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Preparation of interconnected poly(ε-caprolactone) porous scaffolds by a combination of polymer and salt particulate leaching

Joël Reignier *, Michel A. Huneault

Industrial Materials Institute, National Research Council Canada, 75, de Mortagne, Boucherville, QC, Canada J4B 6Y4

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Abstract

This paper examines a new technique for the preparation of porous scaffolds by combining selective polymer leaching in a co-continuous blend and salt particulate leaching. In the first step of this technique, a co-continuous blend of two biodegradable polymers, poly(ε-caprolactone) (PCL) and polyethylene oxide (PEO), and a certain amount of sodium chloride salt particles are melt blended using a twin screw extruder. Subsequently, extraction of the continuous PEO and mineral salts using water as a selective solvent yields a highly porous PCL scaffold with fully interconnected pores. Since, the salt particles and the co-continuous polymer blend morphology lead to very different pore sizes, a particular feature of this technique is the creation of a bimodal pore size distribution. Scanning electron microscopy, mercury intrusion porosimetry and laser diffraction particle size analysis were carried out to characterize the pore morphology. The prepared scaffolds have relatively homogeneous pore structure throughout the matrix and the porosity can be controlled between 75% and about 88% by altering the initial volume fraction of salt particles and to a lesser extent by changing the PCL/PEO composition ratio. Compared to the conventional salt leaching technique and to its different variants, the proposed process allows a better interconnection between the large pores left by the salt leaching and a fully interconnected porous structure resulting from the selective polymer leaching. The average compressive modulus of the different porous scaffolds was found to decrease from 5.2 MPa to about 1 MPa with increasing porosity, according to a power–law relationship. Since, the blending and molding of the scaffold (prior to leaching) can be made using conventional polymer processing equipment, this process seems very promising for a large scale production of porous scaffold of many sizes and in an economic way.

Keywords: Polymer blends; Particulate leaching; Porous scaffolds

1. Introduction

In the last few decades, cell transplantation using a highly porous artificial extracellular matrix, or scaffold, as supporting material has been explored as a route to repair damaged tissues. Indeed, it is known that isolated cells cannot form new tissues by themselves. Rather, they need a specific environment to guide their growth and allow tissue regeneration in three-dimensions. Ideally, the polymeric material should be biocompatible, biodegradable and bioresorbable with a controlled degradation rate to match tissue ingrowth. Surprisingly, the success of such therapy greatly depends on the microstructure and the morphology of the porous structure, which is governed by the fabrication method. The regeneration of specific tissues aided by synthetic materials mostly depends on the porosity (void volume fraction), pore size, pore shape, pore distribution (interconnection between the pores), architecture (overall shape of the object), as well as to the mechanical properties of the scaffolds. In general, a high porosity and a high interconnectivity between the pores are necessary to allow cell growth and flow transport of nutrients and metabolic waste. Thus, beside the choice of the suitable material, the first stage of tissue engineering begins with the fabrication of a porous three-dimensional scaffold.

A number of processing techniques based on textile technologies, particulate leaching, phase separation process, gas foaming, particle aggregation and solid freeform fabrication have already been developed with more or less success to produce porous biodegradable polymeric scaffolds for tissue engineering applications [1–3]. Some of the first scaffolds used to demonstrate the feasibility of tissue regeneration involved the use of non-woven fibers in the form of tassels and felts

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* Corresponding author. Tel.: +1 450 641 5201; fax: +1 450 641 5105.
E-mail address: joel.reignier@cnrc-nrc.gc.ca (J. Reignier).

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consisting in individual fibers placed into a three-dimensional pattern [4–6]. A second family of techniques involves phase separation processes (liquid–liquid or solid–liquid) of polymer/solvent mixture. These techniques have been explored to produce scaffolds with porosity up to 95% [7–10]. Basically, the polymer is dissolved in a solvent and a phase separation is induced by lowering the solution temperature or adding a non-solvent to the solution. In practice this method is so sensitive to process variations that precise control of scaffold morphology is difficult. For this reason, these techniques do not lend well to reproducible production of scaffolds. The presence of polymer solvent or non-solvent residual in the scaffolds can also represent an additional limitation of phase separation techniques.

Foaming is another path to the fabrication of porous polymer scaffolds. It was carried out by dissolving a gas at elevated pressure (physical blowing agent) [11–13] or by incorporated a chemical that yields gaseous decomposition products (chemical blowing agent) [14–16]. The foaming technique generally leads to pore structures that are not as fully interconnected as the previously mentioned ones. Another feature is the ‘skin–core’ structure where the core is porous while the external skin of the sample is solid. In some cases, the resulting scaffolds can have well interconnected macroporous structure with limited core/skin effect [15]. Other techniques include the use of particle aggregation to create macroporous three-dimensional structures with porosity up to 35% [17–19] and solid freeform fabrication technique (SFF) such as 3D-printing [20], selective laser sintering [21], 3D-plotting [22], fused deposition modeling [2,23]. These techniques are time consuming and are limited to pore sizes greater than 50 μm and to porosity lower than 70%.

One of the most common and straightforward technique to prepare porous scaffolds is the particulate leaching method, which involves the selective leaching of a mineral, usually NaCl salt or of an organic compound such as saccharose to generate the pores. Solvent casting/particulate leaching involves the casting of a polymer solution and dispersed calibrated porogen particulates in a mold, removal of the polymer solvent, followed by leaching out of the porogen [24,25]. Because of casting and solvent evaporation step, this technique is suitable for thin scaffolds only. One drawback in this technique is the presence of organic solvent, which may be hard to completely remove from the scaffolds during the drying process. Residual organic solvent may be harmful to adherent cells or nearby tissues. To circumvent this problem, several authors proposed to replace solvent casting by melt-molding resulting in the melt-molding/particulate leaching method. Briefly, the melt-molding step consists in premixing polymer powder and solid porogen particulates and hot-pressing them together. The samples are then subjected to the same solid porogen leaching step as for the solvent-cast samples [26–29]. In a general manner, the major advantage of particulate leaching methods is the effective control of porosity and pore size. Materials with porosity levels up to 90% and pore size varying between 100 and 700 μm have been reported using the particulate leaching technique. The porosity (or void volume fraction) is given by the amount of leachable particles, whereas the pore size and pore shape of the porous structure can be modified independently of the porosity by varying the leachable particles characteristics (size and shape). One potential deficiency of the technique, especially for scaffolds requiring lower porosity levels is the lack of interconnectivity between the pores. Indeed, the spatial organization of the porous structure—including the interconnectivity between the pores—is directly dictated by the spatial arrangement of the porogen particles in the polymer/particulate composite. Therefore, decreasing the volume fraction of porogen particles decreases the number of contact point between particles and thus decreases interconnection between the pores after leaching of the porogen particles. Thus, it can lead to the entrapment in the polymer matrix of porogen particles that are not in direct contact with other particles. This phenomenon is particularly important at low volume fraction of porogen particles, typically less than 65% for rigid spheres. In that case, a completely open-cell structure cannot be manufactured due to the isolated particles in the polymer matrix [24,29]. Another feature that is noteworthy for the scaffold application is that the interconnection between the pores is smaller than the size of the pores. This may limit the propagation of cells from one pore to the other in certain applications. Therefore, even if the pore interconnection can be obtained using high porogen volume fraction, it cannot accurately be controlled. Recognizing this limitation, it has been proposed to partially bond the porogen particles by working in a humid environment in the case of NaCl porogen or by heat treatment in the case of paraffin spheres or sugar particles [24,30,31].

To improve the interconnectivity between the pores, other novel scaffolds preparation methods have been proposed by combining particulate leaching with other fabrication techniques, such as phase separation, emulsion freeze-drying, gas foaming or rapid prototyping [13,32–36]. However, combination of particulate leaching with phase separation technique or combination with gas foaming techniques does not ensure complete interconnectivity of the porous structure. Rather, it results in the creation of a multi-porous structure characterized by different pore sizes and/or pore morphologies, the larger pores typically resulting from the extraction of the porogen particles whereas the smaller pores are characteristic of the combinatory method. In another approach, solvent casting/particulate leaching was coupled with solid freeform manufacturing. This lead to scaffolds containing huge channels created by the computer aided system dispersed in small randomly distributed local pores generated by leaching of porogen particles [34]. In spite of the increase in porosity due to addition of porogen particles, none of these methods allowed a complete control over the interconnected pore structure.

More recently, a new methodology for the preparation of porous scaffolds for tissue engineering has emerged from the melt blending of two immiscible polymers [37,38]. The strategy used consists in melt blending the two polymers in the judicious composition required to create the so-called co-continuous blend morphology, an interconnected structure in which each phase is fully continuous. At dispersed phase