Editorial

Therapeutic Delivery

Reactive and functionalized electrospun polymeric nanofibers for drug delivery and tissue engineering applications

Hesham M Ismail[1], Sandi Ali-Adib[1,2] & Husam M Younes*,[1,2]
[1]Pharmaceutics & Polymeric Drug Delivery Research Laboratory (PPDDRL), College of Pharmacy, Qatar University, PO Box 2713, Doha, Qatar
[2]Office of Vice President for Research & Graduate Studies, Qatar University, PO Box 2713, Doha, Qatar
*Author for correspondence: husamy@qu.edu.qa

"Continuous attempts to produce the ideal biomimetic nanofibrous scaffolds that resemble extracellular matrix have directed researchers to develop modified electrospinning approaches to fabricate scaffolds with optimal fibrous orientation (anisotropy), porosity, conductivity and mechanical properties"

First draft submitted: 13 April 2019; Accepted for publication: 14 June 2019; Published online: 15 July 2019

Keywords: drug delivery • nanofibers • photoreactive • reactive electrospinning • tissue engineering

There has been a great interest in application of polymer-based nanocarriers, such as nanoparticles, nanogels, micelles, dendrimers, liposomes and nanofibers for delivery of therapeutic molecules like drugs and genes, and for tissue engineering (TE) [1]. In the pharmaceutical field, smart, targeted and control-release nanocarriers contribute to enhancing therapeutic efficacy and minimizing adversities of many existing drugs. They have also helped to increase the potency of many suboptimal but pharmacologically active moieties that were previously excluded from the drug development pipelines [2]. In the tissue engineering arena, nanotechnology facilitates attempts to develop the ideal biomimetic scaffold which resembles the protein fibers in the extracellular matrix to facilitate cell proliferation and control spatiotemporal release of hormones or growth factors to eventually lead to complete tissue regeneration [3].

Among the polymeric nanomaterials, nanofibers are currently widely investigated for drug delivery, TE and other biomedical applications. Nanofibers production has been reported in the literature using several methods including drawing, template synthesis, phase separation, self-assembly, melt blowing and electrospinning (ES). Each of these method's advantages and disadvantages has been reported elsewhere [4]. ES is characterized by producing continuous micro or nanofibers with high surface-to-volume ratio, tunable porosity and malleability which are among the main highlights that distinguish nanofibrous scaffolds prepared by ES [5]. ES can be used with various types of blends, fluids and polymers. Synthetic and natural polymers can be electrospun under specific material, process and environmental factors that can be controlled and manipulated. ES can also be utilized to produce nanofibers loaded with drugs or therapeutic hormones and proteins of various particle sizes and properties. The diversity of its uses, simplicity of the instrument, ease of manipulation of the produced fibers according to the intended application and the scalability of the process are the main aspects that make ES one of the most promising methods to produce nanofibrous scaffolds for various pharmaceutical and biomedical applications.

Historically, the first ES attempt to produce nanofibers was carried out in 1934 when Formhals and coworkers used a basic form of ES machine to produce synthetic nanofibers [6]. Due to its flaws, evolution of this basic setup occurred via several modifications in the apparatus leading to two other patents [7]. It was not until 1960s when attempts to understand the mechanism of ES process started. Tylor *et al.* explored the mechanism of ES process by describing the behavior of the polymer droplet at the tip of the needle to reveal what's referred to today as Tylor cone [8]. This was followed in the 1970s by continuous efforts to characterize the ES fibers by different techniques [9]. Finally in 1978, polyurethane mats were used for vascular prosthesis which was followed in 1985

newlands press

by the study of the *in vivo* behavior of arterial prosthesis using ES fibrous scaffolds [10]. These later events marked the very first efforts to use ES fibrous mats for TE purposes that were followed by numerous research works in this new field.

Reactive electrospinning

As stated earlier, one of the main aspects that makes the ES process very promising is the simplicity of the machine setup. It is composed of a syringe with a capillary needle that acts as a polymer solution reservoir, a syringe pump that controls the flow rate of the polymer solution, a metal collector for the collection of fibers and a high voltage power supply with positive and negative terminals. Several parameters must be adjusted in the ES process with which the produced nanofibers' morphology and characteristics can be controlled. These factors are all interconnected and can be classified as follows: Material parameters, which include the type of polymer used, solution concentration, molecular weight of the polymer used, viscosity, conductivity and solvent used; Process parameters, which cover pump flow rate, voltage difference applied, needle to collector distance and type of collector; and Environmental parameters, which include relative humidity, airflow and temperature [11].

Continuous attempts to produce the ideal biomimetic nanofibrous scaffolds that resemble extracellular matrix have directed researchers to develop modified electrospinning approaches to fabricate scaffolds with optimal fibrous orientation (anisotropy), porosity, conductivity and mechanical properties [12,13]. The concept of creating functionalized junctions between fibers that can be further triggered for interconnection by crosslinking during or post-ES process has been introduced. When the traditional ES was combined with post or *in situ* crosslinking process applied to the jet flowing to the collector, the technique was called as reactive electrospinning [14]. *In situ* crosslinking consistently results in superior uniform crosslinking between the surface and the interior parts of the fibrous scaffolds and better reserves the porous 3D structure of the produced fibrous mats [15]. When chemical crosslinkers are used, the process is termed as chemical reactive electrospinning. However, when chemical crosslinking is substituted by photocrosslinking approach in which the flowing jet is exposed to UV light, laser or γ radiation, the process is named photoreactive electrospinning (PRES).

Advantages of PRES

PRES possesses many advantages over chemical reactive electrospinning. First, it is fast, uniform and homogenous crosslinking is taking place within the scaffold. Second, more biocompatible scaffolds are produced as the process avoids using toxic chemical crosslinkers. Third, the process facilitates the stable loading of proteins and growth factors into the nanofibers. Finally, controlling the exposure area, distance, time and intensity of incident radiation source enable precise control of the spatiotemporal, morphological and mechanical properties of produced fibers. PRES technique utilizing UV photopolymerization was carried out previously using various approaches. One commonly reported approach was by the insertion of photoreactive terminal vinyl functional group to the polymers, as in case of poly(decanediol-co-tricarballylate) elastomeric fibers [12]. In this work, researchers demonstrated this technique using acrylated poly(decanediol-co-tricarballylate) polymer as the cross-linking polymer, polyvinyl pyrrolidone as the carrier polymer and photoinitiator, 2,2-dimethoxy-2-phenylacetophenone with UV photoradiation. An optimum concentration of acrylated poly(decanediol-co-tricarballylate) polymer was needed to ensure proper nanofiber formation and beyond which the solution started to solidify at the needle tip without electrospinning jet formation. The produced aligned structured nanofibers possessed the needed mechanical and physicochemical properties to facilitate responses to various signaling routes and simulating the contractile characteristics of the cardiac tissue and the anisotropic structure of myocardial architecture [12].

In another recent example, Zein was modified to photoreactive monomer and electrospinning was carried out in the presence of a UV lamp to provide crosslinking [16]. Addition of an antimicrobial methacrylate monomer and crosslinking during the electrospinning resulted in a very strong antimicrobial property of the electrospun fibers. The novel process used in this study in addition to the embedded antimicrobial property opened up potential dental and biomedical applications of Zein and other similar polymers.

Conclusion

There is no doubt that nanofibrous scaffolds using ES showed great promise and potential for many tissue engineering, controlled drug delivery and other biomedical applications. While the correct selection of polymeric materials and the optimization of the conventional ES fabrication parameters are very important to produce the ideal nanofibrous mats, the development of innovative electrospinning approaches like the disused reactive ES are necessary to keep the ES technology platform continuously offer the versatility and unique nanostructure features of fibers beyond any of the most existing technologies.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1. Shi J, Votruba AR, Farokhzad OC, Langer R. Nanotechnology in drug delivery and tissue engineering: from discovery to applications. *Nanoletters* 10(9), 3223–3230 (2010).
2. Mishra RK, Tiwari SK, Mohapatra S, Thomas S. Chapter 1 – Efficient nanocarriers for drug-delivery systems: types and fabrication. In: *Nanocarriers for Drug Delivery.* Mohapatra SS, Ranjan S, Dasgupta N, Mishra RK, Thomas S (Eds.) 1–41 Elsevier, The Netherlands (2019).
3. Sudhakar CK, Upadhyay N, Verma A, Jain A, Narayana Charyulu R, Jain S. Chapter 1 – Nanomedicine and tissue engineering. In: *Nanotechnology Applications for Tissue Engineering.* Thomas S, Grohens Y, Ninan N (Eds). William Andrew Publishing, Oxford 1–19 (2015).
4. Eatemadi A, Daraee H, Zarghami N, Melat Yar H, Akbarzadeh A. Nanofiber: synthesis and biomedical applications. *Artif. Cells Nanomed. Biotechnol.* 44(1), 111–121 (2016).
5. Liang D, Hsiao BS, Chu B. Functional electrospun nanofibrous scaffolds for biomedical applications. *Adv. Drug Deliv. Rev.* 59(14), 1392–1412 (2007).
6. Formhals A. Process and apparatus for preparing artificial threads. US Patent 1975504 A (1934).
7. Formhals A. Artificial Thread and method of producing same. US Patent US15616737A (1940).
8. Taylor G. Electrically driven jets. *Proc. R. Soc. Lond A* 313(1515), 453–475 (1969).
9. Baumgarten PK. Electrostatic spinning of acrylic microfibers. *J. Colloid Interface Sci.* 36(1), 71–79 (1971).
10. Annis D, Bornat A, Edwards RO, Higham A, Loveday B, Wilson J. An elastomeric vascular prosthesis. *Trans. Am. Soc. Artif. Intern. Organs* 24(1), 209–214 (1978).
11. Haider A, Haider S, Kang I-K. A comprehensive review summarizing the effect of electrospinning parameters and potential applications of nanofibers in biomedical and biotechnology. *Arab. J. Chem.* 11(8), 1165–1188 (2018).
12. Ismail HM, Zamani S, Elrayess MA, Kafienah W, Younes HM. New three-dimensional poly(decanediol-co-tricarballylate) elastomeric fibrous mesh fabricated by photoreactive electrospinning for cardiac tissue engineering applications. *Polymers* 10(4), 455 (2018).
13. Oraib A, Fatemeh J, Somayeh Z *et al.* Fabrication & characterization of 3D electrospun biodegradable nanofibers for wound dressing, drug delivery and other tissue engineering applications. *Pharm. Nanotechnol.* 4(3), 191–201 (2016).
14. Xu X. Process of fabricating nanofibers by reactive electrospinning. US Patent 8066932 B2 (2011).
15. Huang C, Soenen SJ, Rejman J *et al.* Stimuli-responsive electrospun fibers and their applications. *Chem. Soc. Rev.* 40(5), 2417–2434 (2011).
16. Zhang J, wang Y, liao S, Lallier T, Wen Z. Photocrosslinked antibacterial zein nanofibers fabricated by reactive electrospinning and its effects against streptococcus mutans. *Oral Health Dent. Stud.* 1(1), 1–9 (2017).