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Mini Review

Sustainable Electrospinning for Tissue Engineering: Water-Compatible Formulations and Scalable Stabilization

Julia Andrade[1,2]* and Gilmar P Thim[2]

[1]*Institute for Biomaterials, FAU Erlangen–Nürnberg, Germany*

[2]*Instituto Tecnologico de Aeronautica, Sao Jose dos Campos, Brazil.*

***Corresponding author:** Julia Andrade, Institute for Biomaterials, FAU Erlangen–Nürnberg, Germany

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Abstract

Electrospinning enables scalable fabrication of nano and microfibrous matrices with extracellular matrix-like architecture, making it valuable for tissue engineering, wound care, and local drug delivery. However, conventional electrospinning often relies on volatile organic solvents, complicating safety, sustainability, and clinical translation. Green and water-based electrospinning has therefore emerged, aiming to replace hazardous solvents with aqueous or benign alternatives while maintaining morphological control. This mini-review summarizes the mechanistic constraints that define aqueous spinnability, including surface tension, charge transport, viscoelasticity, and drying or solidification kinetics, and surveys recent strategies to overcome these barriers, such as carrier-assisted spinning, polyelectrolyte complexation, and in situ crosslinking, particularly using light-triggered, flavin-based approaches. Finally, we discuss translational bottlenecks, such as wet-state stability, leachables, reproducibility, and scale-up, and propose reporting priorities for clinically relevant green electrospinning.

Keywords: Green electrospinning; Aqueous electrospinning; Hydrogel electrospinning; Nanofibrous scaffolds; Tissue engineering; Crosslinking

Introduction

Electrospinning (ES) is an electrohydrodynamic process for fabricating continuous micro- to nanoscale fibers from polymer solutions or melts, producing nonwoven meshes with high surface area, adjustable porosity, and anisotropic properties [1-3]. These fibrous architectures are crucial in biomedical engineering, as they mimic the extracellular matrix and serve as platforms for drug delivery and tissue regeneration [4,5]. ES outcomes are highly sensitive to formulation and processing parameters that govern jet formation, stability, and solidification, as poor control leads to inconsistent fiber morphologies [1,6,7]. While volatile organic solvents are traditionally used in biomedical ES to improve spinnability and drying, their use raises safety, environmental, and translational concerns [8-11]. Green ES addresses these issues by replacing hazardous solvents with water or other benign alternatives. Water, however, is not a drop-in substitute. Its high surface tension, unique drying kinetics, and the need for wet-

state stabilization require integrated formulation, processing, and crosslinking strategies [11,12]. This mini-review discusses the

constraints of aqueous systems, practical stabilization methods, and reporting standards needed for reproducible and clinically relevant green electrospinning.

Principles of Electrospinning

In ES, a polymer solution or melt is extruded through a needle under a strong electric field. When electrostatic force overcomes surface tension at the meniscus, a Taylor cone forms and a charged jet is emitted [13]. The jet undergoes elongation and bending instabilities, thinning dramatically before depositing as a solid fibrous mat [1,7,14]. Successful fiber formation requires balancing electrostatic stress, viscoelastic cohesion, and surface tension. Sufficient polymer chain entanglement and solution viscosity are essential to stabilize the jet and avoid bead formation [6,15]. Solution conductivity further modulates charge transport and fiber diameter, but excessive charge can destabilize the jet [1,7].

Process parameters, including voltage, flow rate, and needle-to collector distance, influence jet stability and solidification time, while collector design and movement determine fiber alignment [1,2,7,8,14]. Environmental factors such as temperature and humidity also affect viscosity and drying, making strict control and comprehensive reporting essential for reproducibility [1,7].

Why "Green" Electrospinning Is Non-Trivial

Replacing organic solvents with water improves safety and biocompatibility but introduces challenges: higher surface tension and slower, heterogeneous evaporation narrow the spinnability window and increase the risk of bead formation or wet deposition [10,11]. Overcoming these constraints requires careful co-design of spinnable formulations and stabilization steps that preserve fiber morphology under hydration, shifting the focus from spinning parameters alone to an integrated workflow of formulation, processing, and crosslinking [10-12].

Hydrogel Electrospinning in Tissue Engineering

Most native soft tissues, such as skin, cartilage, and mucosa, are hydrogels reinforced by fibrous collagen and elastin. Hydrogel ES aims to replicate this dual structure by producing water-swollen fibers with defined architecture, combining the hydration of hydrogels with the mechanical and topographical cues of fibrous scaffolds [12]. Common approaches include: (i) Blending a hydrogel precursor (e.g., gelatin, hyaluronic acid) with a carrier polymer for electrospinning, followed by post-deposition crosslinking and

optional carrier removal [10,12]; (ii) Electrospinning reactive polymer solutions into a coagulation bath or vapor to induce gelation during or after fiber formation [12]; (iii) Using in-line irradiation (UV or visible light) to crosslink fibers as they are deposited, minimizing dissolution risk [16-19].

Crosslinking Strategies for Wet-State Stabilization

A range of crosslinking methods have been developed to stabilize hydrogel electrospun fibers in aqueous environments. Conventional chemical crosslinkers such as glutaraldehyde and carbodiimides (EDC/NHS) are effective but can leave cytotoxic residues and complicate regulatory approval [10,16]. Milder alternatives include genipin, which crosslinks amines in collagen and chitosan with reduced toxicity, citric acid, which forms ester bonds in hydroxyl-rich polymers under mild heating, and enzymatic agents like transglutaminase, which catalyze specific protein crosslinks with high biocompatibility [12]. Photochemical crosslinking is especially attractive for green electrospinning, as it can be performed in situ and is tunable by light parameters. While synthetic photoinitiators (e.g., Irgacure2959) are widely used, bio-derived photosensitizers such as riboflavin (vitamin B_2) and flavin mononucleotide (FMN) offer improved compatibility and can crosslink a broad range of polymers under UV or blue light [17-19]. Non-photochemical strategies, such as UV-induced stabilization of PVP with benzophenone, also provide wet-state integrity by forming interchain covalent bonds [16]. Ultimately, the choice of crosslinking method should balance stabilization efficiency, processing sequence, compatibility with bioactive agents, and the desired degradation profile in vivo.

Translational Bottlenecks and Priorities

Despite the appeal of green electrospinning, translation is limited by key challenges. Reduced spinnability in water, driven by high surface tension and poor chain entanglement, requires careful formulation and rheological optimization [10,15]. Achieving wet state stability depends on adequate crosslink density and

uniformity to preserve fiber architecture under physiological conditions [12,16,18,19]. Process and environmental factors, such as voltage, flow rate, temperature, and humidity, strongly influence morphology and reproducibility [1,7]. To advance the field, quantitative reporting of structural metrics (e.g., fiber diameter, bead density, pore size, alignment) is essential [1,6].

Conclusions and Outlook

Green and water-based ES are best understood as an integrated manufacturing approach where formulation physics and stabilization chemistry work together to determine success. The electrohydrodynamic fundamentals of ES, such as Taylor cone formation, jet stretching/whipping, and deposition, remain the same, but water narrows the spinnability window and makes wetstate stabilization a key design factor. Hydrogel ES and photochemical crosslinking, including flavin-based systems, offer promising pathways to create fibrous matrices that combine hydrated microenvironments with structural stability. The field's future progress will likely focus less on simply demonstrating "that it spins" and more on standardizing crosslinking dosage, measuring wet-state mechanics and morphology, and adopting

rigorous reporting standards that allow for reliable comparison and effective translation.

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