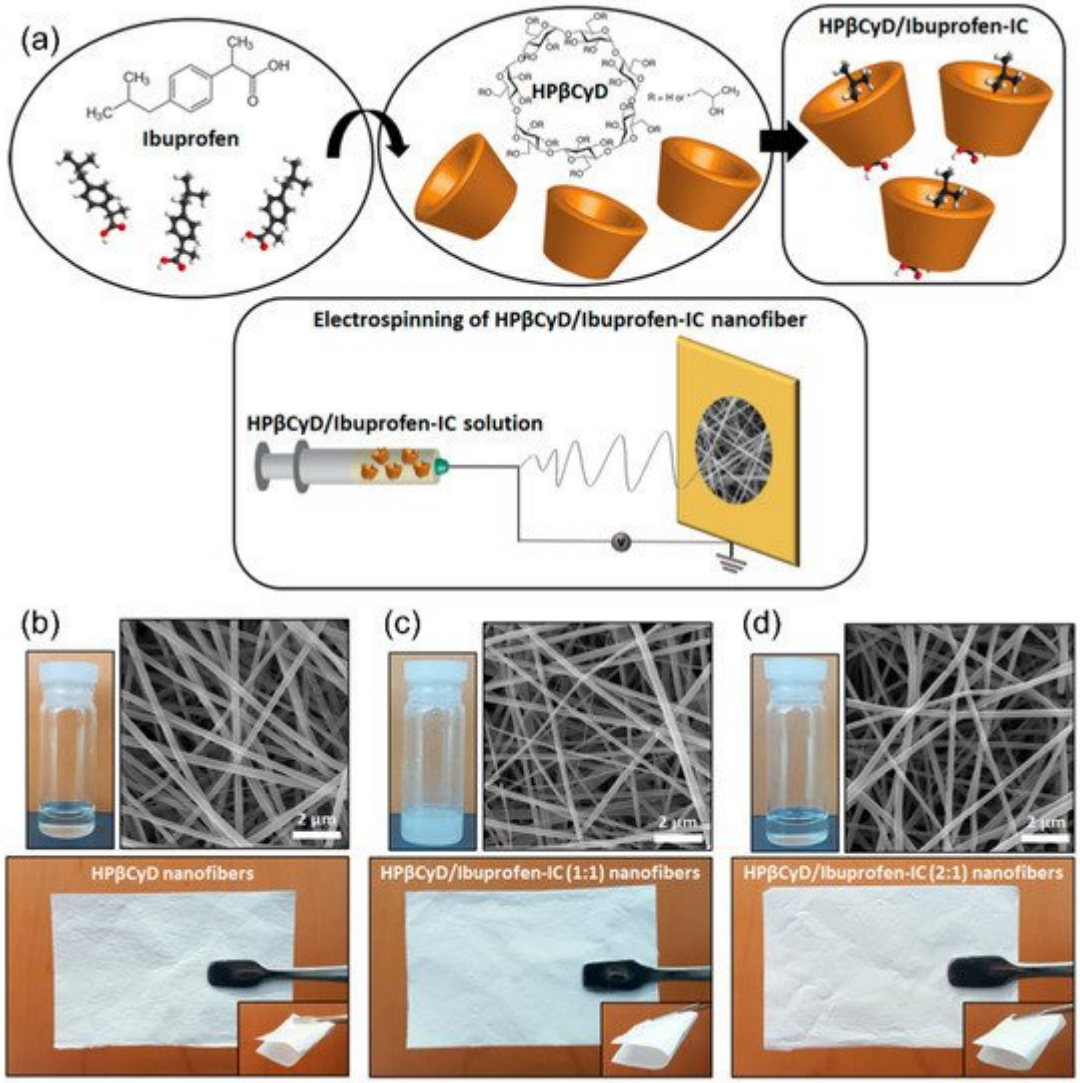

Figure 10. (**a**) Schematic of the inclusion complex formation between ibuprofen and HP*β*CyD molecules and electrospinning of HP*β*CyD/ibuprofen-IC NFs. Photographs of electrospinning solutions and the resulting electrospun nanofibrous webs and representative SEM images: (**b**) pure HP*β*CyD NFs, (**c**) HP*β*CyD/ibuprofen-IC NFs (1:1), and (**d**) HP*β*CyD/ibuprofen-IC (2:1) NFs. Reproduced with permission from [67], Copyright © 2021, American Chemical Society.

IBU was complexed with HP*β*CyD in two distinct molar ratios (1:1 and 2:1, HP*β*CyD/IBU), and the structure and properties of these HP*β*CyD/IBU inclusion complex NFs were examined by utilizing appropriate characterization methods. It is also worth noting that electrospinning was performed using aqueous solutions of the HPβCyD/IBU inclusion complex, which has a significant benefit because HP*β*CyD makes IBU water soluble. As a result, only water can be used to electrospin HP*β*CyD/IBU inclusion complex NFs, whereas hazardous organic solvents and hydrophobic drugs are employed to dissolve the polymeric matrix and electrospin polymer/drug-based fast-dissolving NFs. When exposed to water or wetted with fake saliva, the HP*β*CyD/IBU NFs demonstrated a very quick dissolving nature, indicating that such electrospun HP*β*CyD/IBU NFs have potential as a fast-dissolving oral drug delivery method.

3.2. Implantation

The ability to implant directly at the site of action is a significant advantage of nanofibrous delivery methods, as it reduces the systemic toxicity of the implanted drug [69]. Several stimuli-responsive nanofibrous devices have been developed to improve the specificity of medication action [65]. The ease with which polymeric fibers may be manipulated as macroscopic bulk materials suggests that they can be used as implanted local drug delivery platforms [58]. Wsoo et al. [69] used electrospun cellulose acetate (CA)/polycaprolactone NFs to produce a prolonged drug delivery method. The major goal of their research was to develop a novel implantable DDS (IDDS) based on electrospun polymer NFs. The implants in this method could be utilized to provide vitamin D_3 over a long period through subcutaneous tissues. The IDDS was created using electrospun CA and PCL NFs. The implant core was composed of a drug-loaded CA NF (CA + Vit.D_3) wrapped in a PCL membrane rate-limiting layer (CA + Vit.D_3/PCL). In vitro cytotoxicity tests revealed that HDFa cells had high cell survival and proliferation in the model including CA NFs encapsulated in sintered PCL NFs. Based on the results and ease of use of the technologies described in their study, the created implant may be appropriate for long-term medication administration by being implanted in subcutaneous tissues.

Li et al. [70] demonstrated extremely bioadhesive-implanted NFs that continually release cytostatic and anti-inflammatory drugs to prevent peritoneal adhesions (**Figure 11**). For peritoneal adhesion therapy, the NFs were created using a core–sheath NF filled with hydrophobic HCPT in the sheath and hydrophilic diclofenac sodium (DS) in the core. Electrospinning of mPEG-b-PLGA and dextran emulsion with HCPT in the oil phase and DS in the aqueous phase produced co-loaded NFs. First, an ultraviolet-ozone (UVO) treatment was employed to boost the membrane's bioadhesion, which improved the membrane's physical isolation effect. Second, owing to the well-designed core–sheath structure, the release behaviors of both HCPT and DS were continuous and sustained for several days. Significantly, the UVO-treated and dual-drug-coloaded membranes exhibited the highest anti-adhesion efficiency.

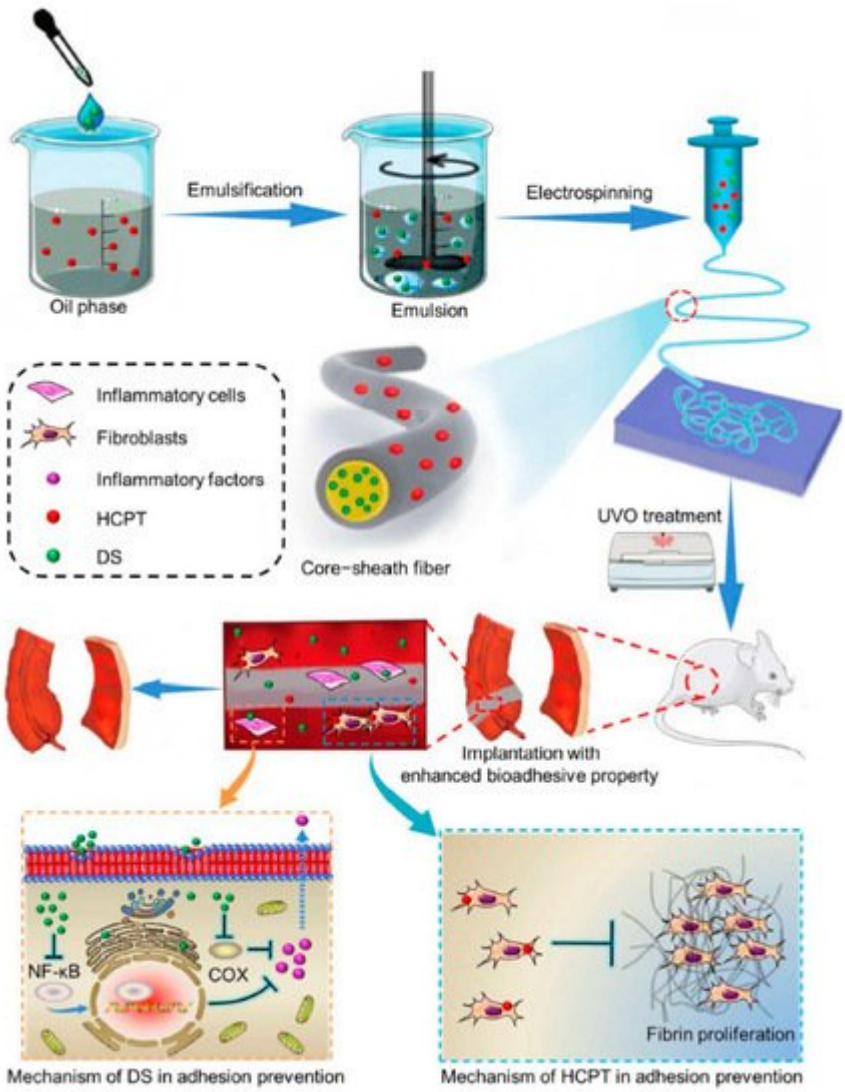

Figure 11. Schematic of preparation and anti-adhesion of HCPT and DS co-loaded NFs for implantation. Reproduced with permission from [70], Copyright © 2021, American Chemical Society.

3.3. Skin Treatment

The distribution of medicines using NFs is based on the simple principle of a higher drug dissolution rate owing to the increased surface area of the drug and the carrier. Because the drug molecules are entrapped inside the polymer framework, NFs function as a controlled drug delivery method. These drug-infused NFs can be placed on the skin to aid in wound healing or for easy drug release for systemic or local therapeutic activity. While the cosmetic use of pharmacological substances on the skin is a key problem, NF-based formulations have shown some potential applications [71]. Rezaei et al. [66] published the results of a drug release study using vitamin C (VC)-loaded SA/PEO NFs for the treatment of a skin disease. VC was integrated into PEO/SA NFs using two distinct electrospinning settings (core shell and blended) to create a medication delivery system for pigmented purpuric dermatosis (PPD) therapy. The results showed that the quantity of VC and SA in the electrospinning solution affected the viscosity and electrical conductivity of the solution, as well as the final fiber diameter. These demonstrated the effective integration of VC into the NFs. The degradation rate was enhanced by adding SA and

VC to the PEO NFs. According to the drug release research results, the core-shell NFs had a lower release rate than the blended NFs because of the presence of VC further from the surface of the NFs. The investigation of the skin absorption of NFs also revealed that core-shell NFs have slower VC penetration than blended NFs. The drug release rate from the stretched core-shell NFs was also somewhat greater during the initial release, according to the findings. Overall, the findings showed that the core-shell NF with a more controlled release behavior of VC has the potential to be used as a drug delivery vehicle in the treatment of PPD.

Yang et al. [72] created multifunctional CS/PCL NFs with variable dual-drug release for wound healing (**Figure 12**). Electrospinning-based wound dressings with multifunctional features such as hemostasis promotion, antimicrobial, medication release, and therapeutic effects are gaining popularity in military and civilian trauma treatment.

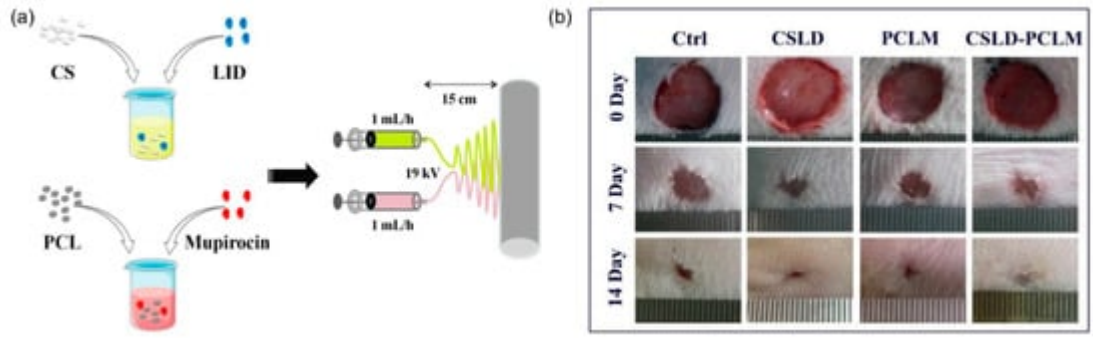

Figure 12. (**a**) Fabrication process of CSLD-PCLM NF scaffolds. (**b**) Wound healing effect of CSLD-PCLM NF scaffolds in a full-thickness skin defect model. Reproduced with permission from [72], Copyright © 2021, American Chemical Society.

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