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Gelatin Nanofibers in Drug Delivery Systems and Tissue Engineering

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Abstract

Compared to conventional drug delivery systems (DDS), which show side effects due to uncontrollable properties of drug release, and nonspecific bio-distribution, smart DDS provide a regulated release for prolonged time and improve therapeutic efficacy. On the other hand, tissue engineering (TE) uses a combination of cells and ideal physicochemical and biochemical properties to renew different types of biological tissues. Both cases require an excellent polymer excipient to achieve controlled release of therapeutic agents to provide the correct matrix for cell proliferation. Besides the choice of polymer, the correct polymer excipient design should also be considered which demands the need for nanotechnology. Nanofibers fabricated from natural polymers are versatile due to their properties favorable for usage as scaffolds for TE, gene and drug delivery. Gelatin has been thoroughly looked into for biomedical applications because of its inherent biocompatibility, biodegradability and non-toxicity. In this review, we have focused on the potential of gelatin biopolymer-based nanofiber matrix in the application of DDS and TE.

Keywords: Drug Delivery Systems; Tissue Engineering; Polymers; Gelatin; Nanofibers; Electrospinning.
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1. Introduction

Drug Delivery Systems (DDS) are used to regulate and target the release of therapeutic compounds while reducing side effects. DDS enhance therapeutic efficacy by enhancing their absorption, distribution, metabolism, and excretion (ADME) profiles.[1] Conventional DDS are formulated for short periods, need repeated administration and display adverse effects due to disorderly release, nonspecific bio-distribution and rapid drug absorption.[1,2] During uncontrolled drug administration, the drug release could reach extreme toxic levels leading to overdose, or insufficient amounts of drug uptake.[1] As biomedical nanotechnology has evolved over the past few decades, conventional DDS have advanced into smart or novel DDS with stimuli-responsive properties.[3] These are designed to provide controlled drug release for prolonged times and improve therapeutic efficacy, which is achieved by selectively and specifically binding to the disease target.[1] Two types of stimuli-responsive DDS: (i) self-regulated and closed-loop mechanisms which identify modulations in temperature, concentration or pH, that instigate or adjust the rate of release of the substance (ii) systems that regulate drug release as a result of external stimuli like light, magnetic or electric fields which provide sustained drug release when triggered externally.[4,5] Tissue Engineering (TE) involves transplantation of cells, development of bioartificial tissues and promotion of endogenous regeneration.[6] TE applications include tissue adhesives, scaffolds, sutures for tissue regeneration, and non-permanent tissue barriers. Porous scaffold biomaterials combine with body cells, behave as regeneration templates for damaged tissues, and direct the development of newer tissues.[7] Bone, skin, skeletal muscle, neural tissues, cartilage, tendon, vascular tissues and ligament are scaffolds used in tissue repair.[8]

Polymers help provide modulated release of therapeutic agents in sustained doses for prolonged times, repeated dosage, and adjustable hydrophilic and hydrophobic release of drugs.[9] Due to the numerous advantages of natural polymers used in the fields of DDS and TE, there is a vast amount of ongoing research which is being reported regularly.[10,11] The drug carriers used in polymeric DDS can be hydrogels, nanofibers, microspheres, nanoparticles, liposomes, phytosomes,

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pharmacosomes, niosomes, transfersomes, ethosomes, and proniosomes.[9] Nanofibers display ideal properties such as structural similarity to Extracellular Matrix (ECM),[12] porosity, adequate cell adhesion, mechanical and physical properties, high efficiency of encapsulation, and high drug loading capacity. They are, therefore, used in drug delivery, regeneration of tissues and dressing of wounds.[13] Their small diameter resembles the ECM fiber size scale that allows them to be utilized as biomimetic scaffolds, high surface area to volume ratios and rates of protein adsorption are ideal for drug loading and cell attachment.[12] Their cost-effectiveness and easy preparatory methods make them suitable for drug delivery usage.[14] Stimuli-responsive or smart polymers display controlled and regulated release and can react and respond to environmental changes like light, pH, electric and magnetic fields, or temperature which categorizes them as intelligent.[5]

Polymeric nanofibers show distinctive mechanical properties like tensile strength, modulus, and shear modulus, which increase as fiber diameter decreases and are utilized to regulate cells' behavior and give strength to withstand cell cytoskeleton forces.[15] The composition of the fiber, alignment, degradation, diameter of the fiber, and mechanical properties can be adjusted for the required application. Polymeric nanofibers can be fabricated by employing techniques like phase separation, self-assembly, and the most frequently used method in DDS, electrospinning.[16] To initiate the regulated and sustained release of drugs, feedback and activation factors of electrospun nanofibers are required and these nanofibers which undergo chemical and physical changes present in feedback regulated or activation modulated systems are called smart electrospun nanofibers. These smart Nanofibers can also act as scaffolds for the regeneration of tissues, just like those Nanofibers that are unresponsive to external stimuli because of their good mechanical properties and biomimicry.[17]

This review will discuss the use of natural polymers, preparation and fabrication of stimuli-responsive polymeric nanofibers using the most common technique of Electrospinning and its various parameters, centering the focus on the versatile Natural Polymer, Gelatin, its nanofiber fabrication and usage in the field of Drug Delivery and Tissue Engineering. A few broad applications of gelatin nanofibers are illustrated in Fig. 1. This study will summarise the various applications of gelatin nanofiber in DDS and TE when combined with crosslinking agents such as genipin, glutaraldehyde, oxidized compounds of phenol, natural polymers like dextran and alginate and synthetic polymers like PCL and PLGA.[18]

2. Natural Polymers used in Drug Delivery and Tissue Engineering

Natural polymers are used as encapsulation vehicles for bioactive molecules and drug delivery.[10] They possess inherent advantages such as good biocompatibility, regulated enzyme degradation, particular interactions between biomolecules, and effortless modification which increases their usefulness in drug delivery.[19] Natural polymers like gelatin, collagen, hyaluronic acid, polysaccharides, chitosan, polyglycolic acid, dextrin, polylactic acid, and arginine have been utilized for polymeric DDS.[20] For example, gelatin's hydrophilic nature enables the penetration of body fluids into the particles and improves the bioactive molecule release mediated by diffusion.[21] The applications of a few natural polymers used to fabricate nanofibers used in drug delivery and TE are mentioned in Fig 2.

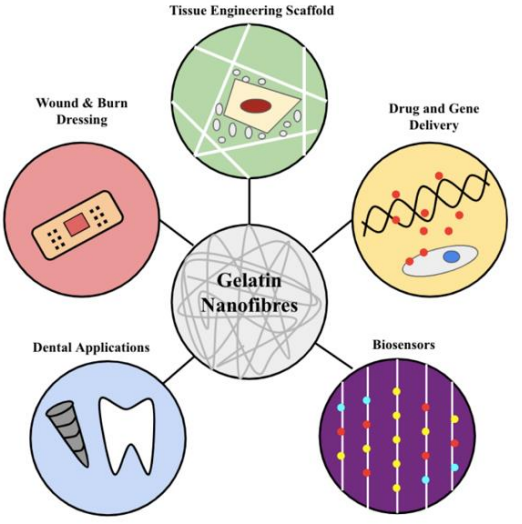

Fig. 1 Gelatin Nanofibers in Drug Delivery and Tissue Engineering.

Nanofibers electrospun from biocompatible and biodegradable natural polymers are used in drug delivery and coating of medical implants since they are easy to manipulate, for obtaining a systematic release of drugs over a set time and specific release rate.[18,22,23] These nanofibers have increased surface area, versatility and flexible porosity and are used as scaffolds for TE, gene and drug delivery, artificial organs, biosensors, dressing of wounds, enzyme stabilization, and dental applications.[18,24]

3. Methods of Gelatin Nanofiber Preparation

Polymeric nanofibers can be prepared by techniques as mentioned below and the most frequently used method in DDS, electrospinning will be discussed in the coming section.[16,25]

3.1. Electrospinning
3.2. Phase Separation
3.3. Self-Assembly
3.4. Bubble Spinning
3.4.1. Blown Bubble Spinning
3.4.2. Bubble Electrospinning
3.5 Centrifugal Spinning
3.6 Freeze Drying

3.1 Electrospinning

The process of electrospinning involves producing the polymer filaments with the help of a polymer melt jet or

electrically charged solution.[26] The early electrospinning apparatus contained two electrodes, one pipette that held the solution of polymer, and a DC voltage supply in the kV range. The large voltage made the polymer fall from the tip of the pipette made into fibers.[27] The electrically charged jet was the reason behind the fibers bending such that the diameter reduced when the polymer fiber looped. When the charges present in the fluid attain a critical amount, this jet of fluid erupts from the droplet at the needle tip forming a Taylor cone. The resulting product on the target surface was accumulated as a web of fibers.[28,29] There are two common types of setups for electrospinning– vertical and horizontal as displayed in Fig. 3. The current laboratory setup consists of a syringe pump, a targeted collector, and a spinneret connected to an increased voltage (5 to 80 kV) DC power supply. A polymer melt or solution is filled into the syringe and it is extruded from the tip of the needle at a constant rate by a syringe pump.[30,31] Coaxial electrospinning is an alternate method to prepare polymer nanofibers loaded with drugs for sustained drug release from two polymers, and consists of a coaxial capillary jet which results in a polymer core and the shell of the second polymer as displayed in Fig. 4.[32,33] Another variation of the regular electrospinning apparatus is the multi-needle electrospinning shown in Fig. 4, which consists of multiple needles arranged in a specific manner to increase the number of Taylor cones arising during the electrospinning process. An increased number of jets are formed and the nanofiber yield is enhanced.[34] Various parameters exist that impact the framework and nature of the electrospun fibers obtained as the result.[27,35] The parameters of the electrospinning process influence the morphologies and arrangements, which are discussed in Table 1.

The bloom value of gelatin or gel strength is a stiffness and strength measure of gelatin, which shows the average molecular weight of its constituents. It is generally between 30 and 300 bloom, where less than 150 is considered a low bloom, 150–220 a medium bloom, and 220–300 a high bloom. The higher the bloom value of gelatin, the higher is its strength. Different boom values of gelatin are applied, based on the required product type and function.[44] In experiments conducted by E. Niehues and M. G. N. Quadri, the effect of Bloom index, concentration, viscosity, and electrical conductivity of various Gelatin solutions on the electrospun fibers formed were evaluated. They produced electrospun membranes at different concentrations for three Bloom values - 90, 250, and 280). Considering the fact that viscosity is the most crucial property for successful electrospinning, they observed that as the Bloom index of gelatin was lower, the solution must be more concentrated to attain the suitable viscosity. They also demonstrated that the fibrous membranes that were electrospun from bloom number 90 displayed different mechanical behavior than the 250 and 280 ones. This suggested that low Bloom gelatin produces brittle fibrous membranes, and high Bloom gelatin produces fibrous membranes that have plastic behavior. Their analysis of the fibrous membrane thicknesses suggested that a more stable Taylor cone is formed above a certain level of viscosity, which promotes better fiber orientation towards the collector.[45,46] The molecular weight of gelatin ranges from 15 to 400 kDa, depending on the manufacturing conditions and process used. The molecular weight distribution and source of gelatin play a significant role in determining its properties, including interfacial properties and film-forming abilities.[44]

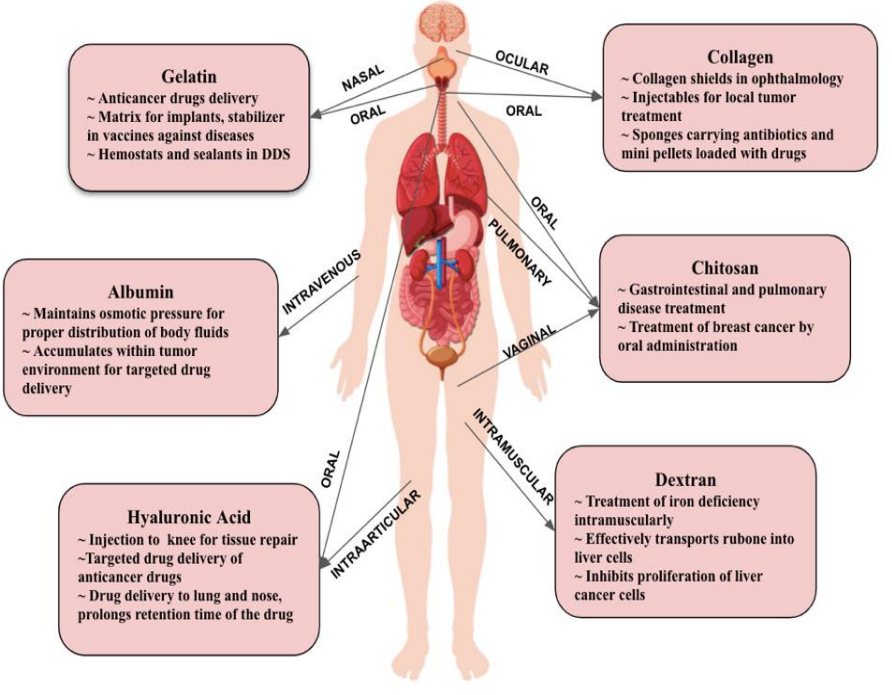

Fig. 2 Drug Delivery & Tissue Engineering applications of few natural polymers used in nanofiber fabrication and their route of administration into the human body.

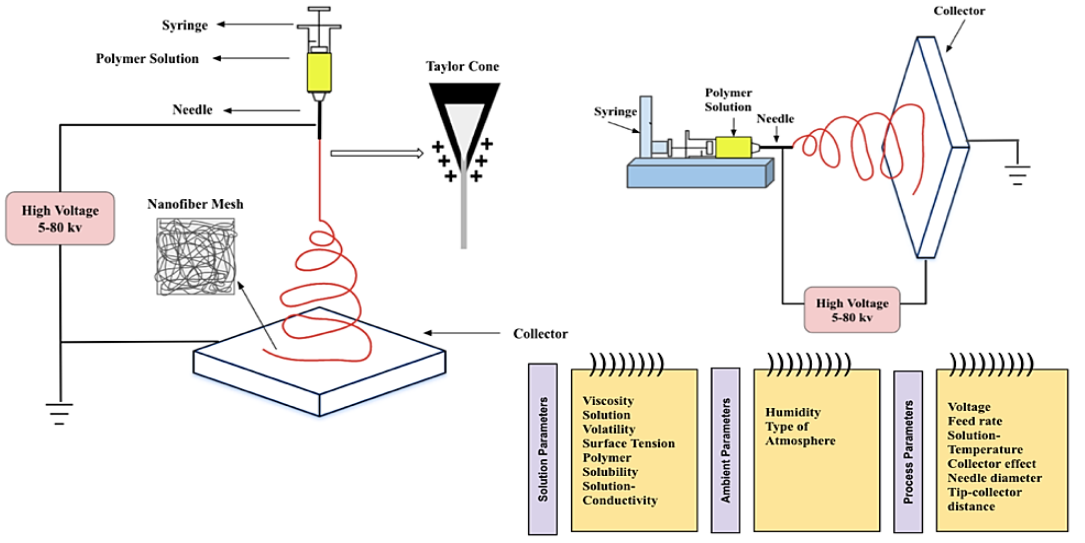

Fig. 3 Schematic diagram of electrospinning setup (a) Vertical Apparatus (b) Horizontal Apparatus and Electrospinning Parameters.

Table 1. Parameter effects on fiber morphology.

Solution Parameters [28,36–39]	Surface Tension	A decrease in Surface tension causes droplets to flatten on the surface resulting in beaded fibers.
	Polymer Solubility	A big difference between solvent and solubility parameters of polymers leads to bead-on-string morphology.
	Viscosity	When the solution viscosity is considerably low, electrospraying might occur and particles of the polymer developed in the place of fibers.
	Volatility (Evaporation) of Solution	When the solvent's evaporation rate is low, fibers may not form and the polymer solution is deposited on the ground target in the form of a thin film.
	Solution Conductivity	Increased charges favor the formation of finer fibers due to an increase in the jet path and deposition area.
Ambient Parameters [28,36,40–42]	Humidity	Increased humidity gives rise to pore formation on the fiber surface.
	Type of atmosphere	A highly electronegative gas environment reduces surface charge loss and enhances the nanofiber quality.
Process Parameters [28,29,35,36,43]	Voltage	With higher voltage, more charges will make the electrospinning jet move faster, and more solution volume will fall from the needle tip resulting in a smaller and unstable Taylor Cone.
	Feed rate	A higher feed rate leads to larger bead size or fiber diameter, as a larger solution volume is observed from the needle tip.
	Solution temperature	The high temperature allows Coulombic forces to exert an increased stretching force on the solution which results in smaller and more uniform fiber diameter.
	Effect of collector	A collector of non-conducting material causes charges on the jet to rapidly accumulate on the collector which results in a lesser number of fibers that are deposited.
	Diameter of the pipette needle	Reduction in the needle's internal diameter decreases the resultant electrospun fiber diameter.
	Distance between tip and collector	A minimal distance leads to excess solvent causing fibers to combine where they meet to form junctions that result in interconnected fiber mesh.

4. Drug release mechanism from gelatin nanofibers

Gelatin-based matrices are developed in varied shapes and are grouped into different delivery systems such as nano-carriers for the purpose of drug delivery. The drugs can be adsorbed onto the surface of these nano-carriers or distributed in a uniform manner within them. A few of these carriers can be designed such that both hydrophilic and hydrophobic drugs are fit within their structure. This indicates versatility in the formation of many structures with varied chemical and physical properties, which is the primary reason behind gelatin-based DDS being adapted as a controlled release matrix.[47] There are three mechanisms through which these drugs/ agents can be released from a delivery system: diffusion, degradation, and swelling of the gelatin matrix. The release mechanisms can be physical or chemical, and generally involve diffusion, in which the movement of drug molecules occurs through a semi-permeable barrier from a high concentration to a low concentration area. It can take place through pores in the matrix of the polymer; by passing through the interstitial space between chains of polymers; or by following degradation of the carrier matrix. This movement of the drug molecules or other active agents is primarily dependent on the solvent-polymer interactions, polymer network properties, and differs in magnitude based on the phase: it is the fastest in gases, slower in liquids, and slowest in solids.[44,47]

5. Applications of crosslinked gelatin nanofibers in TE and DDS

Gelatin is a macromolecule soluble in water, which is procured by restricted hydrolysis of collagen in animal bones, tendons, and skins and dissolution in acidic or alkaline mediums and heated conditions.[48] Different animal by-products are used as raw materials for the production of gelatin such as porcine (pig-based) and bovine (cow-based). Some were extracted from poultry,[49] fish[50] and amphibians.[51] Gelatin can be found in the connective tissue, intestines of the animal, bones, and the skin through a partial hydrolysis process that produces gelatin biopolymer of high molecular weight. There also exists "veggie gelatin" which serves as an alternative to the animal-based one. This can be extracted from modified corn starch, carrageenan, agar, xanthan gum, celluloid, and pectin.[52]

One crucial feature of gelatin's solubility in water is its thermo-responsive property, which undergoes a reversible transition between sol and gel when cooled to its respective critical solution temperature.[53] Gelatin solution is found to solidify at temperatures below 25 °C, because of triple helix and rigid 3-D structure formation. At temperatures above 30°C this structure changes to a gel liquid in the form of a flexible coil.[54] Gelatin supplies a biologically functioning 3D micro environment for regulation of cell growth, differentiation, viability and it is widely used as scaffolds for TE,[55] regenerative medicine, and transporters for regulated drug delivery.[56] It can form complexes with numerous drugs and has been widely researched for applications of regulated release.[57] Parameters like isoelectric point and crosslinking density, have been adapted to optimize degradation of gelatin and kinetics of drug delivery.[58] The mechanical and thermal durability of gelatin and its potential for hydration under physiological conditions can be improved by crosslinking.[58] The gelatin carrier's crosslinking density can be changed by increasing its concentration or increasing the crosslinking reaction period. Consequently, the release period can be modified.[59] An advantage of gelatin nanofibers for their utilization in gene transfer is its reduced cytotoxicity and its easy and reproducible production, which would help to upscale in the future.[60]

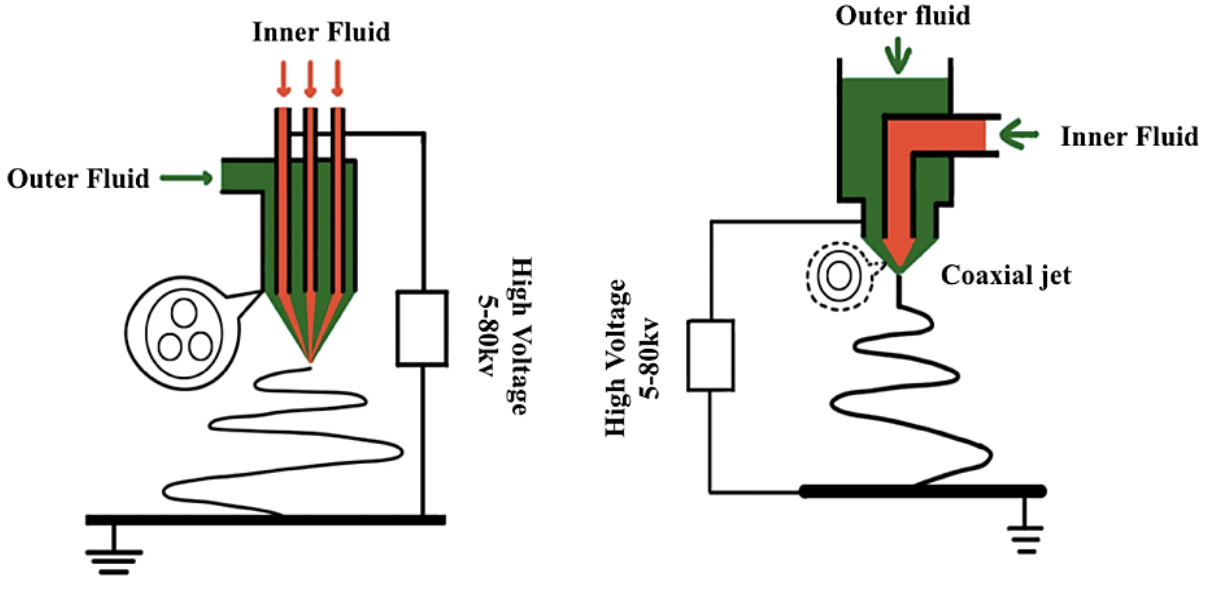

Fig. 4 (a) Multi needle Electrospinning Setup (b) Coaxial Jet Electrospinning Setup.

Ghorani *et al.* conducted experiments to discover the favourable conditions for gelatin nanofiber sheet production, where 25% w/v polymer concentration in acetic acid, to 3:1 v/v water concentration, 25 kV voltage, and flow rate of 0.5 ml/h, and 150 mm distance between the tip and collector.[61] Bead formation in gelatin nanofibers is useful as a drug reservoir for therapeutic medical applications as compared to smooth nanofibers, beaded nanofibers prolonged the release of the active compound.[62] Aprotic dipolar neutrally charged solvents are used to fabricate scaffolds of gelatin nanofibers and are used for prolonged delivery of protein reagents, which find use in repairing, regrowing, or replacing diseased or damaged organs, cells or tissues.[63] Further discussion will be focus on some of the widespread applications of Gelatin nanofibers in drug delivery and TE found in literature, and the approaches taken for their advancements in these fields.

Vast research has gone into production of gelatin nanofibers using a variety of solvents including ethylene glycol, dimethyl sulfoxide,[64] hyaluronic acid,[65] 2,2,2-trifluorothanol (TFE),[66] acetic acid,[67,68] formic acid.[69] Fibrous gelatin structures are soluble in water and have deficient mechanical properties which restrict their utilization in aqueous mediums.[57] Gelatin therefore undergoes crosslinking with different agents like genipin,[70], glutaraldehyde,[71] oxidized products of sucrose,[72] dextran [73,74] and terephthalaldehyde.[75] A lot of these crosslinking agents are expensive and toxic. The sources, toxicity and applications of a few gelatin crosslinkers are discussed in Table 2. Recently, many efforts are going into discovering natural crosslinkers for enhancing the properties of gelatin nanofibers.[76] Elham Tavassoli-Kafrani *et al.* investigated the ability of oxidized compounds of phenol like ferulic, tannic,[77,78] caffeic and gallic acids[76] to crosslink gelatin. Their experiments showed that tannic acid displayed the highest crosslinking potential towards gelatin (13.3 vs 3.45, 4.65, and 7.44% for ferulic, gallic, and caffeic respectively) because of its antimicrobial and antioxidant properties. The crosslinking enhanced the electrical conductivity of the gelatin solution, and reduced the viscosity and surface tension. Thus, it was concluded that this cross-linked gelatin nanofiber might be ideal for various usage in TE and Drug delivery.[76]

5.1 Drug Delivery Applications

Similarly, Laha *et al.* crosslinked gelatin nanofibers by exposure to saturated glutaraldehyde (25% v/v) vapor for six minutes, which was found to regulate early degradation with the fibre morphology kept unchanged. This crosslinking enhanced resistivity to water and the membrane's thermal stability. The resulting electrospun gelatin nanofibers were then demonstrated as a vehicle for piperine, a hydrophobic

Table 2. Sources, Toxicity and Applications of a few Gelatin Crosslinkers.

Crosslinking Agents	Source/origin	Toxicity	Application
Genipin [99]	Geniposide - present in Gardenia jasminoides fruit	Low acute toxicity	Natural cross-linker for proteins, collagen, gelatin, and chitosan cross-linking; Natural dye; Treatment for cholestasis and hepatitis in Chinese medicine.
Glutaraldehyde[100]	Oxidation of Cyclopentene	Toxic, strong irritant	Sterilant to disinfect and clean heat-sensitive medical, surgical, and dental equipment; Cross-linking and tanning agent.
Ferulic acid[101,102]	Commelinid plants (rice, wheat, oats); food plants (pineapple, bananas, spinach, and beetroot)	Low toxicity	Wound healing, skin care formulations.
Tannic acid[103]	Extracted from plant parts; twigs of Chestnut and Oak trees	Acute toxicity	Ointments and suppositories; flavoring agent.
Caffeic acid[104]	Hydroxylation of coumaroyl ester of quinic acid	Non-toxic, but large doses might be harmful	Used in supplements for boosting exercise-related fatigue, athletic performance, weight loss, cancer, HIV/AIDS.
Terephthalaldehyde[105]	Hydrolysis of terephthaldehyde tetraacetate; hydrolysis of α,α,α',α'-tetrabromo-p-xylene	Non-toxic	Intermediate for the preparation of dyes and fluorescent whitening agents.
Dextran[106]	Condensation of glucose	Non-toxic	Medication used in managing and treating hemorrhage, radiological imaging, surgical procedures.

model drug.[79-81] Bigi *et al.* attempted to obtain electrospun nanofibers of gelatin crosslinked with genipin, a low toxicity agent and were able to preserve original nanofiber morphologies after water exposure. Their results showed that these cross-linked nanofibers were free of defects, preserved the original morphology after exposure to water, and the cross-linked mats demonstrated regulatable mechanical properties.[70] Su *et al.* conducted an experiment where genipin vapor acted as a crosslinking agent to improve mechanical characteristics of electrospun nanofibers of gelatin at room temperature for 0, 6, 12, 24, 48 and 72 hours. A model drug, Bovine Serum Albumin (BSA) was integrated in the nanofibers. The resulting crosslinked nanofiber compounds show high potential to act as a drug delivery vehicle.[82]

Poly(d,l-lactide-co-glycolide) (PLGA) was loaded with Fenbufen (FBF) and Gelatin/PLGA nanofiber scaffolds and were fabricated by electrospinning by Meng *et al.* FBF's release rate improved and gelatin/PLGA scaffold's hydrophilicity was boosted due to gelatin. FBF's release rate of aligned nanofiber scaffolds decreased, compared to the scaffold which was oriented randomly.[60] Hu *et al.* used emulsion electrospinning to load 5-fluorouracil and Cefradine, which are hydrophilic and hydrophobic drugs respectively into PLGA nanofiber mats, into which gelatin was added to enhance surface properties like proliferation and adhesion of the cell. They experimented on cell cytotoxicity and this proved that the gelatin fibers fabricated by emulsion electrospinning had lower toxicity and promoted attachment of fibroblast cells.[83]

This study conducted by Laha *et al.* aimed at developing gelatin nanofiber-based drug delivery carriers, by electrospinning, to attain sustainable and controlled hydrophobic drug (piperine) release for a sustained time period. The mesh of gelatin nanofiber loaded with the drug was sandwiched with another matrix of gelatin nanofiber with sequential crosslinking,[84] without the drug operating as a diffusion barrier, and a combination of both. The drug release profiles obtained from their study demonstrated that the sequential crosslinking of piperine loaded gelatin nanofiber displayed that with both enhanced support of the diffusional barrier and sequential crosslinking, a zero-order regulated drug release up to 48 hours might be obtained with an ability to change the loading of the drug according to the therapeutic requirements. Besides the mesh was further investigated for chemical and thermal stability, water resistivity.[81] The objective of a study by Rezaeinia *et al.* was to prepare a sandwich system based on gelatin and Balangu seed gum electrospun mats and to collate the ability for prolonged release of menthol. The release rate in human simulated saliva displayed that the designed sandwich structure extended menthol's burst release from electrospun gelatin mat structure because of its property to dissolve quickly.[85] Laha *et al.* fabricated gelatin nanofibers by electrospinning to utilize for the prolonged release of Amphotericin B (AmB) in the form of tablets for oral administration. The prolonged and controlled release is due to three characteristics, the drug molecule's amphiphilic nature, consistent cross-linking of AmB with the gelatin nanofibers, and the compacted fibers present in the tablet.[86,87]

Prolonged and controlled release of the drug was obtained from the coating of nanofibers of gelatin-ciprofloxacin (Gel-Cip) along with initial, fast release of drug of 20–22% during 12 hours. After this, there was a slow-release stage that could constructively restrain the infection. The addition of 2 to 4 weight percentage of ciprofloxacin into gelatin nanofibers coating improved the resistance to corrosion and antibacterial performance of the alloy of Mg-Ca which was not coated, without showing any constraining effect on the cytocompatibility property. This coat stipulated good antibacterial performance against E. coli and S. aureus.[88] Zandi *et al.* studied the dual delivery release of therapeutics, where the core-shell fibers were prepared by coaxial electrospinning of solutions of gelatin and gelatin/PVA (sheath). The three-stage release kinetics from the core-sheath fibers reported enhanced swelling behavior and mechanical properties. The gelatin sheath consisted of phenytoin sodium which functioned as an obstruction against the burst release from the core and improved the physico- mechanical properties of the core-sheath fibers.[89]

5.2 Tissue Engineering Applications

Another such study was carried out by Mehrasa *et al.,* which involved comparing the nanofiber mean diameters, which were fabricated using electrospinning, and contact angle measurements of the PLGA/gelatin/10 wt% MSNPs scaffolds, pure PLGA scaffolds, and the PLGA/10 wt% MSNPs. Besides the improved hydrophilicity of scaffolds integrated with gelatin and MSNPs, the embedment of scaffolds with MSNPs showed improved tensile mechanical properties. These aligned forms of the PLGA/MSNPs and PLGA/gelatin/MSNPs nanocomposites also displayed a higher satisfactory hydrophilicity, degradation, and morphology, concerning the applications of nerve TE such as nerve regeneration, which is explained by the enhanced cell proliferation, attachment, and long cellular processes. [90]

Poly(ε-caprolactone) (PCL) is a synthetic polymer used in wound healing applications but in comparison with natural polymers such as Gelatin, properties like proliferation responses, cell adhesion, and biodegradability to PCL are restricted. Therefore, Gelatin which consists of specific molecular components which exist in the ECM assists adhesion and proliferation of the cell is often combined with PCL to enhance the physical and mechanical properties and finds its usage in TE. Chong *et al.* studied the Tegaderm-nanofiber (TG-NF) feasibility as an efficient TE scaffold for the healing of wounds. The fibroblasts were placed on either side of a scaffold of PCL/gelatin nanofiber and the porosity was found to be around 60 to 70%. These nanofibers indicated that the gelatin constituent of the copolymer was dissolved during the culture of the cell and made more space for cell

migration. Gelatin's improved deformation and elongation properties facilitated easier space opening for cell penetration to a deeper level in the scaffold.[91,92] Boccaccini *et al.* produced antibacterial mats of PCL-gelatin electrospun nanofiber consisting of clove essential oil (CLV) with the help of a non-toxic solvent, glacial acetic acid (GAA). Their results demonstrated that PCL-gelatin nanofiber mats loaded with CLV had no cytotoxic reactions on cells of normal human dermal fibroblast viability.[93] Preeth *et al.* synthesized a derivative of zinc(II) quercetin complex, Zn(quercetin)(phenanthroline) (Zn+Q(PHt)) and when incorporating it into PCL/gelatin nanofibers, their results proved that the (PCL/gelatin/Zn+Q(PHt)) was biocompatible in-ovo. This acts as a pharmacological medium for treating bone defects and promoting bone regeneration.[94]

Gelatin nanofiber was integrated with alginate hydrogel which formed nanofiber reinforced hydrogel by Tonsomboon and Oyen in 2013. Before crosslinking, gelatin nanofibers fabricated by electrospinning enhanced the hydrogels tensile elastic modulus from 78 ± 19 kPa to 450 ± 100 kPa. Tougher hydrogels consisting of a tensile modulus of elasticity of 820 ± 210 kPa were attained by the gelatin nanofiber crosslinking with carbodiimide hydrochloride in ethanol before the process of infiltration. This complex showed great potential to function as a scaffold for corneal TE because of its strong mechanical properties and transparent nature[95–97] Elamparithi *et al.* electrospun gelatin nanofiber matrices and resulting scaffolds displayed modulus 19.6 ± 3.6 kPa, average porosity of 49.9 ± 5.6%, and fiber diameter 200 to 600 nm which resembled myocardium tissues in humans. Their experiments demonstrated that gelatin nanofibers' mechanical and biophysical characteristics were appropriate for engineered cardiac constructs (ECC) in vitro, for inspecting cardiac functions in drug testing and replacement of tissues.[98]

6. Future Prospects

This review discusses the development of nanofiber technology, emphasizing its synthesis from gelatin and its notable applications. A few review papers exist on gelatin nanofiber-based drug delivery and tissue engineering, but this paper serves as the latest guide for general readers and budding researchers who aim to start research in these fields. With further advancement and maturity in nanofiber technology, the usage of gelatin nanofibers will increase and realize their potential in the biomedical industry due to their distinctive properties discussed in this review. It is apparent from the discussion and facts stated in this review that impressive breakthroughs have been attained pertaining to the use of gelatin nanofibers in the fields of DDS and TE. In the future, gelatin nanofiber-based scaffolds can act as powerful tools in biomedicine, being capable of enhancing therapeutic efficacy and facilitating controlled drug release. These gelatin nanofibers could play an important role in personalized medicine. The discovery of new methods of production of these nanofibers is critical to improving nanofiber structure and properties. Therefore, the future direction of research and development of gelatin nanofibers should be to overcome the limitations of the existing methods of synthesis and enhance their usage in novel applications in various other biomedical fields.

7. Conclusion

Gelatin possesses unique properties like environment-friendly nature, safety, and non-toxicity that make it appropriate for applications like TE and DDS. These fields have advanced exceptionally over the past decade, offering prospects for regeneration of almost every tissue and organ of the human body, and enhanced therapeutic efficacy of drugs. Gelatin can produce poly-ion complexes with charged therapeutic constituents like proteins, nucleotides, polysaccharides, and growth factors, making it suitable as a delivery medium for various biomolecules. The electrospinning technique is widely studied and used as it can be carried out easily and fabrication of Gelatin nanofibers using this method is highly efficient. These nanofibers are ideal for usage in medical applications due to their bead formation that leads to prolonged drug release. Due to the reduced mechanical strength of gelatin, these nanofibers are often combined with other polymers to form co-polymers and polymeric nanofibers for various biomedical applications. Crosslinked gelatin nanofibers displayed additional benefits like the better potential for hydration of gelatin and its enhanced mechanical and thermal durability. In conclusion, it is irrefutable that the usage of gelatin will escalate in the coming years due to its distinctive properties.

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Conflict of interest

There are no conflicts to declare.

Supporting information

Not applicable.

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