Materials Science and Engineering C xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Electrically conductive gel/fibers composite scaffold with graded properties

Sajedeh Khorshidi, Akbar Karkhaneh *

Biomedical Engineering Faculty, Amirkabir University of Technology (Tehran Polytechnic), Tehran, Iran

ARTICLE INFO

Article history:
Received 16 August 2016
Received in revised form 10 November 2016
Accepted 4 December 2016
Available online xxxx

Keywords:
Fiber
Hydrogel
Composite
Gradient
Tissue interface

ABSTRACT

Gradient biomaterials have emerged as fascinating platforms to satisfy the need for imitation of ubiquitous gradients in biology, especially those found at tissue interfaces. In the current study, a gradient fiber-hydrogel scaffold was fabricated to imitate the extracellular matrix of soft-to-hard tissue interfaces. For the fiber proportion, a gradient electrospinning was developed where controlled mixing of solutions with dissimilar concentration of a conductive polymer in injection vessel imparted a composition gradient to electrospinning jet, and thus electrospun fibers. The planar graded fibers were exposed to ultrasound to be three-dimensional and gel permeable. For the hydrogel fraction, a gradient mixing tool was used in which controlled mixing of solutions with disparate concentration of hydrogel components conferred a composition gradient to hydrogel precursor solution. The graded precursor solution was introduced to gradient 3D fibers and then self-crosslinked. Gradient fibers, hydrogel and fiber-gel composite were assessed by many techniques including microscopy, spectroscopy, mechanical analysis and conductivity measurement to ascertain gradient formation. Polymeric constituents' gradient in electrospinning outflow gave rise to not only gradual changes in fiber diameter, also subtle variations in electrical conductivity and other fibers' attributes. Gradient hydrogel making apparatus rendered a steady increase in crosslink involving component and yielded a hydrogel with graded features. The created composite revealed the propitious unification of fibrous and gelation parts into a single scaffold with no detrimental effect on structure and gradient of each part.

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1. Introduction

Gradient biomaterials have emerged as fascinating platforms to satisfy the need for imitation of ubiquitous gradients in biology [1]. With the advent of interface tissue engineering, special attention is given to employ gradient materials to recreate subtle changes along tissue interfaces. Tissue interfaces exhibit gentle variations in composition, mechanics, cell sources, cell signaling factors, etc. from soft-to-hard tissue regions. These smooth variations are indispensable to decrease stress concentration and increase continuity at the interfacial zones [1,2].

Manifold materials with structure and properties gradients have been developed to match those of native soft-to-hard tissue interfaces [3–6]. Among which, fibrous materials with gradient in chemical, morphological and functional properties have received a burgeoning interest. Fibers especially those produced by electrospinning are structurally bioinspired and easy to manipulate [7]. Electrospun fibers can be formed in a graded manner either by gradient electrospinning [3,8,9] or gradient post-spinning processes [4,10]. Hydrogels are other appealing candidates to be gradient materials. Hydrogels have viscoelastic closeness to native tissues and represent tunable properties. Gradient hydrogels can be developed not only by inducing well-designed gradients in hydrogel precursor solutions [11–13], but also by stabilizing hydrogel prepolymers in a graded fashion [5,6].

Although fibers and hydrogels can be made in gradient to be interface tissue engineering constructs, they still have some shortcomings. Hydrogels are mechanically weak and lack the needed support for cell activities, especially for those reside in load bearing regions [14]. Electrospun fibers are structurally compact and impede cell migration [15]. A gradient composite with concomitant fibrous and gelatinous parts will address the above-mentioned concerns and create a perfect resemblance to native extra cellular matrix of interfaces [16,17]. So far, different fiber and hydrogel scaffolds have been processed in gradient forms and utilized in the field of interface tissue engineering. However, a combining gradient scaffold that enables the coexistence of fibers and hydrogel in a single platform is still lacking.

In the current study, we aimed to develop a fiber-gel composite scaffold with gradient in chemical, structural, mechanical and electrical attributes. Our intension in this research was to make electrospun fibers from a conductive polymer and to make hydrogel from a self-crosslinked conductive precursor. So we have chosen a blend of poly (ε-caprolactone) (PCL)/polyaniline (PANi) for fiber preparation and a

* Corresponding author.
E-mail address: a.karkhaneh@aut.ac.ir (A. Karkhaneh).

http://dx.doi.org/10.1016/j.msec.2016.12.014
0928-4931/© 2016 Published by Elsevier B.V.

Please cite this article as: S. Khorshidi, A. Karkhaneh, Electrically conductive gel/fibers composite scaffold with graded properties, Mater. Sci. Eng., C (2016), http://dx.doi.org/10.1016/j.msec.2016.12.014

nanographene loaded aldehyde alginate/gelatin solution for hydrogel synthesis. To fulfill the gradient fiber-gel scaffold, firstly, a gradient electrospinning process was devised in which controlled mixing of solutions conferred a composition gradient to electrospinning jet, and thus electrospun fibers. Next, the graded fibers were expanded through controlled exposure to ultrasound energy to induce inter-fiber spaces relevant for hydrogel precursor infusion. Thereafter, a gradient mixing chamber was designed to introduce hydrogel prepolymer solution to expanded fibers in gradient. The gradient fibers, hydrogel and fiber-gel composite were assessed by *numerous techniques including* microscopy (scanning electron microscopy and atomic force microscopy), inferred spectroscopy, mechanical analysis and conductivity measurement to evidence gradient formation. To the best of authors' knowledge, this the first report on preparation of a fiber-hydrogel composite with graded features.

2. Materials and methods

2.1. Materials

Poly (ε-caprolactone) (PCL, average M_n ~ 80,000), polyaniline-emeraldine base (PANi-EB, average M_w ~ 5000), *hexafluoroisopropanol* (HFIP), sodium alginate (low viscosity grade), gelatin (microbiology grade), sodium metaperiodate and absolute ethanol were all supplied from Sigma-Aldrich. Camphor sulfonic acid (CSA) was obtained from Merck.

2.2. Fabrication of gradient nanofibers

To constitute PCL/PANi electrospun scaffold with graded properties along thickness, a controlled mixing system and a designed concentration gradient were developed. For this purpose, firstly, PANi solutions (0.15% and 0.3% w/v) were prepared by mixing the equal amount of CSA and PANi-EB in HFIP for 1 h at room temperature. Meanwhile, PCL pellets were dissolved in HFIP to make 9% and 18% w/v solutions. 9% PCL solution was added to 0.3% PANi solution and 18% PCL solution was combined with 0.15% PANi solution, both of which in 30:70 mass ratio. The blended contents were magnetically stirred at room temperature overnight. Thereafter, a compartmented reservoir was created in which 0.15% and 0.3% PANi laden composite solutions were separated through an interfacial port. The interfacial port was crafted by insertion of a segment of a 20 G metal needle into the rubber cap of a syringe plunger. The port was employed to control the extent of mixing between the solutions and to create a gentle gradient of polymeric components [8]. In brief, 0.3% PANi laden composite solution was firstly placed into a 3 mL disposable syringe, interfacial port was inserted and 0.15% PANi laden composite solution was then positioned on top of the port. The syringe was fixed horizontally in a syringe pump and the outward solution delivered through a 20 G blunt needle at a constant flow rate of 4 mL/h. The needle was placed 20 cm from an aluminum foil covered static collector and the spinning voltage was kept constant at 28 kV. The fibers were allowed to be accumulated until the syringe plunger touched the interfacial port. Thereafter, the fibers were dried in a vacuum oven for 24 h to insure complete solvent removal.

2.3. Transformation of 2D nonwovens to 3D scaffold

To fabricate a composite scaffold comprising fibrous elements and gelatinous background, transformation of the 2D planer fibers to a 3D gel permeable structure was necessary. To this end, the fibers were subjected to ultrasonication in a controlled manner. The circular pieces (diameter = 8 mm) of the gradient fibers were removed and submerged in 10 mL of deionized water. The ultrasonication was carried out for 5 min under prearranged conditions. The fibrous samples then underwent *lyophilisation* for 48 h.

2.4. Preparation of hydrogel fraction

The background hydrogel was formed based on Schiff's base reaction between aldehyde containing polysaccharides and gelatin. Alginate dialdehyde (ADA) was synthesized by controlled oxidation of alginate using sodium periodate as described in detailed elsewhere [18]. To prepare 12% w/v ADA and 12% w/v gelatin solutions, ADA and gelatin were dissolved in phosphate buffered saline (PBS) and deionized water, respectively. Graphene nanoparticles were then loaded into ADA solution at 0.01% and 0.03% w/v ratios via ultrasonication for 1 h.

2.5. Fabrication of gradient fiber-gel composite

To form a gradient fiber-gel composite, the hydrogel precursor solutions were mixed in a gradient manner and introduced to the graded fibers. To describe in detail, the ADA containing 0.01% graphene and gelatin solutions were blended in 50:50 mass ratio and loaded into a 3 mL syringe. The interfacial port was then inserted on top of the said solution, and the ADA solution containing 0.03% graphene was placed over the port. The interfacial port was crafted by insertion of segments of a 20 G metal needle into the rubber cap of a syringe plunger. The port was utilized to control the extent of mixing between the hydrogel constituents and to create the gradual increase in ADA and graphene content in the final flow. Later on, the syringe was installed into the syringe pump and the solution was fed at a flow rate of 8 mL/h. The 3D gradient nonwoven was fixed into a homemade plastic mold in a manner that the surface supplied with 0.15% PANi and 18% PCL solution was in contact with the mold bottom. The outflow was directly dropped in the mold and soaked the fibers. The injection was over when the syringe plunger touched the interfacial port. The composite samples were then incubated at 37 °C for 4 h to gel. The full schematic of fiber-gel composite preparation is represented in Fig. 1.

2.6. Scaffold characterization

2.6.1. Scanning electron microscopy (SEM)

Morphology of the graded fibers, gradient hydrogels and gradient fiber-gel composites was evaluated via scanning electron microscopy (SEM; AIS2100, Seron Technology) at an accelerating voltage of 20 kV after being sputter coated with Au particles. The fiber and pore diameters were measured using image processing software (Image- Pro Plus 8.0) and the results are presented as average ± standard deviation. To confirm size gradient in fibers, the fibrous samples were collected at 4-min intervals throughout the spinning process and imaged. Also to corroborate structure gradient in hydrogels, multiples parts throughout the thickness were assessed. The hydrogel surface and cross-sectional morphology were observed after being freeze-dried.

2.6.2. Atomic force microscopy (AFM)

Morphology of the gradient hydrogels was further investigated by atomic force microscopy (AFM; DS 95, Danish Micro Engineering) in tapping mode. Areas of 1 μm × 1 μm were scanned and AFM image processing was carried out using a statistical parametric mapping (SPM) software (*ScanTool™*). To validate composition and structure gradient in hydrogels, multiples parts throughout the thickness were assessed.

2.6.3. Porosimetry

To clarify the impact of ultrasonication on fibers packing, nanofibers porosity and pore size were measured using liquid intrusion procedure and SEM imaging, respectively. For the former, the rectangular fibrous specimens were weighed, soaked in absolute ethanol as an intruding liquid, left overnight on a shaker incubator to allow ethanol intrude into the void spaces, wipe with tissue paper and weighed again instantly. Thereafter, the porosity was approximated as $P\% = \frac{V_{EtOH}}{V_{EtOH}+V_s} \times 100$. where V_{EtOH} (the ratio between mass change after liquid intrusion and

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