Iranian Journal of Basic Medical Sciences
ijbms.mums.ac.ir

Localized chemotherapy through nanofiber scaffolds: Progress, challenges, and future directions

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ARTICLE INFO

Article type:
Review

Article history:
Received: Oct 31, 2025
Accepted: May 4, 2026

Keywords:
Cancer treatment
Drug delivery
Electrospun nanofibers
Localized chemotherapy
Nanomedicine

ABSTRACT

Nanofiber-based localized chemotherapy has attracted growing attention as an effective approach to address the shortcomings of conventional systemic cancer therapies by enabling site-specific, sustained, and controlled drug delivery. This review focuses on the emerging role of implantable nanofibrous drug delivery systems in improving cancer treatment outcomes by reducing systemic side effects, enhancing therapeutic efficacy, and improving local tumor management. Special emphasis is placed on electrospinning, a widely used and flexible fabrication method for producing nanofibrous scaffolds, and on the development of chitosan-based nanocomposites and other functional polymer systems that offer high drug-loading capacity and adjustable release behavior. In addition, tumor-targeted drug delivery strategies, including surface modification and ligand–receptor-mediated targeting, are discussed for their potential to improve treatment selectivity and address multidrug resistance. Key challenges related to clinical translation, safety considerations, large-scale fabrication, and long-term performance are also critically analyzed. Finally, the review outlines future research directions aimed at advancing nanofiber-based localized chemotherapy toward practical clinical applications.

▶ Please cite this article as:
Firouzi Amndi A, Shahrtash SA, Moradi S, Dadashpour M, Kazemi T. Localized chemotherapy through nanofiber scaffolds: Progress, challenges, and future directions. Iran J Basic Med Sci 2026; 29: 1296-1312. doi: https://dx.doi.org/10.22038/ijbms.2026.92375.19939

Introduction

Cancer is one of the leading causes of death globally, with significant implications for public health (1). According to the latest statistics, it is estimated that there will be approximately 19.3 million new cancer cases and nearly 10 million cancer-related deaths worldwide in 2020 alone (2). This alarming trend underscores the urgent need for innovative treatment strategies. Traditional cancer treatments, including surgery, radiotherapy, and chemotherapy, are commonly employed; however, they often result in suboptimal outcomes and adverse side effects (3). Current chemotherapy regimens face numerous challenges, such as cytotoxicity, lack of specificity, the induction of stem-like cell growth, and the development of multidrug resistance. These limitations highlight the necessity for research focused on emerging therapies that can improve treatment efficacy and patient quality of life. Addressing these challenges is critical to advancing cancer care and reducing the global burden of this disease (4). This alarming trend underscores the urgent need for innovative treatment strategies. Traditional cancer treatments, including surgery, radiotherapy, and chemotherapy, are commonly employed but often result in suboptimal outcomes and adverse side effects. Current chemotherapy regimens face numerous challenges, such as cytotoxicity, lack of specificity, the induction of stem-like cell growth, and the development of multidrug resistance (5). To better understand these challenges, it is essential to consider the "tumor microenvironment," which refers to the complex and dynamic environment surrounding a tumor, including various cell types, signaling molecules, and extracellular matrix components. This microenvironment plays a crucial role in tumor growth, progression, and response to treatment, often contributing to the resistance observed in conventional therapies (6). In response to these challenges, nanotechnology-based drug delivery has emerged as a promising approach. This strategy involves the use of nanoparticles (NPs)—tiny particles typically ranging from 1 to 100 nanometers in size—to deliver therapeutic agents directly to tumor sites (7). By leveraging the unique properties of NPs, such as their ability to encapsulate drugs and target specific cells, researchers aim to enhance the therapeutic efficacy while minimizing side effects.

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Addressing the challenges of current therapies through the development of nanotechnology-based solutions is critical to advancing cancer care and reducing the global burden of this disease (8). Nanotechnology, which involves controlling matter on the smallest scale, has the potential to create unique devices and structures used in oncology and cancer research (9). These structures, combined with molecular discoveries, could provide the tools needed for the development of advanced cancer diagnosis, treatment, and prevention (10). NPs-based drug delivery systems have demonstrated many advantages in cancer therapy, including precise targeting of tumor cells, good pharmacokinetics, drug resistance, and reduced side effects (11). NPs used in drug delivery systems are typically designed based on their physicochemical properties and size, depending on the pathophysiology of the tumors. Mechanistically, nanocarriers target tumor cells through both passive carrier effects and active targeting mechanisms. After accumulation at the tumor site, therapeutic agents—such as nucleic acids and conventional chemotherapeutic drugs—are released to exert cytotoxic and gene-regulatory effects (12). This article mainly focuses on nanomedicine in cancer treatment, including chitosan-based nanocomposites, polymeric NPs, and nanofibers (NFs). It further discusses the therapeutic potential of nanofibers in cancer treatment, PLGA-based nanofibers as systemic anticancer platforms, electrospun nanofibers, and the kinetics of drug loading and release of chemotherapeutic agents from polymer–drug nanofiber blends, providing a comprehensive overview of nanofiber-based strategies in cancer therapy.

Approaches in cancer treatment

Over recent decades, cancer treatment has advanced markedly, reflecting ongoing efforts to achieve complete remission while addressing persistent challenges such as therapeutic resistance and treatment-related adverse effects. A range of established treatment modalities is currently employed in cancer management. Among these, surgery remains a fundamental component, particularly for solid tumors. Surgical approaches focus on complete excision of tumor tissue with appropriate margins and are widely regarded as a primary therapeutic strategy for many solid malignancies (13).

Surgical approaches remain central to the management of many solid tumors. In breast cancer, for example, procedures such as lumpectomy and mastectomy aim to remove the primary tumor along with an appropriate margin of surrounding tissue (14).

Radiation therapy uses high-energy ionizing radiation to destroy malignant cells or reduce tumor burden. It may be used as definitive treatment or as an adjuvant modality in combination with surgery and chemotherapy. External beam radiation therapy (EBRT) is commonly used to treat prostate cancer, whereas brachytherapy involves placing radioactive sources directly within or adjacent to the tumor and is frequently used in cervical cancer management (15).

Chemotherapy involves the systemic administration of cytotoxic agents that target rapidly dividing cancer cells. These agents can be delivered orally or intravenously and are often used as part of multimodal treatment regimens. Widely used chemotherapeutic drugs include cisplatin, effective against various malignancies such as testicular and bladder cancers; doxorubicin, commonly used to treat breast cancer and lymphomas; and paclitaxel, frequently used for ovarian and lung cancers (15).

Targeted therapy is a more selective treatment strategy designed to interfere with specific molecular pathways or genetic alterations that drive tumor growth, thereby reducing damage to normal tissues. For instance, trastuzumab (Herceptin) targets HER2-positive breast cancer, while imatinib (Gleevec) treats chronic myeloid leukemia (CML) by inhibiting the BCR-ABL fusion protein (14).

Immunotherapy has emerged as a transformative approach in oncology, leveraging the host immune system to recognize and eliminate cancer cells. Immune checkpoint inhibitors, such as pembrolizumab (Keytruda) and nivolumab (Opdivo), block inhibitory pathways that suppress T-cell activity and are widely used to treat melanoma and non-small cell lung cancer (16). In addition, chimeric antigen receptor (CAR) T-cell therapy is a personalized immunotherapeutic strategy in which a patient's T cells are genetically engineered to enhance tumor recognition and cytotoxicity, showing remarkable efficacy in certain leukemias and lymphomas (17).

Hormone therapy is indicated for hormone-dependent malignancies, including breast and prostate cancers, and works by inhibiting hormone production or blocking hormone receptor signaling. Tamoxifen is commonly used to treat estrogen receptor–positive breast cancer, whereas leuprolide, a gonadotropin-releasing hormone (GnRH) agonist, is used in prostate cancer to suppress testosterone production (17, 18).

Finally, innovative therapeutic strategies have increasingly focused on the tumor microenvironment, recognizing its critical role in cancer progression and therapeutic resistance. One such approach involves angiogenesis inhibition; for example, bevacizumab (Avastin) targets vascular endothelial growth factor (VEGF) to prevent the formation of new blood vessels essential for tumor growth and metastasis.

Each of these methods presents unique challenges and benefits, and the choice of treatment often depends on the type of cancer, its stage, and the individual patient's health. The integration of these therapies, along with ongoing research into the tumor microenvironment, continues to shape the future of cancer treatment.

Nanomedicine in cancer therapy

The origins of nanomedicine date back to ancient times, when colloidal gold particles were used for medicinal purposes (19). Ancient medical literature describes methods for preparing drugs by crushing them to achieve the required concentration. This practice was later recognized as a nanoscale manufacturing technique (13). Nanomedicine in its present form has been considered possible since Richard Feynman introduced the concept of nanotechnology in 1959 (19, 20). Cancer remains one of the leading causes of death globally, and current treatments are often insufficient, highlighting the need for more advanced solutions. Rapid progress in nanotechnology, particularly in the development of nanomedical products, offers promising improvements for cancer treatment strategies (21). The nanomedicine field offers opportunities to develop complex, multifunctional targeting strategies. These strategies can expand the pharmacodynamic (PK) and pharmacokinetic properties of conventional treatments and thereby optimize

the efficacy of current anticancer compounds (22). In other words, the results show that nanomedicine improves the clinical outcomes of cancer treatment by altering the PK and biodistribution of bioactive agents while reducing their adverse effects and systemic toxicity (21). As shown in Figure 1, continuous innovations in nanoparticle engineering have led to the development of advanced delivery systems, including EPR-based passive targeting, mitochondrial-targeted nanocarriers such as DQASomes and R8-modified Mito-Porter liposomes, and high-throughput screening technologies such as PRISM profiling. These advances have substantially improved therapeutic precision, drug accumulation at tumor sites, and treatment efficacy while reducing systemic toxicity.

Nanotechnology-based drug delivery

Effectively treating human diseases depends on the ability to deliver therapeutic compounds to affected areas. Unfortunately, the non-specific distribution and rapid metabolism of free drug molecules in conventional therapies require higher systemic doses to achieve effective targeting (24). Nanotechnology enables the development of drug delivery systems (DDS) at the nanometer scale, allowing precise modification of the pharmacological and therapeutic properties of drug molecules. These new DDS, due to their minute size, offer distinct advantages over conventional macroscopic systems, including modified pharmacokinetic behavior and enhanced payload capacity (25). Moreover, their surface chemistry can be easily modified to incorporate targeting and therapeutic moieties tailored for specific applications. Diverse nanostructures can be engineered using various multifunctional building blocks, including those with targeting, detection, imaging, and therapeutic capabilities. Targeted cells and organs require a suitable carrier to deliver drugs, enabling the drugs to extend and concentrate their impact by engaging specifically with the diseased part of the organ. Such precise interaction enables optimal therapeutic efficacy (26).

Many strategies focus on encapsulating drug molecules within NPs to achieve site-specific delivery. These NPs have been engineered to accumulate selectively at diseased sites while avoiding healthy tissues (13). Their ability to efficiently penetrate cell membranes directs them to target tissue, allowing reduced dosages, more uniform effects, and fewer side effects (27). Several methods exist for synthesizing NPs for drug delivery, necessitating a comprehensive evaluation of their effectiveness, safety, scalability, and cost. Mesoporous silicon-based materials are a widely used class of inorganic nanocarriers. These systems exploit the extremely stable porous surface of silicon mesoporous materials to encapsulate bioactive cargo (28). The goal is to cap the loaded pores and release the cargo intracellularly. Mesoporous silica NPs (MPSNPs) offer a key benefit in their stability, enabling them to withstand physical stresses such as changes in temperature and pH in their environment. Their ability to adjust pore size from 3 to 50 nanometers allows them to hold large amounts of drugs and selectively bind desired molecules to their surface, due to their large surface area and pore volume (29). Numerous synthesis methods have been developed to produce well-controlled, large-pore mesoporous nanocarriers, demonstrating potential for delivering proteins, enzymes, antibodies, and nucleic acids. A schematic representation of a mesoporous silicon-based nanocarrier is presented in Figure 2.

Chitosan-based nanocomposites in cancer therapy

Chitosan $[C_6H_{11}NO_4]_n$ (Figure 3) was first identified and described by Rouget in 1859 as the deacetylated form

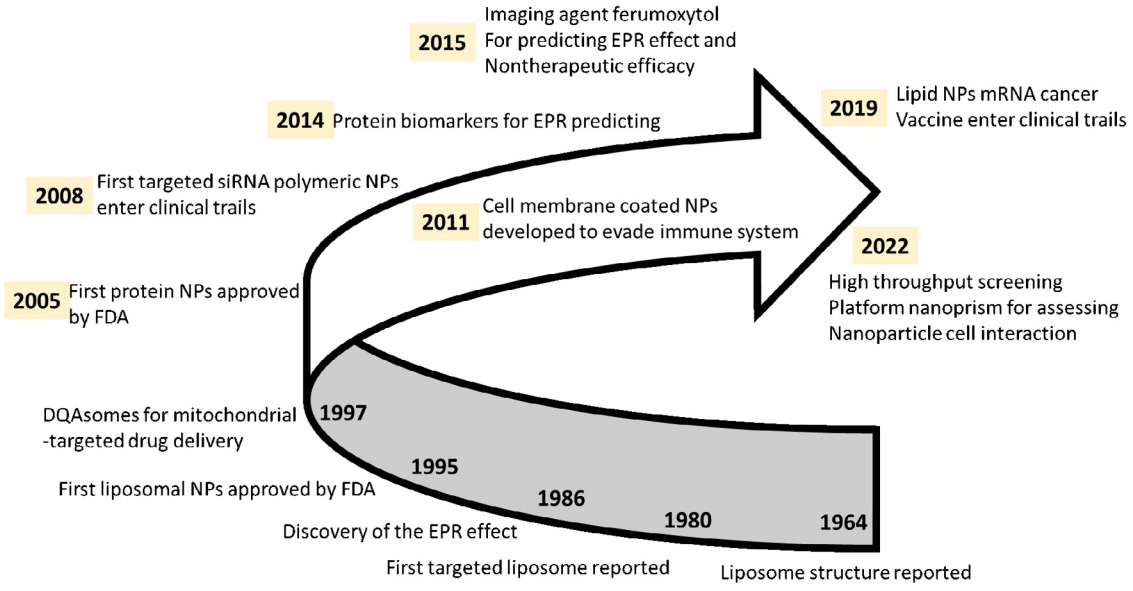

Figure 1. A three-decade journey in cancer nanomedicine

This figure summarizes the major milestones in the design and application of NPs for cancer therapy and diagnosis. It traces the evolution from early generations of simple, passive drug carriers to advanced, stimuli-responsive, and tumor-targeted nanoplatforms. These innovations have progressively enhanced the precision and effectiveness of cancer treatments while minimizing systemic side effects. The figure highlights how multifunctional nanocarriers now integrate targeted delivery, controlled drug release, and imaging capabilities, reflecting the growing sophistication and impact of nanomedicine in oncology. Dequalinium-based liposome-like vesicles, enhanced permeability and retention, Mito-Porter Octaarginine-modified liposomes made of 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine and sphingomyelin, and PRISM profiling for simultaneous relative inhibition in mixtures. Adapted from reference (23) under CC BY license 4.0

NPs (Nanoparticles), DQASomes (Dequalinium amphiphilic cationic vesicles), EPR (Enhanced Permeability and Retention (effect)), R8 (Octaarginine (eight-arginine peptide), PRISM (Profiling for Relative Inhibition Simultaneously in Mixtures), DOPE (1,2-dioleoyl-sn-glycero-3-phosphoethanolamine)

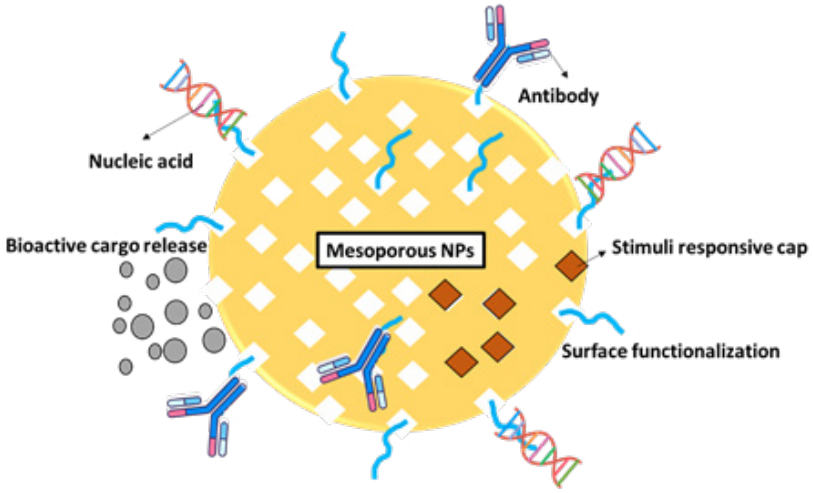

Figure 2. Nanocarriers based on mesoporous silica nanoparticles (MPSNPs)
The diagram illustrates a nanocarrier composed of mesoporous silica, in which the porous regions can be used to passively adsorb bioactive cargo through natural surface adsorption without external energy, or to actively anchor bioactive molecules via specific interactions. Stimuli-responsive caps (Caps that change their properties or behavior in response to specific external stimuli, such as temperature or pH) can be designed to prevent premature cargo release and to detach from the pores for controlled delivery. Targeted delivery can be achieved by attaching targeting agents to the particle surface after functionalization. Adapted from ref (30) license under CC BY 4.0

of the natural polymer chitin. In the early 1990s, chitosan entered the pharmaceutical field, attracting the attention of researchers and businessmen seeking to develop new, more effective therapeutic systems based on it (31). Chitosan's versatility stems from its active amino groups, which serve as reaction sites for attaching various functional groups under mild conditions. Its cationic nature, attributed to the amino groups, classifies it as an aminopolysaccharide(32).

Mercaptopurine (6MP) is a purine derivative with anti-cancer and immunosuppressive properties. It is commonly used to treat conditions such as acute inflammatory diseases and lymphoblastic leukemia. 6-MP is metabolized to methylated thioinosinic acid, which inhibits the production of new purines, and is subsequently converted to 6-thioguanine, a DNA-incorporating metabolite. Similar to other chemotherapeutic agents, 6MP may cause various side effects, including hepatotoxicity and allergic reactions (33). An important feature of chitosan as a drug delivery material is its pH sensitivity. A novel nanocomposite, GNPS-loaded chitosan (Cs), has been developed to encapsulate 6MP for combined chemo-photothermal therapy in breast cancer (34). In another study, celecoxib-loaded hydroxyapatite-CS nanocomposite showed promising potential for colon cancer treatment. Experimental results revealed significant apoptosis and antiproliferative effects, as well as time-dependent cytoplasmic endorsement of celecoxib-loaded Hap-Cs NPs in HT 29 and HCT 15 colon cancer cells (35). chitosan-decorated iron oxide nanoparticles (CS-IONPs) and MTX-PEG-CS-IONPs-Cy5.5 nanocomposites, functionalized with near-infrared fluorescent cyanine dye (Cy5.5) and polyethylene glycol–conjugated methotrexate (MTX-PEG), have also been fabricated for cancer therapeutic applications (36). Doxorubicin (Dox), an anthracycline antibiotic derived from Streptomyces peucetius caesius, exhibits strong anticancer activity even at low doses and is widely used to treat various tumors (37). Coupling Dox and Bcl-2 siRNA in CS-modified polymer NPs enables synergistic cancer therapy. Recent studies have demonstrated that CS/PVP/α-Fe_2O_3 nanocomposites are suitable for DOX delivery. These NPs are spherical, and Fe_2O_3 can be loaded into CS/PVP. The particle size of the nanostructures was 247 nm, and the binding of α-Fe_2O_3 prolonged the increase and release of DOX retention at the tumor site (38). A novel co-delivery system including oleanolic acid (OA) and doxorubicin (DOX) based on CS nanocarrier was advanced for breast cancer treatment. The developed system demonstrated significant potential for treating multidrug-resistant breast cancers and holds promise as a platform for targeting other cancer types. (39). The finding indicated that CS-based nanosystems are used as natural antioxidants in breast cancer therapy (40). Small-sized CSNPs recommend important benefits in improving the bioactivity of encapsulated phytochemicals through reduced toxicity and enhanced pharmacokinetics, targeted delivery (41). Chitosan-based platforms for cancer therapy are listed in Table 1.

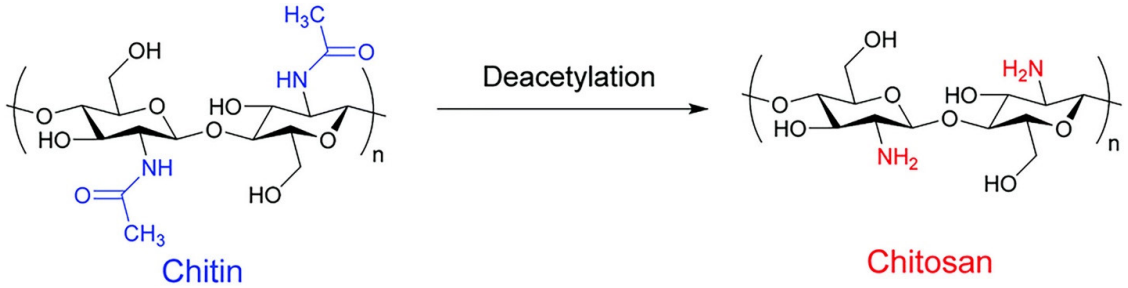

Figure 3. Chemical structure of chitosan production

Table 1. Developed a chitosan-based platform for cancer therapy

Cancer type	Drugs	NPs	NPs size	Ref
Breast	6MP	GNPs	19 to 140 nm	(34)
Colon	Celecoxib	Hydroxyapatite (Hap)	-	(35)
Tumor	MTX-PEG	CS-IONPs	50-100 mm3	(36)
Tumor	Doxorubicin	CS/PVP/α-Fe_2O_3/Dox	247 nm	(42)
Breast	Doxorubicin	FA-CS-g-OA@DOX	180 nm	(39)

MTX-PEG: Polyethylene glycolated methotrexate; CS-IONPs: Chitosan-decorated iron oxide nanoparticles; CS/PVP/α-Fe2O3/Dox: Chitosan/Polyvinylpyrrolidone/Alpha Iron(III) Oxide (Hematite)/Doxorubicin nanocomposite; FA-CS-g-OA@DOX: Folic acid-conjugated chitosan-graft-oleic acid loaded with doxorubicin; GNPs: Gold Nanoparticles

Polymeric nanoparticles in cancer therapy

Polymer-based NPs offer advantages over conventional systems, such as reduced toxicity and targeted drug delivery (43). These nanoparticles are highly promising because of their excellent stability, high drug-loading capacity, and ability to specifically target tissues or cells. On the other hand, developing these NPs presents challenges, and they require careful material selection (44). These particles can transport both water-repelling and water-attracting medications, and are used in vaccinations, gene therapy, and cancer treatment (45).

The polymer shell protects the drug from enzymatic decomposition in the body (13). Enzymatic degradation, diffusion, hydrolysis, and aggregation are responsible for the release of anticancer agents from polymer nanoparticles (PNPs). Examples of non-toxic, hydrophilic, and blood-compatible product polymers were used to modify the surface of PNPs (46). These polymers create a hydrophilic shell on the outer surface of the nanoparticles, which helps to prevent their recognition and uptake by plasma proteins, thereby reducing opsonization and phagocytosis (46). The Rac1-GTP inhibitor NSC23766 has been shown to suppress the growth of prostate cancer (PCa). On the other hand, these treatments successfully focus on tumors that are located in the lower part of the body. It is crucial to develop a drug delivery system that specifically targets the tumor site. New polymers called poly (ester amide) (Phe-PEA) derived from l-phenylalanine were created and filled with NSC23766 (NSC23766@8P6 NP). These polymers have nanometer dimensions and a high capacity for NSC23766 loading, enabling faster release. A novel approach has been developed using a reactive oxygen species (ROS)-responsive prodrug nanoparticle (CPT-TK-HPPH/PT NP) integrated with a platinum nanozyme (PTNP) for the treatment of colon cancer. The ROS-responsive prodrug comprises a photosensitizer, 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH), and camptothecin (CPT) linked by a thioketal bond (47). An original co-delivery system, including caffeic acid phenethyl ester and quercetin via PNP, was proposed to improve antitumor efficacy in colon cancer cells (48). A newly developed nanosystem containing 7-ethyl-10-hydroxycamptothecin with polymeric nanoparticles (methoxy-polyethylene glycol-chitosan/hyaluronic acid) was synthesized to assist in colon cancer management (49). Polymer nanoparticles demonstrated their effectiveness against colorectal cancer (CRC) by developing a 3D model based on the CRC multicellular tumor spheroid (MCTS) model by incorporating mitogens, human intestinal fibers, colon cancer epithelial cells (HCT116), and monocytes (50). A co-delivery nanosystem consisting of curcumin and paclitaxel with PNP (PTX-CUR-NP) was improved for breast cancer chemotherapy. The present study shows that the PTX-CUR-NP drug delivery system can be used for effective breast cancer treatment soon (51). A custom-designed polymeric nanoplatform called dmma-p-dox/lap was suggested for effectively treating breast cancer. This platform combines 2,3-dimethylmaleic anhydride, polyethylene glycol, ε-poly-l-lysine, and doxorubicin/lapatinib to capture lapatinib in biopolymer-doxorubicin conjugate nanoparticles that can switch charges in response to the pH of the environment (52). Advanced PNP platforms for cancer treatment are listed in Table 2.

Various nanofiber synthesis techniques

Nanofibers, characterized by their high surface area-to-

Table 2. Presents a polymeric nanoparticle platform developed for cancer therapy

Cancer type	Drugs	NPs	NPs size	Ref
PCa	Rac1-GTP	NSC23766@8P6 NPs	162.3±6.7 nm	(53)
Colon	CPT-TK-HPPH/Pt NP	PtNP	4 nm	(47)
Colon	Quercetin	QuCaNP	237.8±9.670 nm	(48)
Colon	SN38	SN38-NPs- mPEG	226.7 nm	(49)
CRC	Nutlin-3a	Dextran	-	(50)
Breast	Paclitaxel (PTX)	PTX-CUR-NPs	27.97±1.87 nm	(51)
Breast	Doxorubicin and lapatinib	PNPs	_	(52)

QuCaNP: quercetin- caffeic-acid; NSC23766@8P6 NPs: NSC23766-loaded 8P6 peptide-functionalized nanoparticles; PtNP: Platinum Nanoparticle; QuCaNP: Quercetin–Calcium Nanoparticle; SN38-NPs-mPEG: SN-38-loaded PEGylated nanoparticles; PTX-CUR-NPs;Paclitaxel–Curcumin co-loaded nanoparticles; PNPs: Polymeric Nanoparticles

volume ratio, excellent mechanical properties, and tunable porosity, are widely used in diverse applications such as drug delivery, filtration, tissue engineering, and energy storage (54). The synthesis of nanofibers employs several techniques, each with unique mechanisms and advantages. Below are the most common methods for nanofiber production:

Electrospinning

Electrospinning, derived from the term "electrostatic spinning," is a technique used to produce continuous fibers with nano- or microscale dimensions from materials in a viscoelastic solution or molten state (55). The electrospinning system typically comprises a syringe pump, a spinneret, a high-voltage power supply, and a collector (Figure 4). In this process, the material solution is loaded into a syringe equipped with a conductive needle. Surface tension initially holds the liquid at the needle tip, while the applied electric field deforms it into a conical shape (Taylor cone). When a high voltage, usually between 1-30 kV, is applied between the needle and the collector, the electric repulsion between charges overwhelms the surface tension, leading to the formation of a conical shape known as a "Taylor cone." A charged jet of the solution is then ejected from the apex of the cone. As the solution jet accelerates, it stretches into long, thin fibers while the solvent evaporates. The electrospinning process can be monitored using a high-speed camera, enabling detailed observation and improved control of fiber formation. By adjusting the processing parameters, fibrous mats with tailored geometries can be produced using this versatile technique (56).

Self-assembly

Self-assembly is a natural and efficient method for creating nanofiber architectures, relying on molecules' inherent ability to organize into well-defined structures. This process occurs spontaneously under carefully controlled environmental conditions, including specific pH levels, temperatures, and ionic concentrations. The self-assembly approach is highly valued for producing nanofibers with precise, highly organized arrangements, making it particularly suitable for applications in the biological and biomedical fields (58). The nanofibers formed through self-assembly often exhibit superior biocompatibility, which is essential for applications such as tissue engineering, drug delivery systems, and biosensors. By mimicking the natural assembly processes seen in biological systems, this technique allows researchers to design nanofibers with properties tailored to specific functions, such as enhanced stability or targeted interactions with biological molecules. Additionally, self-assembly offers a versatile and scalable approach, as it can be adapted to a variety of materials, including peptides, polymers, and other biomolecules (59).

Phase separation

Phase separation is a thermodynamic technique used to fabricate nanofibers by splitting a polymer solution into two distinct phases: one enriched with polymers and the other depleted. Once the phases are established, the material solidifies, and the solvent is removed, forming nanofiber structures. This approach is particularly effective for generating fibers with porous, interconnected networks. The unique structure of these fibers makes phase separation an ideal method for applications requiring high porosity and structural integration. It is widely used to create scaffolds for tissue engineering, where the interconnected pores facilitate cell attachment and nutrient flow (60). Furthermore, this method is valuable for producing filtration systems because it can form fibers with customizable pore sizes for efficient particle separation. The versatility and adaptability of phase separation ensure its continued relevance in advancing nanotechnology applications (61).

Electrospun nanofibers for chemotherapeutic applications

Nanofibers have emerged as promising one-dimensional nanomaterials for many commercial applications and research efforts due to their exceptional physicochemical properties (62). They can form highly porous networks with strong interconnectivity between pores, making them an attractive choice for a wide range of advanced applications. The significant impact of nanofiber technology stems from the ability to use a diverse range of materials as the base for synthesizing nanofibers. These materials include artificial polymers, organic polymers, semiconductors, carbon-based materials, and complex materials (63).

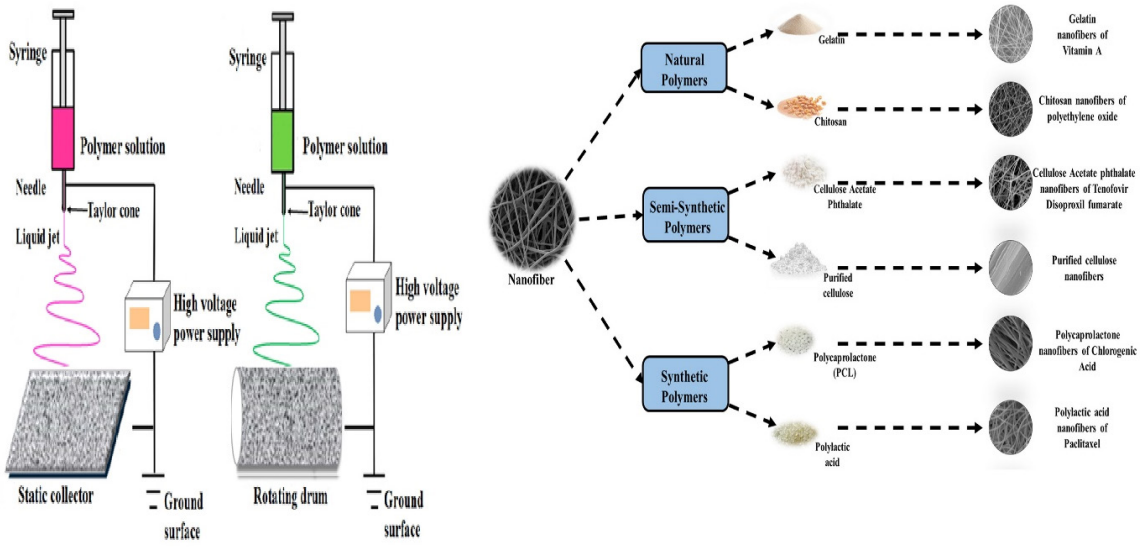

Figure 4. Schematic illustration of the electrospinning technique. Reproduced from (57), licensed under CC BY 4.0

Nanofibers are highly valued in the biomedical field for their ability to retain moisture near wounds, stimulate cell growth, prevent scar tissue formation, and replicate the extracellular matrix (64). Nanofibers are widely used in diverse fields, including wound healing, tissue engineering, drug delivery, bone regeneration, antibacterial mats, blood vessel construction, cartilage repair, and implants, owing to their distinctive properties (65). Bulk materials cannot offer these properties because they require a larger quantity of bioactive molecules than nanofibers. In addition, the surface-to-volume ratio of bulk materials is significantly lower than that of nanofibers, resulting in less cell proliferation. Therefore, nanofibers are preferred over bulk materials (66).

Bringing nanofiber-based treatments to market presents several challenges, including regulatory, economic, and ethical issues. The regulatory landscape is complex because approval processes require extensive safety and efficacy data for novel nanomaterials, and a lack of standardized testing methods further complicates this process. Economically, high manufacturing costs associated with advanced production technologies can hinder competitive pricing and make securing funding for research and development difficult, especially for smaller companies. Ethical concerns also arise regarding potential environmental impacts and long-term health effects, necessitating transparent communication with the public about the benefits and risks. Additionally, gaining market acceptance from healthcare providers and patients can be challenging due to skepticism about the safety and effectiveness of new treatments, while navigating intellectual property rights may lead to legal disputes that complicate commercialization efforts. Addressing these multifaceted challenges requires collaboration among researchers, industry stakeholders, regulatory bodies, and the public to ensure the safe and effective introduction of nanofiber-based treatments (67).

Strategies for drug loading in nanofibers

Effective drug loading into nanofibers is essential for developing advanced drug delivery systems that ensure controlled release, stability, and therapeutic efficacy. Various strategies have been developed to incorporate drugs into nanofibers, leveraging their structural and functional versatility. Below are three prominent methods for drug loading:

Single electrospun nanofibers

Single electrospun nanofibers have emerged as promising drug delivery systems because of their distinctive structural properties, including a high surface-area-to-volume ratio, porosity, and adaptability. These nanofibers can be fabricated from a variety of materials, such as polymers, ceramics, and metals, and are engineered to carry therapeutic agents. They enable controlled and targeted drug release, increasing the accuracy and efficiency of treatment strategies (68). The main characteristics, possible applications, and challenges associated with different types of nanofibers are summarized in Table 3 and Figure 5.

Physical blending of drugs

Physical blending involves mixing the drug with the polymer solution prior to fiber fabrication, typically through electrospinning. This method is straightforward and widely used, as it allows the drug to be evenly dispersed within the polymer matrix. The resulting fibers offer a consistent release profile and are suitable for a range of pharmaceutical applications. However, the compatibility between the drug and polymer, as well as the potential influence of solvents on drug stability, must be carefully optimized (76).

Core-shell structures for targeted release

Core-shell nanofiber structures are fabricated using techniques such as coaxial electrospinning, in which the drug is encapsulated in the core and surrounded by a protective polymer shell. This design enables targeted, sustained drug release while shielding the drug from environmental degradation or premature release (77). Core-shell fibers are particularly beneficial for drugs requiring precise delivery to specific sites, such as in cancer therapy. The controlled release mechanism also minimizes side effects by preventing burst release and ensuring prolonged therapeutic action. The study successfully developed chitosan-polycaprolactone (CS-PCL) core-shell nanofibers using coaxial electrospinning, with CS as the core and PCL as the shell. The study also confirmed *in vitro* degradation of the nanofibers in PBS and reported a two-stage drug release pattern for tetracycline hydrochloride (TCH)-loaded CS-PCL nanofibers—an early burst release followed

Table 3. Key properties, potential applications, and limitations of different types of nanofibers

Type of nanofiber	Key properties	Potential applications	Limitations	Ref
Polymer nanofibers	High surface area, lightweight, flexible	Filtration, tissue engineering, and drug delivery	Limited thermal stability, may degrade over time	(69)
Ceramic nanofibers	High strength, thermal stability, chemical resistance	Structural materials, sensors, and catalysts	Brittle nature, complex fabrication processes	(70)
Metal nanofibers	High electrical conductivity, strength	Electronics, catalysis, sensors	Corrosion susceptibility, high cost	(71)
Carbon nanofibers	High tensile strength, electrical conductivity, and lightweight	Composites, energy storage, reinforcement	Expensive production, potential health risks	(72)
Biopolymer nanofibers	Biodegradable, non-toxic, renewable	Medical applications, environmental remediation	Limited mechanical properties, variability in source materials	(73)
Composite nanofibers	Enhanced properties from multiple materials	Advanced materials, protective clothing	Complexity in processing, potential incompatibility of components	(74, 75)

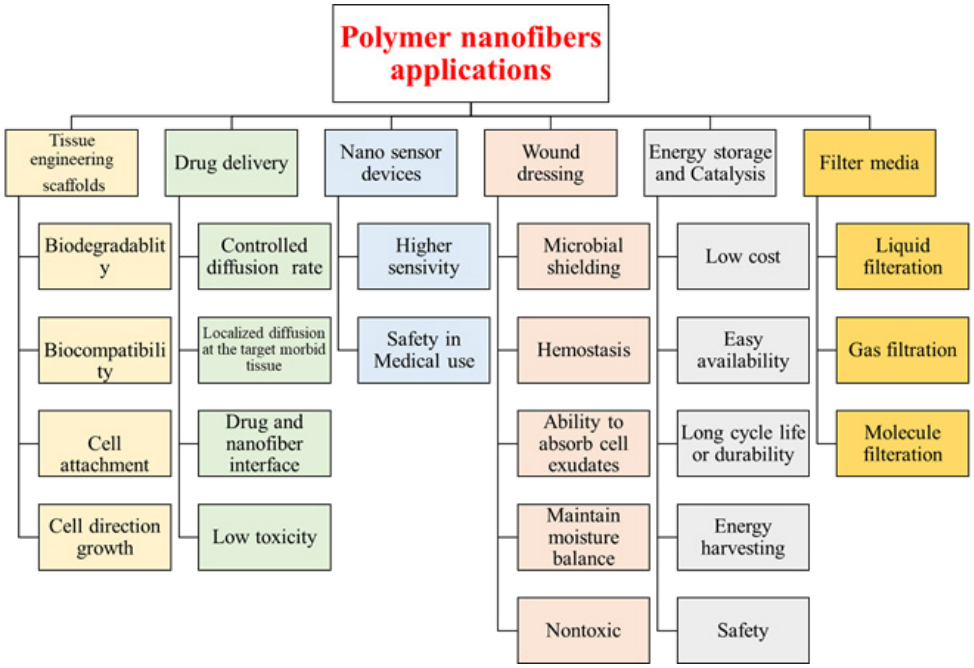

Figure 5. Illustrates the various applications of polymer nanofibers, highlighting their versatility across multiple fields
These nanofibers are utilized in areas such as biomedical, environmental, energy, and electronics applications. Each of these applications leverages the unique physical and chemical properties of polymer nanofibers, making them indispensable in advancing technology and addressing global challenges

by sustained release (78).

Surface functionalization for improved bioavailability

Surface functionalization involves modifying nanofiber surfaces to attach drugs via physical adsorption or chemical bonding. This method can improve bioavailability by enabling rapid, direct drug release. Functionalization can also enhance drug interactions with biological targets, improving therapeutic outcomes (79). However, this approach requires careful consideration of drug stability on the fiber surface and the potential for desorption under physiological conditions.

Multilayered 3D electrospun nanofibers

Multilayered 3D electrospun nanofibers are a state-of-the-art invention in nanotechnology, engineered to reproduce complicated natural structures and deliver enhanced performance. These materials consist of multiple layers of electrospun fibers, prepared or combined to create a three-dimensional (3D) framework (79). Their layered design offers remarkable adaptability, making them suitable for various applications, including tissue engineering, drug delivery systems, filtration technologies, and advanced composite materials. To meet the demands of clinical applications, multilayered 3D electrospun nanofiber-based drug delivery systems have been developed in recent years, offering precise control over drug-release kinetics. The nanofibrous layers that do not contain biomolecules serve as a physical barrier, hindering water diffusion and thereby delaying the release of drugs from the adjacent drug-loaded nanofibrous layers (80). According to this approach, Falde and coworkers developed a trilayered superhydrophobic electrospun fiber composed of PCL and poly(glycerol monostearate-co-ε-caprolactone)(PGC-C18). The design combined the chemotherapeutic agent 7-ethyl-10-hydroxy-camptothecin (SN-38) within the core layer, which was positioned between two outer protective layers of the fiber that did not contain any drugs (81).

Stimuli-responsive (smart) nanofibers

Stimuli-responsive nanofibers, often called "smart" nanofibers, are advanced nanomaterials engineered to respond to specific external or environmental cues. These nanofibers exhibit controlled, predictable changes in their physical, chemical, or mechanical properties when exposed to triggers such as changes in temperature, pH, light, electric or magnetic fields, or biological signals. Their ability to adapt to changing conditions makes them highly versatile, with a wide range of potential applications in fields such as biomedicine, environmental science, and industry (82).

Stimuli are categorized into two main classes: endogenous and exogenous. Endogenous stimuli are natural conditions within cancer cells, including acidic microenvironments, oxidative stress, and specific enzymes. By contrast, exogenous stimuli are external factors such as variations in temperature, light, electric fields, and ultrasound (83). Among these categories, thermo-responsive nanocarriers have emerged as the most extensively studied approach for stimulus-triggered drug delivery in cancer therapy. These nanocarriers are engineered to maintain therapeutic agents at the body's normal temperature of 37 ˚C while enabling rapid drug release when exposed to temperatures in the 40-42 ˚C range, known as hyperthermia. This temperature change can be induced by mechanisms such as light-activated heating of gold nanoparticles or magnetic field-induced hyperthermia (84).

Aoyagi and colleagues fabricated an innovative electrospun fiber featuring a smart hyperthermia on/off function, enabling simultaneous heat generation and drug discharge under an alternating magnetic field (AMF) to prompt apoptosis in skin cancer cells. The system used a temperature-sensitive copolymer of N-hydroxymethylacrylamide

(HMAAm) and N-isopropylacrylamide (NIPAAm) to load DOX as a chemotherapy agent and magnetic nanoparticles (MNPs) as a heat source during the electrospinning (85).

Therapeutic potential of electrospinning nanofibers in cancer therapy

Chemotherapy is an important characteristic of cancer treatment as it is designed to inhibit the division and proliferation of cancer cells. On the other hand, chemotherapy is highly toxic, has drug resistance, and has limited selectivity, which also results in systemic side effects. Trials in tumor treatment include rapid drug degradation, insufficient supply to tumor tissue, and the risk of metastasis to other organs (86). Therefore, cancer treatment with chemotherapy often leads to adverse reactions and side effects like nerve damage, weakened immune system, and hair loss (Table 4). Electrospinning is a method that can incorporate medications into nanofibers, leading to slower release rates, extended release periods, and reduced drug dispersion, ultimately decreasing the risk of side effects from administering multiple drugs. Moreover, electrospun drug-loaded nanofibers can accommodate multiple drugs simultaneously, creating a synergistic effect that can initially activate drug-resistant compounds and generate new therapeutic effects (87).

Using the electrospinning method, the fiber diameter can be adjusted by properties of the polymer solution, such as elasticity, viscosity, electric field intensity, polymer concentration, and conductivity; by the distance between the spray and the metal collector; or by external parameters such as humidity and temperature (88). The noteworthy aspect is that these nanofibers can capture and store chemotherapy drugs using two primary techniques, one of which is coaxial electrospinning, in which two polymer liquids are rapidly spun together. For option B, mixed electrospinning combines the drug with the polymer solution at the start of the electrospinning process (89). The general system of this "core/shell" electrospinning process

Table 4. Electrospinning nanofibers in cancer therapy

Cancer/Cell line	Polymer	Solvent	Drugs	Size (nm)	Ref
Cervicovaginal	PEG	NCs@PDA-PEG	NCs@PDA-PEG NFs	385.6±35.47	(93)
CRC	PLC	Chloroform/methanol	CPT-11, SN-38	6800-8400	(94)
HepG2 cell lines	PLGA-gelatin	Hexafuoro-2-propanol	Doxorubicin hydrochloride and camptothecin	370-430	(95)
lung and breast cancer	PLC	DMF/dichloromethane Methanol/chloroform	Curcumin and natural extracts	222-518	(96)
Orthotropic cancer cells	PLC	Trifluoroethanol	Indomethacin, doxorubicin	400-600	(97)
HepG2	PLA	Chloroform	Daunorubicin	100	(98)
Graffi myeloid	Co-PLA	DMF/DMSO	DOX and quaternized chitosan	590	(99)
MCF-7 breast cancer cells	Co-PLA	DMF/DMSO	DOX and quaternized chitosan	260-945	(100)
K562 leukemia cancer cells	PLA	Chloroform	Daunorubicin	100	(101)
Breast	PFA	DMSO	ISL-NF	-	(102)
MCF-7 cells	PCL	N+L@PCL	N, L, N@PCL, and L@PCL	63.4-231.6 nm	(103)
CRC	PLLA	NA	5-Fluorouracil and oxaliplatin	300 nm	(104)
Glioma C6 cells	PEG–PLLA	NA	Carmustine	690 nm	(105)
HeLa cells (human cervical cancer)	pNIPAM	Trifluoroethanol (TFE, 99%)	Doxorubicin	600-800	(106)
SKOV3 cells (ovarian cancer)	PVA	Acrylic acid (AA) and (DMSO)	Doxorubicin	260	(107)
A549 (lung carcinoma) and MCF-7 (breast carcinoma)	PEO	poly (ethylene oxide)-b-poly (e-caprolactone) (PEO-PCL)	nic@Ag NPs	340	(108)
Breast cancer 4T1 cells	PEG	DMF/DMSO	SWNT@MS-PEG/DOX	300	(110)
Cancer	PCL–PEG	poly (vinyl alcohol) (PVA) and the micelles	Hydrophobic doxorubicin (Dox)	211.20 39.89	(111)
CRC ((HCT-116))	PLA	PLA/paclitaxel nanofibers	-	32 and 68	(112)
MCF-7 and 4T1 breast tumor cell lines	PCL	PIP-PCL^{75}-Coll^{25} nanofiber	PCL^{75}-Coll^{25}	-	(113)
MCF-7 and MDA-MB-231 cells	PLGA	PLGA/Ge-PG and PLGA/Ge-F127/PG nanofibers	Pluronic F127 and prodigiosin (PG)	535	(114)
Prostate cancer	PEO	PTX-loaded nanofiber mats	Hyaluronic acid (HA)	300	(115)

Colorectal cancer (CRC), – poly lactic-co-glycolic acid (PLGA), poly (L-lactic acid (PLLA), poly (N-isopropyl acrylamide) (pNIPAM), PEG–PLLA-poly (ethylene glycol)–poly (L-lactic acid), poly (ecaprolactone) (PCL), poly (vinyl alcohol) (PVA), Poly (ethylene oxide)(PEO)

consists of two needles arranged in a coaxial configuration. Certainly, drugs can be incorporated into nonwoven fabrics through physical adsorption (including electrostatic interactions), covalent binding, or methods such as coaxial electrospinning or solvent mixing. By using some of the techniques mentioned earlier, electrospinning also enables the creation of hybrid nanofiber composites (90, 91). Electrospinning was developed to plan a drug delivery system containing fGO-Si-CUR nanofibrous mats to exploit its anticancer properties. Since no toxic organic solvents are used to prepare this drug delivery system, it can be considered an environmentally friendly and safe drug carrier that can also improve the bioavailability and biological activity of Curcumin (CUR) (92). An innovative electrospun nanofiber system featuring PEGylated paclitaxel nanocrystals was developed to enhance transmucosal penetration and provide in situ retention, aiming for more effective treatment of cervicovaginal cancer. (93). 3D superhydrophobic electrospun meshes, as strengthening agents, were advanced for sustained local drug delivery against CRC cells. The findings indicate that superhydrophobic meshes have the necessary mechanical properties for surgical reinforcement of the anastomosis. They also allow for non-invasive tracking of mesh placement, verification of drug release using ultrasound, and gradual release of chemotherapy for more than three months, leading to substantial tumor cell death in human colorectal cancer (94). A hydrophilic drug (doxorubicin hydrochloride, DOX) and a hydrophobic drug (camptothecin, CPT) with an innovative mesoporous ZnO/poly (lactic-co-glycolic acid)/gelatin (mZnO/PLGA/GE) electrospun composite fiber encapsulated were fabricated for potential postsurgical cancer treatment (95). Natural extract-loaded nanofibres in combination with CUR were fabricated for potential treatment of lung and breast cancer. The sustained, long-term, spontaneous release of the drug suggests that this formulation could be carried as a local medical device, specifically an implant or a drug-eluting stent (96). Constructed electrospinning nanofibrous fabrics (labeled as MC/UCNPS/DOX) with core-shell arranged Yb@mSiO_2-polyethylene glycol (UCNPS) with $NaGdF_4$:Yb/Er@$NaGdF_4$ (NPs) were developed for in vivo orthotopic cancer treatment (97). In a research study, emulsion-electrospun fibers with intratumoral grafting-induced core loading of hydroxycamptothecin exhibited antitumor activity (98). Similarly, quaternized chitosan-based electrospun implants showed anti-meloid tumors in Graffi. Additionally, attachment of QCh/coPLA/DOX implants at the site of the removed tumor led to an increase in the animal survival rate and a reduction in the recurrence rate (99). The finding indicated that nanofibers containing doxorubicin-loaded quaternized chitosan induce apoptosis and exhibit antiproliferative activity against the MCF-7 human breast carcinoma cell line (100). Fe_3O_4 and Polylactide nanofibers, as novel nanocomposites, exhibited the cell death properties of leukemia cancer cells. The results indicate that the nanocomposite can effectively promote the interaction of daunorubicin with leukemia cells and significantly improve the uptake of anticancer drugs into cancer cells and their penetration, thereby causing cell death in leukemia cells (101). An original study showed that breast cancer proliferation and invasion were inhibited by using isoliquiritigenin (ISL)-infused electrospun nanofibers due to downregulation of MMP2/9 and PI3K/Akt/mTOR pathways (102). Nedaplatin (n)- loaded PCL-based electrospun nanofibers were designed for the controlled release of substances in cancer cells, which depends on pH levels. The planned nanofibers showed minimal degradation, had nano-scale diameters, and maintained exceptional thermal stability under physiological conditions. Additionally, n+l@pcl demonstrated greater apoptotic effects and the highest cytotoxicity on MCF-7 breast cancer cells when compared to pcl-based electrospun nanofibers containing both loaded and free drugs used in single therapy (103). The electrospun polylactide nanofibers loaded with 5-fluorouracil and oxaliplatin demonstrated antitumor activity against CRC. Moreover, results confirmed that anticancer activities of oxaliplatin and 5-Flu against CRC can be considerably enhanced by using PLA electrospun nanofibers as a local drug delivery system (104). Ultrafine fibers of PEG–PLLA with BCNU demonstrated anti-tumor effects on glioma C6 cells. Advanced systems are suitable for administering postoperative chemotherapy for cancer treatment and feature controlled release of BCNU (105). PNIPAM/Gelatin Nanofibers with cross-linked construction were used against HeLa cells (human cervical cancer). In other words, a direct method for releasing and encapsulating drugs *in situ* EDC/NHS cross-linked PNIPAM–gelatin nanofibers by reversibly and dynamically swelling/deswelling properties (106). Polyvinyl alcohol/chitosan (PVA/CS) core-shell nanofibers are effectively engineered via a simple coaxial electrospinning technique, in which CS forms the shell layer, and PVA forms the core layer (107). Drug delivery systems using silver and niclosamide nanoparticles (nic@Ag NPs) incorporated into poly (ethylene oxide)-poly (caprolactone) composite nanofibers were developed to target MCF-7 cells. The nic@Ag NPs demonstrated enhanced therapeutic efficacy against MCF-7 cells. Various cell-based assays were conducted to confirm the mechanism of cell death induced by the nic@Ag NP nanocomposites in MCF-7 cells (108, 109). Coated SWCNTs with mesoporous silica were proposed as a multifunctional light-responsive system for cancer combination therapy. DOX was loaded into SWCNTs to form the SWNT@MS-PEG/DOX nanocomposite (110). An implantable polymeric nanofiber combination of an active-targeting micellar system and localized drug delivery was developed for safe and efficient cancer therapy. This system is first achieved by constructing hydrophobic doxorubicin (Dox)-encapsulated active-targeting micelles derived from a folate-conjugated PCL–PEG copolymer (111). Similarly, PLA/PTX nanofiber displayed anti-cancer activity. Moreover, the results have verified the potential of a novel PLA/paclitaxel nanofiber-based organization as a continuous-release patch for post-surgical drug delivery of cancer therapeutics (112). An implantable, controlled-release anticancer delivery system was developed using piperine-loaded electrospun nanofibers for postsurgical breast cancer treatment. The PIP-PCL75-Coll25 nanofiber formulation was identified as optimal due to its excellent mechanical properties, sustained piperine release, and enhanced cytotoxicity (113). For the treatment of triple-negative breast cancer (TNBC), prodigiosin-loaded electrospun nanofiber scaffolds were designed. In this study, prodigiosin (PG) and nanoscale fibers of PLGA/Ge pluronic F127 were produced *via* blend electrospinning (114). The

electrospinning of chitosan/polyethylene oxide (PEO) produced highly porous chitosan nanofibers for a mat perspective in chemotherapy against prostate cancer. The results showed that chitosan/hyaluronic acid fibers controlled the release of paclitaxel effectively, making them a suitable option for postoperative chemotherapy in prostate cancer (115). Yang *et al*. explored an implantable micelle-in-nanofiber system with active-targeting capabilities for localized cancer treatment [62]. They incorporated active-targeting DOX-loaded micelles (FM) into core-shell nanofibers (FM-Nanofiber). The core phase consisted of a mixture of micelles and poly (vinyl alcohol)(PVA), while the shell was made from a gelatin solution (Figure 6).

One of the primary advantages of nanofibers in drug delivery is their ability to encapsulate therapeutic agents, including chemotherapeutics, proteins, and nucleic acids. This encapsulation not only protects the drugs from degradation but also facilitates controlled release, ensuring that the therapeutic agents are delivered at the right dose and time (117, 118). This targeted delivery minimizes systemic side effects and enhances treatment efficacy, which is particularly crucial in cancer therapy, where traditional methods often cause significant collateral damage to healthy tissues (117, 118). Moreover, nanofibers can be functionalized with targeting ligands, such as antibodies or peptides, which can specifically bind to cancer cells. This targeted approach enables selective delivery of drugs to tumor sites, increasing the therapeutic agent concentration at the target site while reducing exposure to non-target tissues. This specificity can lead to improved patient outcomes, including higher response rates and reduced toxicity. The biocompatibility and biodegradability of many nanofiber materials further enhance their potential in clinical applications. As these materials can be designed to degrade over time, they reduce the risk of long-term complications associated with non-biodegradable carriers. Additionally, the ease of fabrication and scalability of nanofiber production techniques, such as electrospinning, make them an attractive option for widespread clinical use.

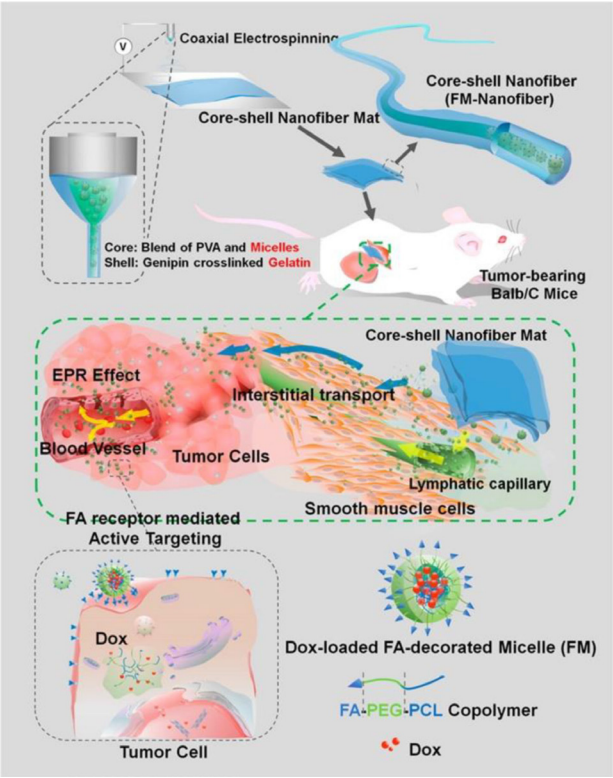

Figure 6. PImplantable doxorubicin-loaded micelle-innanofiber platform synthesized by coaxial electrospinning
Reproduced with permission (116). Copyright 2015, American Chemical Society
DOX: Doxorubicin, ACS: American Chemical Society, ES: Electrospinning, NF: Nanofiber

Recent studies have demonstrated the effectiveness of nanofiber-based drug delivery systems in various cancer models, showing promising results in enhancing therapeutic efficacy and improving survival rates. By optimizing the design of nanofibers, researchers are exploring ways to overcome challenges such as drug resistance and tumor heterogeneity, which are significant barriers in cancer treatment (119). In conclusion, the integration of nanofibers into cancer drug delivery systems holds great promise for improving patient outcomes. By enabling targeted, controlled, and efficient delivery of therapeutic agents, nanofibers can enhance the effectiveness of cancer treatments while minimizing adverse effects. As research advances in this field, the potential of nanofiber technology to transform cancer therapy and improve patients' quality of life is significant (119). Continued research is crucial to overcoming the current challenges associated with nanofiber-based therapies and advancing them toward clinical application. Despite the promising potential of nanofibers in cancer drug delivery, issues such as production scalability, regulatory hurdles, and the need for a comprehensive understanding of their interactions within biological systems remain significant barriers. Ongoing studies are essential to optimize the design and functionality of nanofibers, ensuring their safety, efficacy, and reproducibility in clinical settings. By addressing these challenges through innovative research and collaboration among scientists, clinicians, and industry stakeholders, we can accelerate the translation of nanofiber technologies from the laboratory to the clinic, ultimately improving treatment outcomes for cancer patients and enhancing the overall landscape of cancer therapy.

Loading and release kinetics of chemotherapeutic agents from nanofibers drug/ polymer blend nanofibers

Understanding the kinetics and mechanisms of drug release is essential for characterizing a delivery system. Various models have been employed to investigate drug release from different delivery systems (120, 121). The release of drugs from polymeric films can be accurately modeled by first-order kinetics, indicating that the drug-release mechanism is concentration-dependent. As a result, the release of the drug was proportional to the remaining amount of drug in the matrix. The drug release decreased as the concentration gradient reduced over time (122). The composite matrix mainly facilitated the diffusion of the medium, which drove the release of the drug. Despite this, the zero-order model and the Hopfenberg model were unable to accurately explain the drug release (123). Studies have indicated that diffusion primarily controls the transfer of solute (drug transport) from nondegradable polymer systems. Two categories of devices, "reservoir" and "matrix," can be used to produce these polymers (123). In matrix-type devices, the release of drugs is primarily caused by Fickian diffusion, which is affected by the concentration gradient,

distance, and swelling (124). For example, the different kinds of liposomes that can be created by adjustments are illustrated in Figure 7, along with the drug-release kinetics models from the liposomes.

Although extensive research has focused on managing drug delivery with nanocarriers, the importance of regulating drug release from nanocarriers is sometimes overlooked because of well-established large-scale drug delivery systems. Controlling drug release from nanoparticles presents unique challenges compared with traditional drug carriers, primarily because nanoparticles have a higher surface area-to-volume ratio and shorter diffusion distances (11).

Nanofibers hold significant potential in clinical cancer treatment, primarily by enhancing drug delivery, improving targeting of tumor cells, and minimizing side effects associated with conventional therapies. Their high surface area-to-volume ratio and tunable properties enable the encapsulation of therapeutic agents, supporting sustained release and localized treatment. This targeted approach can improve therapeutic efficacy and reduce systemic toxicity. Future research could focus on developing multifunctional nanofibers that combine therapeutic agents with imaging capabilities, enabling real-time monitoring of treatment efficacy. Additionally, exploring biodegradable nanofibers could enhance safety and biocompatibility, paving the way for personalized cancer therapies. Hypotheses about the synergistic effects of combining nanofiber-based delivery systems with immunotherapy or gene therapy could also be investigated, potentially leading to more effective and tailored treatment strategies for various cancer types. Overall, integrating nanofiber technology into cancer therapy represents a promising frontier that warrants further exploration and innovation.

Challenges and potential risks associated with nanofibers

Nanofibers, particularly those derived from synthetic materials, pose several health and safety risks, primarily due to inhalation. Their minuscule size enables them to penetrate deep into the lungs, potentially resulting in respiratory issues (126). Additionally, the toxicity of certain nanofibers can vary based on their chemical composition and morphology; for example, metal nanofibers may pose health risks if ingested or absorbed through the skin. From an environmental perspective, the biodegradability of nanofibers is a significant concern (126). While biopolymer nanofibers can decompose naturally, many synthetic variants do not, leading to environmental accumulation and pollution, especially in aquatic ecosystems. Furthermore, the production processes for nanofibers are often energy-intensive and may involve hazardous chemicals, raising questions about their overall sustainability (127). Mechanical limitations also hinder the application of nanofibers. Certain types, particularly ceramic and some polymer nanofibers, exhibit brittleness, making them unsuitable for load-bearing applications. Additionally, the properties of nanofibers can vary significantly with production methods and conditions, leading to performance inconsistencies (128). Cost and scalability are further challenges in the adoption of nanofibers. The production costs, especially for advanced materials like carbon or metal nanofibers, can be prohibitively high, limiting their use in cost-sensitive applications (129). While laboratory-scale production is well-established, scaling up to industrial levels while maintaining quality and consistency remains a significant hurdle. Regulatory challenges also complicate the landscape for nanofiber technologies. The rapid advancement in this field has outpaced existing regulatory frameworks, resulting in a lack of standardized testing methods to assess safety and efficacy (129). This gap can hinder commercialization efforts. Additionally, public perception of nanomaterials, often influenced by safety concerns, can lead to resistance that impacts market acceptance and regulatory approval. Finally, there is a limited understanding of the long-term effects of nanofiber exposure, particularly in occupational settings. Research on chronic exposure is still in its infancy, necessitating further studies to elucidate potential chronic health effects associated with nanofibers. Overall, while nanofibers hold promise for various applications, addressing these multifaceted concerns is crucial for their safe and effective integration into products and processes.

Conclusion and future directions

Over the past decade, the incidence of cancer has continued to rise, underscoring the urgent need for safer and more effective therapeutic strategies. Conventional

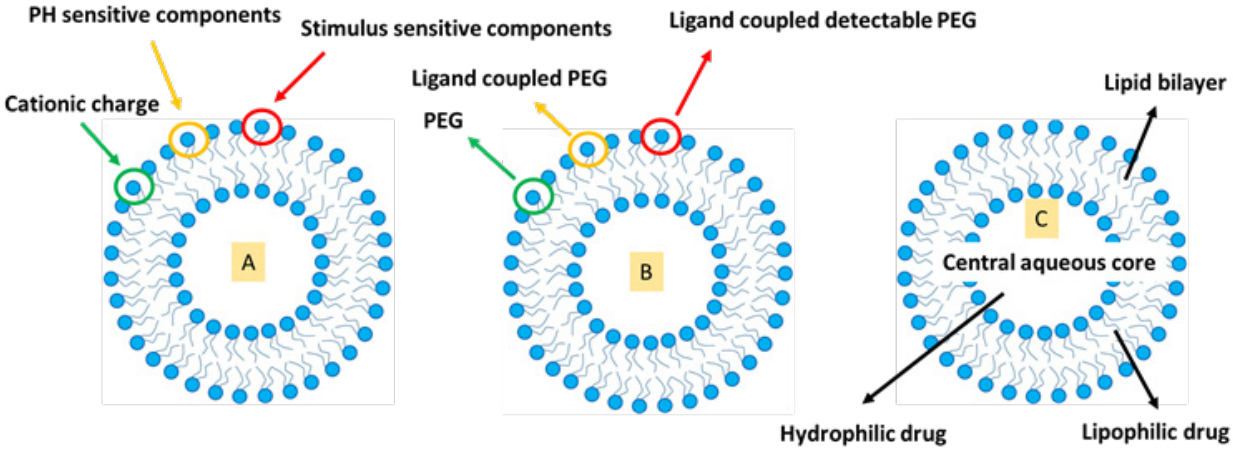

Figure 7. Various liposome modifications and their release kinetics models include: a) cationic or stimuli-sensitive liposomes; b) release kinetics profiles; c) PEGylated or targeted liposomes. Reproduced from (125), licensed under CC BY 4.0
PEGylated, Poly (ethylene glycol)-modified, PEG (Poly (ethylene glycol)

anticancer drugs are often limited by systemic toxicity and suboptimal targeting, which can compromise treatment outcomes. Electrospun nanofibers have emerged as a versatile and highly promising platform for localized drug delivery and tissue engineering due to their distinctive features, including high drug-loading capacity, large surface-area-to-volume ratio, structural flexibility, and tunable fabrication parameters. These scaffolds can incorporate multiple drugs, nanoparticles, and bioactive agents, enabling controlled, sustained release directly at the target site. This review highlights recent advances in the use of electrospun nanofibers for cancer therapy, including applications such as drug and gene delivery, targeted treatment of cancer cells, and 3D scaffold-based tissue regeneration. Importantly, the integration of localized drug delivery with biomimetic 3D nanofiber scaffolds presents the opportunity to simultaneously achieve effective chemotherapy and tissue repair, particularly in filling post-surgical tumor cavities. Despite these promising developments, several critical challenges remain. Limited *in vivo* data, concerns regarding long-term scaffold stability, and barriers to clinical translation continue to hinder the full potential of these systems. Future research should aim to address these challenges by optimizing scaffold composition and architecture, validating therapeutic efficacy in relevant animal models, and developing scalable strategies for clinical application. Successfully translating electrospun nanofiber platforms from the laboratory to the clinic could significantly enhance the precision, safety, and effectiveness of cancer treatments.

Acknowledgment

The authors would like to thank the Immunology Research Center, Tabriz University of Medical Sciences, Iran, for their financial support of this project (Grant NO. 70790).

Ethics Approval and Consent to Participate

The ethical approval for this paper was obtained from Tabriz University of Medical Sciences (IR.TBZMED.VCR.REC.103.095)

Authors' Contributions

AF A, SA S, and S M conducted the investigation, developed methodology, curated data, prepared the original draft, and handled reviewing and editing. M D and T K provided supervision, conceptualized the study, secured funding, and contributed to reviewing and editing. All authors reviewed the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Declaration

The authors acknowledge using ChatGPT (OpenAI) to support drafting the introduction. All content has been reviewed and validated by the authors.

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