Materials and Design 109 (2016) 415–424

Contents lists available at ScienceDirect

Materials and Design

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

Combination of fused deposition modeling and gas foaming technique to fabricated hierarchical macro/microporous polymer scaffolds

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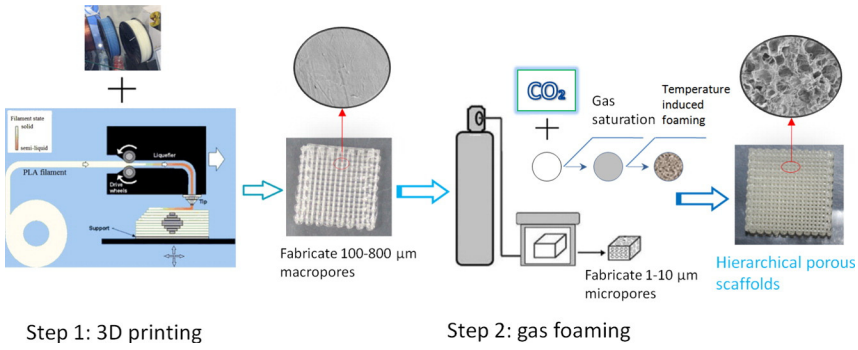
HIGHLIGHTS

- Hierarchical macro/microporous polymer scaffold was fabricated.
- Scaffolds with 100–800 μm macropores were initially fabricated by using FDM technique.
- Scaffolds with 1–10 μm micropores were then fabricated by using gas foaming.
- The integrated manufacturing method can fabricate grotesque and large scaffolds for bone tissue engineering application.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 31 May 2016
Received in revised form 15 July 2016
Accepted 18 July 2016
Available online 19 July 2016

Keywords:
Scaffolds
3D printing
CO_2 gas foaming
Bone tissue engineering

ABSTRACT

The design and fabrication of porous scaffold remains a major challenge in bone tissue engineering. Hierarchical microporous and macroporous structures in scaffold contribute different biological functions to tissue regeneration. This study introduced an integrated manufacturing method to fabricate hierarchical porous polymer scaffolds. Firstly, polylactic acid (PLA) scaffolds with 100–800 μm macropores were fabricated by applying fused deposition modeling (FDM) techniques. Then, 1–10 μm micropores were generated in scaffolds through gas foaming. This combined technique avoids the disadvantages of pure 3DP or gas foaming technology and elicits positive cooperative effects to fabricate hierarchical porous scaffolds. The design of porosity in scaffold could offer innovative opportunities to control cell performance within 3D microenvironments.

1. Introduction

Tissue engineering involves the use of porous scaffolds to repair damaged biological tissues [1,2]. In the past few years, researchers have focused on development of three-dimensional (3D) tissue scaffolds, which offer significant advantages in terms of tissue regeneration [3]. However, appropriate design and fabrication of porous biodegradable scaffold remains a major challenge in bone tissue engineering [4,5]. To achieve bone tissue reconstruction, scaffolds must satisfy several specific requirements, such as mechanical strength, suitable pore size, suitable porosity and interconnectivity. Adequate pore dimensions and porosity allow cell migration, vascularization, nutrient and

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http://dx.doi.org/10.1016/j.matdes.2016.07.094
0264-1275/

metabolite diffusion [6]. Interconnectivity influences the degree and the path of tissue regeneration [7–9]. Furthermore, high surface area and roughness of porous scaffolds are necessary to facilitate cell seeding and fixation. The design of porosity in scaffold could offer innovative opportunities to control cell performance within 3D microenvironments [10,11].

In bone tissue engineering, macroporosity (pore size > 100 μm) [9,12], which is defined by the ability to be colonized by cells, provides space for cell adhesion and ingrowth. Macroporosity affects cell distribution and migration and allows in vivo blood vessel formation to sustain bone formation [5,13,14]. Microporosity (pore size <10 μm), which is defined by the capability to be impregnated by biological fluids [15], creates a greater surface area for protein adsorption and an increased ionic solubility. Both macroporosity and microporosity are essential for new bone tissue formation [16,17]. For example, Zhang et al. [18] reported that macroporous (300–700 μm) and microporous (1–10 μm) calcium phosphate bioceramics exhibit specific osteoinduction properties, which can generate new bone formation on non-bony sites. However, this phenomenon cannot be observed in non-microporous scaffolds. Wang and Lan et al. [19,20] indicated that the embedded osteocytes distributed throughout microporous rods may form a mechanosensory network, which is impossible in non-microporous scaffolds. Hence, these two pores are intentionally introduced into tissue scaffold [21–25]. With regard to porous scaffold fabrication, many techniques have been developed, conventional techniques include gas foaming, phase separation, emulsion freeze drying, fibremeshes/fiber bonding, and solution casting have been well developed [26–29]. However, single use of a conventional method is difficult to precisely control pore size and geometry, as well as the spatial distribution of pores, thus resulting imperfect biological performances of 3D scaffolds [30–32]. Moreover, porous scaffolds fabricated by using conventional techniques can not fulfill the customer personalized requirements [32–34].

Advances in computational design and additive manufacturing (AM) have resulted in quick and accurate fabrication of 3D porous scaffolds with well-controlled architectures [35]. As an AM technology, 3D printing (3DP) techniques are increasingly recognized as ideal methods to produce 3D structures with optimal pore size and spatial distribution [36,37]. 3DP produces complex scaffolds from a 3D design file by decomposing an object's structures into a series of parallel slices. Internal 3D structures are then fabricated by reproducing these slices one layer at a time by using a sized nozzle [38]. However, the printing capability of printing nozzles is limited. For most 3DP technologies, objects with an accurate porosity of <10 μm are difficult to fabricate because pressure remarkably increases as nozzle diameter decreases [39–41]. Gas foaming technology provides advantages that result in the generation of microporous scaffolds and efficiently fabricate pores of <10 μm in polymers [42–44]. For instance, CO_2 is a potential foaming gas used as a foaming agent to create 3D porous scaffolds; with this gas, the use of organic solvents and high temperature can be avoided [45]. In gas foaming, the prepared polymer is initially saturated with CO_2 at a certain temperature and pressure. As CO_2 diffuses into the polymer matrix, it reaches a two-phase CO_2/polymer solution equilibrium [46]. Once system equilibrium is broken, pore nucleation can be induced by either increasing temperature or reducing pressure, and these nuclei can finally form micropores in the polymer [47]. According to gas foaming theory [48], processing parameters, such as saturation pressure, foaming temperature and pressure drop rate, can be manipulated to control the morphological characteristics and dimensions of pores.

In the present study, a novel integrated manufacturing process, known as FDM and gas foaming, is proposed to fabricate PLA scaffolds with hierarchical macro/microporous structures. The potential and feasibility of this novel combined technology opens the opportunity to create both macro scale porosity (100–800 μm) and 1–10 μm micro pores within a scaffold. The precise control of scaffold porosity, pore dimensions, and internal architecture on different scales is necessary to understand structure–bioactivity relationship and to create rational designs of enhanced scaffolds in bone tissue engineering.

2. Experimental

2.1. Materials

The PLA 3D Printer filament was used in the study. PLA was purchased from Zhuhai Sunlu Industrial Co., Ltd. as acquired in thin wires (Φ1.75 mm) with a density of 1.25 g/cm^3, variations of ±0.1 mm and roundness of ±0.05 mm. PLA is a semicrystalline polymer with crystallinity of approximately 5%. Glass transition temperature is about 65 °C. Medical grade CO_2 (99.90% purity; Qiaoyuan Gas, Inc., Sichuan, China) was used as the foaming agent.

2.2. Fabrication of hierarchical macro-/microporous scaffolds

Fabrication of hierarchical macro-/microporous scaffolds is shown in Fig. 1. One of 3DP technique, fused deposition modeling (FDM) is the first fabrication step. PLA filament with a diameter of 1.75 mm was melted at 180 °C and extruded by a sized printing nozzle (XYZprinting, da Vinci 1.0 Professional). Smaller PLA printing fibers were continually stacked layer by layer to form a porous scaffold. The macroporosity of the scaffold was designed by precisely controlling the printing nozzle motion path. The nozzle diameter of the FDM 3D printer was 0.4 mm, the printing temperature was set at 180 °C, and the moving speed during operation was 40 mm/s. CURA slicing software was used, and the print layer thickness was 0.1–0.3 mm. The microporosity of the printed scaffold was obtained in the second step, that is, the CO_2 gas foaming process. CO_2 gas foaming is a two-stage batch process. In the first stage, the polymer scaffolds were impregnated with high-pressure CO_2 through a pressure vessel. In the second stage, the absorbed CO_2 nucleated and formed

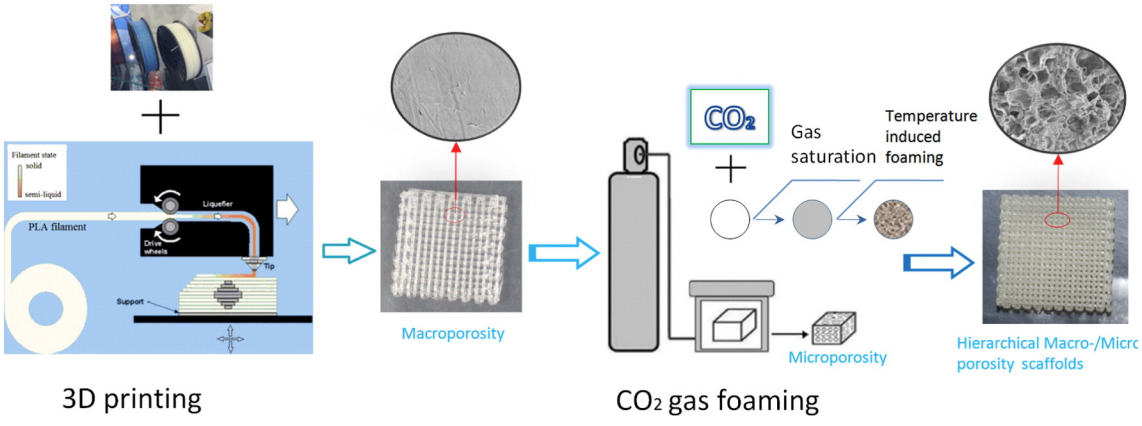

Fig. 1. Schematic of the combined 3D printing and CO_2 gas foaming techniques for fabrication of hierarchical macro-/microporous polymer scaffolds.