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Georgian Biomaterials Journal

Review Article

Biodegradable nanofiber scaffolds as dual-action platforms for drug delivery and enhanced tissue healing

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ABSTRACT

Biodegradable nanofiber scaffolds are an innovative platform that combine controlled drug delivery with enhanced tissue healing. Mimicking the extracellular matrix, they offer a porous, breathable, and moist environment that supports cell growth and migration. Their large surface area allows for efficient loading and sustained release of bioactive agents like growth factors and antimicrobials, promoting hemostasis, reducing inflammation, stimulating angiogenesis, and preventing infection. This dual action accelerates tissue regeneration, especially in complex wounds such as bone defects. Recent advances show that sequential, time-controlled release of multiple therapeutics from these scaffolds improves healing outcomes over single-agent treatments. Despite challenges in optimizing drug loading and release timing, biodegradable nanofiber scaffolds hold great promise for regenerative medicine and targeted drug delivery. This mini-review covers their fabrication, drug incorporation and release mechanism, biomedical applications, limitations, and future prospects for enhancing therapeutic performance.

Peer review under responsibility of UGPH.

ARTICLE INFORMATION

Article History:
Received 27 February 2025
Received in revised form 25 June 2025
Accepted 27 June 2025

Keywords:
Nanofiber
Drug delivery
Tissue healing
Biodegradable

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1. Introduction

Biodegradable nanofiber scaffolds represent a groundbreaking advancement in biomedical engineering, offering dual roles in drug delivery and enhancing tissue repair [1]. Their nanofibrous design closely resembles the natural extracellular matrix (ECM), forming a porous, breathable, and moisture-retentive environment that promotes cell adhesion, growth, and differentiation [2-4]. This structural mimicry supports tissue regeneration and also acts as an efficient carrier for therapeutic substances, making them ideal for intricate wound management and tissue engineering applications [5, 6]. Biodegradable polymers in nanofiber scaffolds aid tissue repair by degrading gradually, aligning with the healing process, which minimizes long-term inflammation and foreign body reactions [7, 8].

Recent developments emphasize the multifunctional nature of these scaffolds, which act as both structural supports and drug storage systems [6, 7]. For instance, cellulose-based electrospun nanofibers offer excellent biocompatibility and can be embedded with nanoparticles for antimicrobial purposes, thereby greatly enhancing wound healing [9-11]. Similarly,

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DOI: https://doi.org/....

nanofibers made from silk fibroin and collagen have been designed to release therapeutic agents uniformly, aiding tissue regeneration and combating infection and inflammation [8, 12]. Despite their potential, challenges remain in maximizing drug loading without compromising scaffold integrity and in attaining accurate control over drug release in both space and time [13]. Current research focuses on stimulus-responsive delivery systems integrated into nanofibers that respond to environmental cues such as pH or temperature, releasing drugs accordingly [14]. These developments seek to enhance the therapeutic effectiveness and adaptability of nanofiber scaffolds across different clinical applications, including chronic wound management and cancer therapy [13]. This mini review offers a detailed overview of biodegradable nanofiber scaffolds functioning as dual-action platforms. It emphasizes their design, fabrication techniques, and biomedical uses. The review examines how these scaffolds combine drug delivery with tissue regeneration, discusses recent technological progress, and highlights potential future developments to enhance scaffold performance for regenerative medicine and drug therapy.

2. Materials of Biodegradable Nanofibers

Biodegradable nanofibers are primarily composed of natural and synthetic biopolymers, including composite variants that decompose environmentally. They offer sustainable solutions for applications such as biomedical devices, filtration, and packaging [15]. Fig. 1 illustrates various types of materials used for biodegradable nanofibers.

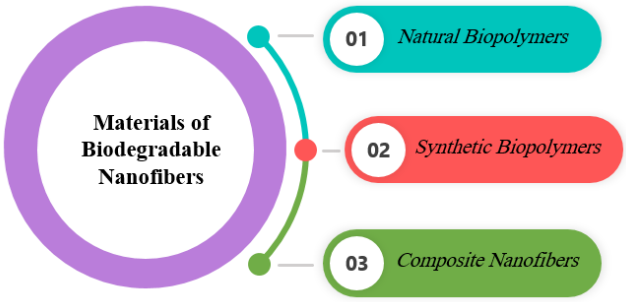

Fig. 1. Materials of Biodegradable Nanofibers.

2.1. Natural Biopolymers

Commonly used natural biopolymers include cellulose, chitosan, starch, alginate, silk fibroin, and gelatin [16]. These materials originate from renewable sources and are prized for their biodegradability, biocompatibility, and sustainability [17, 18]. Cellulose, present in plant cell walls, is popular due to its abundance and strength [19, 20]. Chitosan, sourced from shellfish shells, is known for its antibacterial effects [21, 22]. Starch and alginate are also widely used because they are biodegradable and eco-friendly [23]. Silk fibroin and gelatin, derived from animals, are favored for their excellent biocompatibility and mechanical qualities [24].

2.2. Synthetic Biopolymers

Synthetic biodegradable polymers such as polylactic acid (PLA) and polycaprolactone (PCL) play crucial roles in creating biodegradable nanofibers [25]. PLA, produced from renewable resources like corn and sugarcane, is widely used in biomedical fields and filtration membranes because of its superb biodegradability and biocompatibility [26]. It can be fashioned into nanofibers with porous structures that improve filtration performance [27]. PCL is another synthetic polymer valued for its biodegradability and flexibility.

2.3. Composite Nanofibers

Composite biodegradable nanofibers are sophisticated materials created by combining biodegradable polymers with nanoscale fillers or biofibers, often through electrospinning [28]. These nanofibers usually merge polymers like polyhydroxyalkanoate (PHA) or its derivatives with natural nanoscale fillers like treated fish-scale powder (TFSP), which contains hydroxyapatite similar to bone tissue, thus boosting mechanical strength and compatibility with biological systems [29].

Adding these fillers enhances tensile strength and hydrophilicity, providing a conducive environment for cell growth, making them highly suitable for biomedical uses such as tissue engineering and filtration membranes. Furthermore, biofiber-reinforced nanocomposites are lightweight, stiff, biodegradable, and mechanically improved, broadening their applications across medical, environmental, and sustainability sectors [30]. The combination of natural nanofibers and biodegradable polymers enables customization of performance, including improved strength and controlled degradation, while being environmentally friendly [31]. Table 1 presents the properties and uses of various types of biodegradable nanofibers.

3. Dual-Functionality: Drug Delivery and Tissue Regeneration

Biodegradable nanofiber scaffolds have become a revolutionary tool in regenerative medicine, providing dual functions by combining drug delivery with tissue regeneration [32, 33]. Their distinctive structure and material qualities allow for controlled release of therapeutic agents while creating a biomimetic environment that promotes cell adhesion, growth, and differentiation.

3.1. Mechanisms of drug incorporation and release

The efficiency of drug loading and the accuracy of release profiles in biodegradable nanofiber scaffolds depend on the interplay among drug incorporation methods, polymer properties, and scaffold architecture. This makes them versatile platforms for controlled drug delivery [6, 34, 35].

3.1.1. Drug Incorporation Mechanisms

Drugs can be integrated into biodegradable nanofiber scaffolds through various methods like physical adsorption and chemical conjugation, each affecting loading efficiency and release behavior [6, 36]. A common technique is physical adsorption, where drugs attach to the scaffold surface via non-covalent forces like van der Waals and electrostatic interactions [37, 38]. This method is simple and maintains the drug's chemical integrity and activity, but it often leads to a faster release because the drug is on the surface and has limited loading capacity, which depends on the scaffold's surface area and the drug's solubility [6]. Blending is a common technique, involving mixing the drug with the polymer solution prior to fiber formation, typically through electrospinning [34]. This method disperses the drug evenly within the fiber matrix, leading to greater loading capacity and a more sustained release profile [39].

Table 1. Characteristics of Different Types of Biodegradable Nanofibers.

Material Type	Examples	Source	Properties/Applications	References
Natural Biopolymers	Cellulose, Chitosan, Chitin, Collagen, Gelatin, Silk fibroin, Pectin, Alginate, Hyaluronic acid	Derived from plants, shellfish, animals	Biocompatible, biodegradable, bioactive, used in tissue engineering, wound healing, drug delivery, packaging	[40, 41]
Synthetic Biopolymers	PLA, Poly lactic-co-glycolic acid (PLGA), Polyethylene oxide (PEO), PCL, Polybutyrolactam (PBY)	Bioplastic or synthetic bio-based	Tunable biodegradability, mechanical stability, used in drug delivery, tissue engineering, flexible electronics	[42]
Composite Nanofibers	Collagen-PCL, Gelatin-PCL, Chitosan-PEO, PLGA-collagen, Cellulose-chitosan-PEO	Combination of natural and synthetic polymers	Improved spinnability, controlled degradation rate, enhanced mechanical properties	[29, 43]

Additionally, core/shell and multilayer nanofiber structures can fine-tune drug incorporation [44]. In core/shell fibers, the drug resides in the core and is shielded by a polymer shell that acts as a diffusion barrier, allowing for extended and controlled drug release [34, 45].

Surface modification involves chemically or physically changing the nanofiber surface to enhance drug attachment or add functional groups that interact with the drug [46]. Also, the physical state of the drug, whether crystalline or amorphous, influences release behavior, as crystalline drugs on the fiber surface can lead to an initial burst release [46, 47].

3.1.2. Drug Release Mechanisms

Drug release mechanisms are varied and can include processes such as dissolution, diffusion, osmosis, partitioning, swelling, erosion, and targeting. These mechanisms depend on the specific application and may occur simultaneously or at different stages during the delivery process. The main process is diffusion, where drug molecules move from inside the fibers to the outside, driven by concentration differences [48].

The release of drugs from biodegradable nanofiber scaffolds involves multiple mechanisms, often working together [34]. Polymer degradation is an essential process, particularly for biodegradable scaffolds [49, 50]. As the polymer matrix breaks down via hydrolysis or enzymatic action, the encapsulated drug is released gradually.

The rate of degradation depends on factors such as the polymer's composition, molecular weight, and environmental conditions like pH and temperature [35, 51]. The hydrophobic nature of the polymer matrix can greatly slow water infiltration, which in turn delays drug diffusion and results in a more controlled, sustained release [34].

In certain cases, drug release occurs in multiple phases. It starts with a rapid burst of drug molecules on or near the fiber surface, then shifts to a slower, diffusion-driven stage as the drug moves from deeper inside the fibers. Finally, as the scaffold degrades, drugs embedded within the matrix are released when the polymer network breaks down [52].

The nanofiber scaffold's structure, including fiber diameter and porosity, affects the drug release profile [53, 54]. Thinner fibers or more porous scaffolds facilitate quicker drug diffusion, whereas thicker fibers and denser matrices tend to slow it down. Adding barrier layers or nanoparticles to the scaffold can further control the release rate, allowing for customized delivery suited to specific therapeutic requirements [55, 56].

Le et al. [34] examined Berberine-loaded PLA nanofiber scaffolds as a drug delivery system, linking their chemical properties to release behavior and antibacterial activity. The BBR/PLA scaffold's release fit best with the Ritger–Peppas model, indicating Fickian diffusion, while BBR NPs/PLA aligned with both Higuchi and Ritger–Peppas models, showing a combined diffusion and degradation mechanism. In BBR/PLA, release involved water dissolving surface BBR and slow diffusion from the core. For BBR NPs/PLA, rapid surface dissolution was followed by gradual internal diffusion via pore formation. Overall, BBR release is mainly influenced by drug distribution, wettability, and nanofiber pore structure, with PLA degradation being a slow process. Fig. 2 shows in vitro release patterns of BBR from BBR/PLA (blue line) and BBR NPs/PLA (pink line) nanofiber scaffolds [34].

3.2. Tissue healing support: physical cues and bioactive loading

Biodegradable nanofiber scaffolds facilitate tissue healing by offering physical cues that mimic the native ECM environment, alongside bioactive loading that delivers therapeutic agents or cells [57]. These combined approaches actively modulate the healing microenvironment, promoting cell survival, ECM remodeling, angiogenesis, and immunomodulation. As a result, they contribute to faster wound closure and better skin regeneration [58, 59]. Physical cues encompass the scaffold's structural and mechanical characteristics that affect cell behavior and tissue growth. Electrospun nanofiber scaffolds composed of blends of natural and synthetic polymers such as PCL, gelatin, chitosan, collagen, and silk fibroin imitate the ECM architecture, creating a supportive microenvironment for cell attachment, growth, and differentiation. Their nanofibrous structure helps retain moisture and facilitate gas exchange, both essential for healing [8, 57].

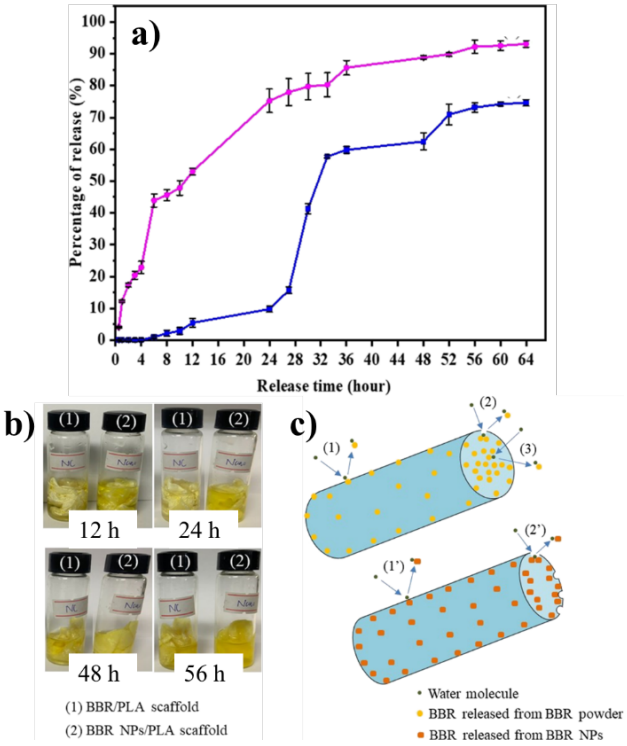

Fig. 2. a) In vitro release patterns of BBR from BBR/PLA (blue line) and BBR NPs/PLA (pink line) nanofiber scaffolds, b) photographic images depicting the BBR release outcomes at 12, 24, 48, and 56 hours, and c) suggested mechanism underlying BBR release from the BBR/PLA and BBR NPs/PLA nanofiber scaffolds [34].

Modifying scaffold stiffness, porosity, fiber orientation, and surface topology can enhance cell migration, promote blood vessel formation, and support ECM remodeling faster tissue regeneration [60]. For instance, scaffolds with optimized stiffness improve cell migration, while particular topological features can attract immune cells and trigger new angiogenesis [61]. Bioactive loading involves embedding therapeutic agents, such as growth factors, extracellular matrix proteins like fibrinogen and collagen I, nanoparticles, or stem cells, into scaffolds to actively influence the healing process. This method enables the sustained and local release of bioactive molecules that stimulate cellular responses, reduce inflammation, and support tissue regeneration [62]. For example, coaxial nanofiber scaffolds that mimic the dynamic ECM composition during wound healing by sequentially releasing fibrinogen and collagen I have been shown to boost immunomodulation and direct macrophage polarization toward a regenerative phenotype, thereby enhancing chronic wound healing [59]. Additionally, incorporating skin-derived precursor cells or mesenchymal stromal cells into scaffolds encourages ECM formation, cell proliferation, and integration at the wound site [58].

4. Current Limitations and Future Perspectives

The current limitations of biodegradable nanofiber scaffolds as dual-function platforms for drug delivery and tissue repair mainly involve difficulties in managing their degradation rate, drug loading, and release patterns. It is essential to align biodegradability with tissue regeneration; if the scaffold degrades too rapidly, it may not offer sufficient structural support, resulting in poor tissue formation and buildup of byproducts that could cause toxicity or inflammation. On the other hand, slow degradation might lead to scaffold encapsulation and immune rejection, hindering integration with surrounding tissue. Various factors such as material composition, scaffold architecture, surface modifications, and physiological conditions influence the degradation rate, complicating precise control [63].

A major challenge is ensuring controlled drug loading and precise spatiotemporal release without negatively affecting drug activity [6]. While nanofibers provide a high surface area and porous structure that mimics the extracellular matrix, facilitating efficient drug incorporation and sustained

release, keeping the drug stable during scaffold fabrication and release is still difficult [64]. Additionally, customizing release profiles to align with various tissue healing stages involves advanced stimulus-responsive systems, which are still being developed [6]. Future perspectives emphasize advancing fabrication methods like electrospinning, 3D printing, and molecular self-assembly to create multifunctional scaffolds with improved mechanical strength, biodegradability, and drug delivery features [65]. Innovations involve designing composite nanofibers that integrate biocompatible polymers with bioactive molecules such as growth factors and anti-inflammatory agents to enhance healing synergistically. Stimulus-responsive nanofiber scaffolds, which release drugs upon environmental triggers like pH or temperature changes, offer more precise treatment options. Moreover, gaining a deeper understanding of scaffold–tissue interactions and patient-specific factors will support the development of personalized scaffolds that improve integration and effectiveness [5]. Addressing these challenges is essential to fully solve the potential of biodegradable nanofiber scaffolds as dual-function platforms for drug delivery and tissue regeneration [1].

5. Conclusion

Biodegradable nanofiber scaffolds are a highly promising dual-action platform that combines targeted drug delivery with improved tissue healing. Their unique structure mimics the extracellular matrix, creating an optimal environment for cell attachment, growth, and differentiation. Additionally, their ability for controlled, localized drug release tackles key issues in treatment effectiveness and side effects. Advances in material science and nanotechnology have made it possible to create customizable scaffolds that safely degrade in the body, removing the need for surgical removal and lowering long-term complications. As research progresses to improve scaffold composition, drug loading methods, and release kinetics, these multifunctional systems are set to transform regenerative medicine and wound care, leading to better clinical outcomes and enhanced patient quality of life. Future investigations into in vivo performance, scalability, and regulatory processes will be vital for moving these innovative platforms from labs to widespread clinical use.

Author Contributions

Ebadullah Asadi: Conceptualization, Writing – original draft, Writing – review & editing. **Noushin Ezati:** Writing – original draft, Writing – review & editing. All authors read and approved the final version of manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data is available.

Ethical issues

The authors confirm full adherence to all ethical guidelines, including the prevention of plagiarism, data fabrication, and double publication.

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