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Mini Review

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

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ABSTRACT

Biodegradable nanofiber scaffolds are a newly emerging platform that provide the advantages of controlled drug delivery with improved tissue repair. They can replicate an extracellular matrix by introducing a porous, breathable and moist environment for the subsequent proper growth and migration of cells. The relatively large surface area provides an ideal medium for loading and sustained release of the bioactive agents (e.g., growth factors and antimicrobials), and can help promote hemostasis, reduce inflammation, stimulate angiogenesis and limit infection. Each of these processes contributes to the development of new tissues, however, in complex injuries (e.g. bone defects) this dual purpose can accelerate the rate of regeneration. Recently, researchers have reported that a temporally specific, sequential drug delivery by a biodegradable nanofiber scaffold could provide more effective healing opportunities compared to delivering one agent at a time. While we may still have challenges in getting or matching the drug loading with the temporal delivery, biodegradable nanofiber scaffolds will continue to be a promising and emerging platform for tissue regeneration and drug delivery. This mini-review discusses the different aspects related to biodegradable nanofiber scaffolds: designs and strategies for fabrication, methods of drug incorporation and drug release mechanisms, their biomedical applications, limitations and future pathways for enhancing therapeutic effects using biodegradable nanofiber scaffolds.

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1. Introduction

Biodegradable nanofiber scaffolds are a novel innovation in biomedical engineering, functioning as a vehicle for drug delivery and for stimulation of tissue repair [1]. The nanofiber modular design of the nanofiber scaffold

accurately simulates the extracellular matrix (ECM), creating a porous, breathable, and moisture-retentive environment conducive to cell adhesion, growth, and appropriately programmed differentiation [2-4]. This structural simulation provides the scaffold with the ability to support tissue regeneration, and serve as an effective carrier for therapeutic agents; making these scaffolds

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excellent candidates for multifaceted wound management, and tissue engineering applications [5, 6].

Biodegradable polymers incorporated in nanofiber scaffolds help repair tissues by degrading at a controlled rate that is consistent with the healing process, which leads to less chronic inflammation and foreign body response [7, 8]. New advances show the scaffold possess multi-functional properties as scaffolds and drug storage carriers [6, 7]. For example, cellulose-based electrospun nanofibers show favorable biocompatibility, may be incorporated with nanoparticles for antimicrobial activities, which will by far, improve wound healing [9-11]. Nanofibers composed of silk fibroin and collagen were shown to release therapeutic agents in a sustained manner while enhancing tissue regeneration by lessening the effects of infection and inflammation [8, 12]. Even though scaffolds are promising, challenges still exist in balancing drug loading without damaging the integrity of the scaffold, and in precisely controlling the spatial and temporal drug release rate [13]. Current studies are focusing on stimulus-responsive delivery systems based on nanofibers that can respond to environmental cues (e.g. pH or temperature) to induce drug release [14]. These developments are intended to maximize the therapeutic utility and flexibility of nanofiber scaffolds in various clinical contexts, including, but not limited to, chronic wound care and oncologic therapy [13].

This mini review provides a comprehensive overview of biodegradable nanofiber scaffolds serving as dual-use platforms. It emphasizes their design, fabrication methods, and biomedical applications. The review considers how the scaffolds integrate drug delivery alongside tissue regeneration, discusses recent advances in the field, and considers potential future applications for improving scaffold performance for both regenerative medicine and drug delivery.

2. Materials of Biodegradable Nanofibers

Biodegradable nanofibers are made of natural and synthetic biopolymers (including composite versions) that environmentally degrade. They are alternative supplies that are sustainable for applications in biomedical devices, filtration, and packaging [15]. The different types of materials used to produce biodegradable nanofibers are shown in Fig. 1.

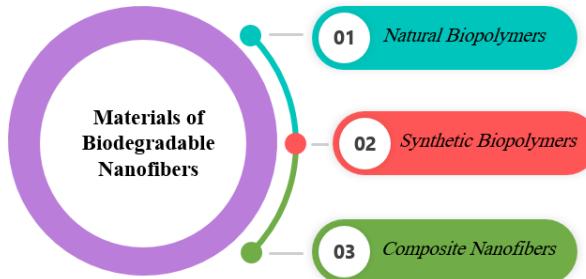


Fig. 1. Materials of Biodegradable Nanofibers.

2.1. Natural Biopolymers

Commonly used natural biopolymers involve: cellulose, chitosan, starch, alginate, silk fibroin, and gelatin [16]. These materials are sourced from renewable resources and have a lot of value for their biodegradability, biocompatibility, and sustainability [17, 18]. Cellulose, which forms the basis of the plant cell wall, is very popular because it is abundant and strong [19, 20]. Chitosan, which is derived from shellfish shells, is known for its antibacterial effects [21, 22]. Starch, and alginate are both used frequently as they can biodegrade and are eco-friendly [23]. Silk fibroin and gelatin, which derive from animals, are attractive due to their excellent biocompatibility and mechanical properties [24].

2.2. Synthetic Biopolymers

Synthetic biodegradable polymers, including polylactic acid (PLA) and polycaprolactone (PCL), are essential to producing formidable biodegradable

nanofibers [25]. PLA is produced from renewable resources like corn and sugarcane and is used in a variety of applications in the biomedical fields and also in filtration membranes due to its outstanding biodegradability and compatibility with human cells [26]. PLA can also be formed into nanofibers with porous nanofiber structures that enhance filtration performance [27]. PCL, a synthetic polymer, is another biodegradable polymer and is used due to its biodegradability and flexible characteristics.

2.3. Composite Nanofibers

Composite biodegradable nanofibers are advanced materials formed by blending biodegradable polymers with nanoscale fillers or biofibers, typically using electrospinning [28]. These nanofibers typically contain polymers such as polyhydroxyalcanoate (PHA) or its derivatives, together with a natural nanoscale filler, such as treated fish-scale powder (TFSP), that contains hydroxyapatite similarly found in bone tissue, thereby improving the mechanical strength, bioactivity and compatibility with biological systems [29]. The use of fillers provides improved tensile strength and hydrophilicity, yielding a better environment for cell growth and therefore, are highly versatile for applications in biomedicine, including, 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 [36, 37]. 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 effectiveness of drug loading and the precision of release profiles in biodegradable nanofiber scaffolds are based on the combination of drug incorporation method, polymer properties and scaffold design. This makes them flexible platforms for controlled drug delivery [6, 38, 39].

3.1.1. Drug Incorporation Mechanisms

Drugs can be incorporated into biodegradable nanofiber scaffolds using a number of different methods, including physical adsorption and chemical conjugation, and each method will impact loading efficiency and release behavior [6, 40]. A very useful method is physical adsorption; drugs are physically adsorbed to the scaffold because of non-covalent forces of attraction such as van der Waals interactions and electrostatic forces [41, 42]. Physical adsorption has advantageous because it is very easy, does not alter the physical or chemical integrity of the drug, or any function that its activity may possess, however, surface adsorption will usually release faster as these drugs are only on the surface of the scaffold and loading capacity is limited on the surface of the scaffold and the solubility of the drug is dependent on surface area [6]. Blending is a common technique, involving mixing the drug with the polymer solution prior to fiber formation, typically through electrospinning [38]. This method disperses the drug evenly within the fiber matrix, leading to greater loading capacity and a more sustained release profile [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 [38, 45].

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	[32, 33]
Synthetic Biopolymers	PLA, Poly lactic-co-glycolic acid (PLGA), Polyethylene oxide (PEO), PCL, Polybutyrolactam (PBL)	Bioplastic or synthetic bio-based	Tunable biodegradability, mechanical stability, used in drug delivery, tissue engineering, flexible electronics	[34]
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, 35]

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 [38]. 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 [39, 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 [38].

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. [38] 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 [38].

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].

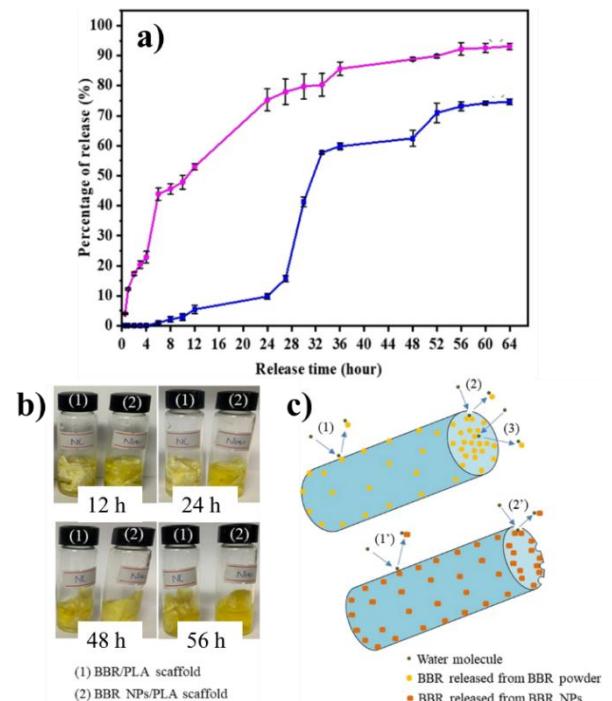


Fig. 2. a) In vitro release patterns of BBR from BBR/PLA (blue line) and BBR NPs/PLA (pink line) nanofiber scaffolds, b) photographic images depicting the BBR release outcomes at 12, 24, 48, and 56 hours, and c) suggested mechanism underlying BBR release from the BBR/PLA and BBR NPs/PLA nanofiber scaffolds [38].

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]. In particular, scaffolds with modified stiffness enhance cell migration, whereas specific topological features may attract immune cells and result in new angiogenesis [61]. Bioactive loading is the active incorporation of therapeutic agents into scaffolds (i.e. growth factor, ECM proteins, such as fibrinogen and collagen I, nanoparticles, or stem cells) in order to facilitate a healing process. This technique takes into consideration prolonged, localized release of the bioactive molecule, which can elicit cell responses, decrease inflammation, and aid tissue regeneration [62]. For example, coaxial nanofiber scaffolds that sequentially release fibrinogen and collagen I, mimicking dynamic ECM composition during wound healing, have been used to promote immunomodulation and shift macrophage polarization to a regenerative macrophage phenotype, thereby promoting healing of chronic wounds [59]. Scaffolds with incorporated skin-derived precursor cells or mesenchymal stromal cells support formation of ECM, increased cell proliferation, and integration into the wound area [58].

4. Current Limitations and Future Perspectives

The existing constraints of biodegradable nanofiber scaffolds as dual-purpose platforms for drug delivery and tissue repair. These limitations lie primarily in their degradation rate, drug loading capacity and release profiles. Managing biodegradability aligns with tissue regeneration; for example, a scaffold that degrades too quickly may not provide enough structural stability and time for adequate tissue formation due to accumulation of byproducts that may cause toxicity or inflammation.

In contrast, a scaffold that degrades slowly may become encapsulated in scar tissue or experience immune rejection, preventing integration into surrounding tissue [63, 64]. The degradation rate is influenced by several factors including the composition of the material, but also the architecture of the scaffold, surface modifications, and the physiological environment, making it difficult to precisely control [63].

There is an obvious challenge to controlling drug loading and spatiotemporal release such that the activity of the drug is not inhibited [6]. Although nanofibers provide an important high surface area and porous structure that resembles the extracellular matrix to allow efficient drug loading and sustained drug release, they still have the challenge to keep the drug stable during the fabricating of the scaffold and the releasing of the drug [65]. Furthermore, customizing for release profiles of various tissue healing stages is still required into advanced stimulus-responsive systems that are still developing [6].

Future directions call for the development of manufacturing technologies like electrospinning, 3D printing, and molecular self-assembly, to generate advanced scaffolds with multi-functionality and improved mechanical stability, biodegradability, and drug-delivery capabilities [66]. Advances would involve the design of composite nanofibers based on biocompatible polymers incorporating bioactive substances, including growth factors and anti-inflammatory molecules to facilitate integrated healing. Also, scaffold-loaded and stimulus-response nanofiber scaffolds, to deliver drugs in response to stimulations including changes in pH or temperature, may offer more specific treatment opportunities. Also, a better understanding of the scaffold-tissue interactions, and patient-specific variables, may lead to personalized scaffolds for better binding and efficacy [5]. Successful completion of these aims is necessary to achieve the full potential of biodegradable nanofiber scaffolds as dual-function platforms for drug delivery and tissue regeneration [1].

5. Conclusion

Biodegradable nanofiber scaffolds are a promising dual-functionality technology that allows for targeted drug delivery and enhanced tissue repair. These scaffolds provide structural conditions that mirror the extracellular matrix to provide an ideal cell attachment, growth, and differentiation environment. Additionally, scaffolds that allow for localized controlled drug release will address the clinically significant challenges of effectiveness and side effects of treatment regimens. New advances in both material science and nanotechnology have begun to provide scaffolds that are customizable, biomimetic, biocompatible, and safely biodegradable in the body - eliminating the surgical intervention for material removal and reducing the risk of long-term complications.

As research advances to enhance scaffold composition, drug loading strategies, and the kinetics of drug release, these multifunctional scaffolds could be game changers in regenerative medicine and wound care, providing better clinical outcomes and promoting improved patient quality of life. Future research into regulatory pathways, *in vivo* performance, and large-scale production will be critical to translating these innovative scaffolds from research use to the clinic, where they can benefit patients across healthcare.

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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