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Poly(lactide-*co*-glycolide)/hydroxyapatite composite scaffolds for bone tissue engineering

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Abstract

Biodegradable polymer/bioceramic composite scaffolds can overcome the limitations of conventional ceramic bone substitutes such as brittleness and difficulty in shaping. However, conventional methods for fabricating polymer/bioceramic composite scaffolds often use organic solvents (e.g., the solvent casting and particulate leaching (SC/PL) method), which might be harmful to cells or tissues. Furthermore, the polymer solutions may coat the ceramics and hinder their exposure to the scaffold surface, which may decrease the likelihood that the seeded osteogenic cells will make contact with the bioactive ceramics. In this study, a novel method for fabricating a polymer/nano-bioceramic composite scaffold with high exposure of the bioceramics to the scaffold surface was developed for efficient bone tissue engineering. Poly(D,L-lactic-*co*-glycolic acid)/nano-hydroxyapatite (PLGA/HA) composite scaffolds were fabricated by the gas forming and particulate leaching (GF/PL) method without the use of organic solvents. The GF/PL method exposed HA nanoparticles at the scaffold surface significantly more than the conventional SC/PL method does. The GF/PL scaffolds showed interconnected porous structures without a skin layer and exhibited superior enhanced mechanical properties to those of scaffolds fabricated by the SC/PL method. Both types of scaffolds were seeded with rat calvarial osteoblasts and cultured in vitro or were subcutaneously implanted into athymic mice for eight weeks. The GF/PL scaffolds exhibited significantly higher cell growth, alkaline phosphatase activity, and mineralization compared to the SC/PL scaffolds in vitro. Histological analyses and calcium content quantification of the regenerated tissues five and eight weeks after implantation showed that bone formation was more extensive on the GF/PL scaffolds than on the SC/PL scaffolds. Compared to the SC/PL scaffolds, the enhanced bone formation on the GF/PL scaffolds may have resulted from the higher exposure of HA nanoparticles at the scaffold surface, which allowed for direct contact with the transplanted cells and stimulated the cell proliferation and osteogenic differentiation. These results show that the biodegradable polymer/bioceramic composite scaffolds fabricated by the novel GF/PL method enhance bone regeneration compared with those fabricated by the conventional SC/PL method.

Keywords: Bone regeneration; Bone tissue engineering; Hydroxyapatite; Osteoblast; Scaffold

1. Introduction

Bone grafts have been used to fill bone defects caused by disease or trauma, such as bone fractures, infections, and tumors [1,2]. Autografts have the distinct advantage of histocompatibility without the risks of disease transfer and are still the best material for bone repair. However, their limited availability necessitates the development of alternative bone substitutes. Although allogenic bone grafts have better availability than autografts and avoid the need for a second surgical procedure to obtain an autograft, the use of allogenic bone grafts may transmit diseases and cause immune responses, which can lead to the graft failure [3]. Over the past decade, the main goal of bone tissue engineering has been to develop biodegradable materials as bone graft substitutes for filling large bone defects [4–6]. These materials should maintain adequate mechanical

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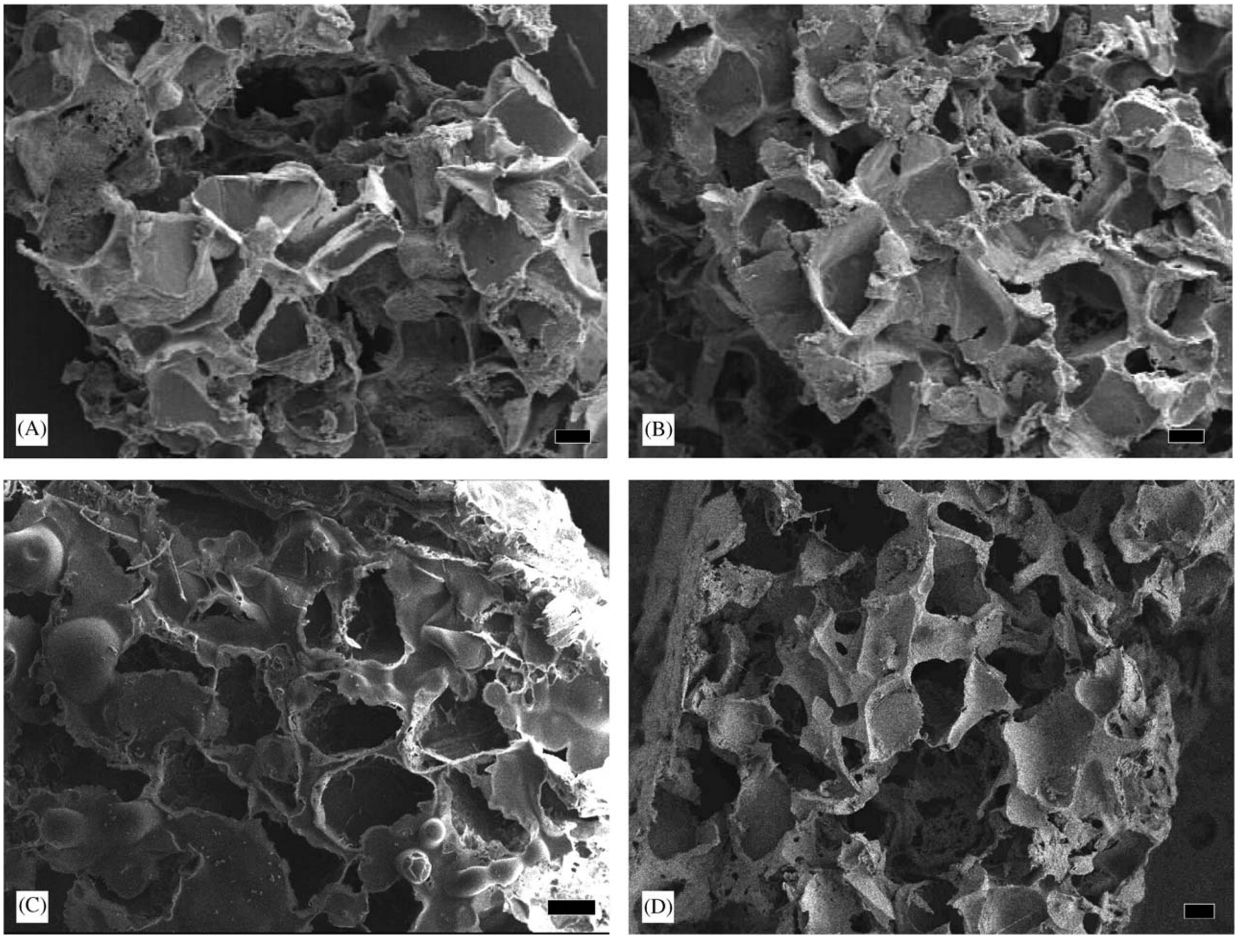

Fig. 1. Scanning electron micrographs of (A,C) surfaces and (B,D) cross-sections of the PLGA/HA composite scaffolds fabricated by (A,B) the SC/PL method and (C,D) the GF/PL method. The scale bars indicate 100 μm.

strength, be osteoconductive, and degrade at a controlled rate to provide space for the formation of new bone [5].

There has been widespread use of calcium phosphate bioceramics, such as hydroxyapatite (HA) and tricalcium phosphate (TCP), for bone regeneration applications. Their biocompatibilities are thought to be due to their chemical and structural similarity to the mineral phase of native bone [5]. The interactions of osteogenic cells with bioceramics are important for bone regeneration [6]. Bioactive ceramics are known to enhance osteoblast differentiation as well as osteoblast growth [7,8]. Bioactive ceramics have been used in dental and orthopedic surgery to fill bone defects and to coat on metallic implant surfaces to improve implant integration with the host bone. However, their clinical applications have been limited because of their brittleness, difficulty of shaping [9], and an extremely slow degradation rate in the case of HA [10]. HA has poor mechanical properties and new bone formed in a porous HA network cannot sustain the mechanical loading needed for remodeling [9].

The use of biodegradable polymer/bioceramic composites could be a solution to this problem. The addition of biodegradable polymers such as poly(glycolic acid), poly(L-lactic acid), and poly(D,L-lactic-*co*-glycolic acid) (PLGA) to calcium phosphate ceramics would allow for better manipulation and control over both the macro- and microstructure in shaping composites to fit bone defects. In addition, biodegradable polymers can be used as binders for HA or TCP to reduce the brittleness of the ceramics [11,12]. Biodegradable polymer/bioceramic composites would be promising materials for bone grafts, and have been extensively investigated [12–16].

Most of the previous methods for fabricating polymer/bioceramic composite scaffolds, such as the solvent casting and particulate leaching (SC/PL) method or the phase separation method, use organic solvents [16–19]. However, residual solvents in the scaffolds may be harmful to transplanted cells or host tissues [20–24]. Furthermore, the polymer coating on the ceramics created by polymer solutions may hinder the exposure of the ceramics to the scaffold surfaces (Fig. 1A), which could decrease the chance that osteogenic cells make contact with the bioactive ceramics.

In the present study, we used the gas forming and particulate leaching (GF/PL) method to fabricate PLGA/HA composite scaffolds for bone tissue engineering. This