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Preparation of highly porous interconnected poly(lactic acid) scaffolds based on a novel dynamic elongational flow procedure

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ABSTRACT

Sodium Chloride (NaCl) is a common porogen to be used in preparing porous scaffolds in tissue engineering. However, NaCl particles are easily broken during melt blending with the matrix polymer by conventional processing techniques, such as twin extrusion, which causes uncontrollable pore size and entrapped residues after leaching in the prepared scaffolds. To address these problems, this study reported a novel scaffold fabrication method based on self-developed vane extruder, which applies global dynamic elongational flow to the polymer compounds. We found that NaCl particles not only preserved their original size, but also could retain high loading content when been blended with poly(lactic acid) (PLA) matrix using vane extruder. Based on these high porogen composites, we are able to prepare PLA porous scaffolds with porosity as high as 93% via supercritical carbon dioxide (Sc-CO_2) foaming and particulate leaching hybrid method. Detailed analyses confirmed that the NaCl porogens could be completely leached within 24 h. The biocompatibility of the scaffolds prepared was verified by culturing human mesenchymal stem cells. Therefore, the proposed approach based on vane extruder compounding has great potential to be used in tissue engineering scaffold fabrication.

1. Introduction

Tissue engineering scaffolds are used as temporary templates to support the regeneration of new tissue [1,2]. An ideal scaffold should be highly porous with an interconnected, open porous structure to provide a three-dimensional (3D) substrate for cell growth and nutrition transport. Various techniques have been introduced or developed to produce porous scaffolds, such as fiber bonding [3–5], solvent casting/particulate leaching [6–8], phase separation technology [9–11], gas foaming [12–15], and solid freeform fabrication [16–18]. However, so far, there is not a single method that can produce scaffolds that meets all requirements of tissue regeneration because of the complex in vivo environment and the diversity of tissue kinds. Therefore, hybrid methods have been attracting attentions in recent years in order to combine the advantages of different technique and overcome their disadvantages.

The great advantage of solvent casting/particulate leaching over other approaches is that it is capable of directly controlling the pore size and structure by adjusting the porogen size and concentration [6–8]. However, one drawback of this technique is that the presence of organic solvent, which is hard to completely remove from the scaffolds and the release of the residue solvent in the scaffolds will be harmful for cell growth and nearby tissues when implanted. Another drawback of this method is the difficulty in production of three-dimensional structures. To overcome these problems, melt-molding/particulate leaching was proposed to replace the solvent casting step [19,20]. Although the organic solvent is avoided, the potential deficiency of this technique is the lack of interconnectivity between the pores at low volume fraction of porogen particles. To improve the interconnectivity between the pores, conventional immiscible polymer blending technique was adapted to produce interconnected, porous, three-dimensional scaffolds [21,22]. The strategy consists of melt blending of two immiscible polymers to create a so called co-continuous blending morphology. One of the polymer phases is subsequently sacrificed by selective removing from the blends to form the continuous channels within the polymeric matrix. Typically, the sacrificial phases used in this technique are water soluble polymers.

To reduce the cost and improve efficiency of scaffold fabrication, and develop a more controllable approach, researchers have been trying to employ the melt blending and injection molding techniques in scaffold preparation. However, the drawback of these techniques is that the maximum porosity achieved was 50–60% which is not suitable to be used as tissue engineering scaffolds without further modification. Recently, Reignier et al. have improved the above method by combining the polymer leaching and particle leaching to obtain highly porous interconnected networks [23]. By removing the sacrificial polymer phase and porogens, the porosity of the scaffolds can be achieved to

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88%. To further improve the porous structure of the scaffolds, Botchwey et al. combined gas foaming with polymer leaching technique to prepare poly(ε-caprolactone) (PCL) scaffolds without the use of NaCl particles and harsh chemicals [24]. Turng group employed polymer/particle leaching combined with gas foaming to prepare porous PLA, PCL and thermoplastic polyurethane (TPU) scaffolds. In the studies, water soluble polymers such as poly (vinyl alcohol) (PVA), poly (ethylene oxide) (PEO) and NaCl as porogens were first blended with polymer matrix such as PLA, PCL and TPU. The prepared blends were then foamed with supercritical CO_2 or N_2 to obtain the foamed blends. After leaching the water soluble phases, porous scaffolds with multimodal porous structure and interconnected channels were obtained [25–28].

However, the most significant drawbacks in these methods are the difficulty to retain porogen size and to achieve high porogen concentration. It is well known that the polymer melts subject to strong shear deformation in the screw extrusion process. High shear stresses especially in the melting zone can cause great attrition of particulate, which affects the pore structure of porous scaffolds consequently [23,28]. In addition, the inorganic porogens such as NaCl have different properties from polymer melts. They are difficult to achieve good dispersion in polymer matrix under shear deformational flow. To address these problems, elongational flow field was proposed and it is widely recognized that elongational flow in polymer processing has many advantages over the conventional shear deformational field [29]. Recently, inspired by such concept, we have recently designed a novel polymer processing equipment, known as vane extruder, which applies strong elongational flow to polymer melt during processing by consecutively compression and stretching using a series continuous dynamical converging channels [30–32]. Experimental study demonstrated that the vane extruder has a much higher dispersive mixing efficiency than twin-screw extruder. Moreover, compared to shear deformation field, elongational field consumes less energy to generate the same deformation of polymer [33].

The purpose of this study is to prepare porous scaffolds using vane extruder combined with particulate leaching and Sc-CO_2 foaming techniques. Poly(lactic acid) (PLA), a popular biodegradable polymer, was chosen as the scaffold matrix material. NaCl and PVA were used as water soluble porogens. The effect of NaCl concentration on the scaffold morphology and the porosity was investigated. Human mesenchymal stem cells were used as cell model to investigate the potential of the prepared scaffolds for bone tissue engineering.

2. Experimental

2.1. Materials

Biodegradable PLA (2002D, Mw = 208.000 g/mol, 4.25% D-lactic acid) was supplied by Nature Works LLC. It has a melt flow index of 3.4 g/10 min (190 °C, 2.16 kg) and a density of 1.24 g/cm^3. The PLA pellets were dried at 80 °C in vacuum oven for 4 h before use.

PVA (GM-14S) with density of 1.27 g/cm^3 was provided by Japanese Synthetic Chemistry Corp. It has been 88% hydrolyzed with an average polymerization degree of 1700. The material in powder form was dried at 60 °C in vacuum oven for 8 h before use.

Edible NaCl with a specific gravity of 2.16 g/cm^3 was purchased from Guangdong Province Salt Industry Group Corp., China. It was sieved to desired size ranging from 75 to 150 μm, and dried for 8 h at 80 °C under vacuum prior to using.

Commercial purity grade CO_2 (purity grade, 99%) used as physical blowing agent was purchased from Shengtong Corp., China.

2.2. Vane extruder device

A novel polymer processing equipment known as vane extruder was employed in this study to prepare the PLA/PVA/NaCl blends. The structure schematic of the vane extruder is shown in Fig. 1. Instead of using screws in conventional extruder, the vane extruder is comprised of several vane plasticizing and conveying units (VPCUs) along the axial direction. The stator, vanes, baffles and the rotor of VPCUs composes a closed chamber. The volume of the closed chamber changes periodically as rotor rotates during processing because of the eccentric distance from the stator to the rotor. A dynamical converging channel is obtained along the circumferentially direction. Thus, high stress and dynamic elongational flow field could be generated. The vane plasticizing units feed materials as the volume increases and discharge materials as the volume decreases. The detailed working principle of the vane extruder has been introduced in the previous studies [30]. The vane extruder used in this study consists of 12 VPCUs. The inner diameter of the stator is 46 mm, the outer diameter of the rotor is 40 mm, and eccentric distance between the rotor and stator is 3 mm.

2.3. Preparation of porous PLA scaffolds

Pre-dried PLA, PVA and NaCl were dry-mixed at certain proportions and compounded via the vane extruder at a rotation speed of 100 rpm. The temperature profiles were 160 °C, 170 °C, 170 °C, and 160 °C from hopper to die. For the melt blending, the PLA/PVA was kept constant at 50/50 by volume to ensure a co-continuous morphology of the polymer matrix, while the NaCl content was varied from 10% to 40% of the polymer matrix by volume. Then, the prepared PLA/PVA/NaCl blends were saturated with Sc-CO_2 in a high-pressure vessel. The vessel was heated to the saturation temperature 150 °C in 1 h. Then, the vessel was filled with Sc-CO_2 to desired saturation pressure 10 MPa. The sample was kept in equilibrium at 150 °C and 10 MPa for 1 h and subsequently cooled to the foaming temperature of 100 °C. Then, the high-pressure vessel was instantaneously depressurized to the atmospheric pressure to induce cell nucleation and growth. The sample was solidified by water-cooling system. Finally, the water soluble phase PVA and NaCl were leached with circulating water at 40 °C for at least 72 h

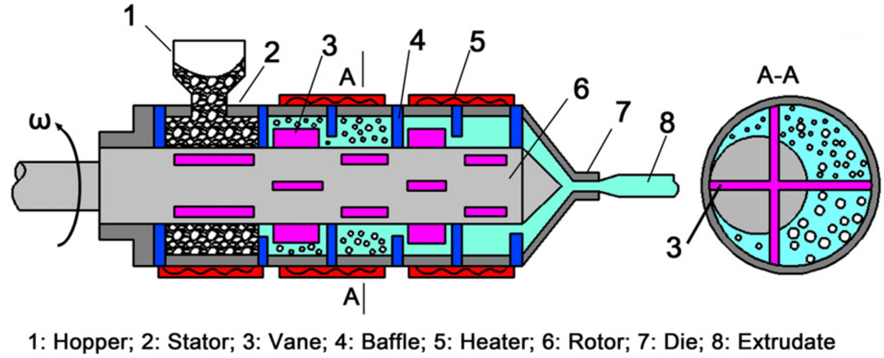

Fig. 1. Schematic illustration of the vane extruder.