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Porous stable poly(lactic acid)/ethyl cellulose/hydroxyapatite composite scaffolds prepared by a combined method for bone regeneration

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A B S T R A C T

A major challenge in bone tissue engineering is the development of biomimetic scaffolds which should simultaneously meet mechanical strength and pore structure requirements. Herein, we combined technologies of high concentration solvent casting, particulate leaching, and room temperature compression molding to prepare a novel poly(lactic acid)/ethyl cellulose/hydroxyapatite (PLA/EC/HA) scaffold. The functional, structural and mechanical properties of the obtained porous scaffolds were characterized. The results indicated that the PLA/EC/HA scaffolds at the 20 wt% HA loading level showed optimal mechanical properties and desired porous structure. Its porosity, contact angle, compressive yield strength and weight loss after 56 days were 84.28 ± 7.04%, 45.13 ± 2.40°, 1.57 ± 0.09 MPa and 4.77 ± 0.32%, respectively, which could satisfy the physiological demands to guide bone regeneration. Thus, the developed scaffolds have potential to be used as a bone substitute material for bone tissue engineering application.

1. Introduction

Bone defects caused by trauma, congenital malformations, osteoarthritis, osteoporosis and cancer have led to an increasing demand for bone substitute materials (Yunus Basha, Sampath Kumar, & Doble, 2015). How to repair bone defects ideally is a hot topic in clinical research. Bone tissue engineering, as a supplement to autogenous, xenogeneic or allograft bone grafts, provides an important alternative for bone defects repair (Melke, Midha, Ghosh, Ito, & Hofmann, 2015; Venkatesan, Bhatnagar, Manivasagan, Kang, & Kim, 2015). Bone scaffold is the core of bone tissue engineering. It mimics the extracellular matrix and provides a suitable environment for the growth of cells. In general, ideal bone tissue engineering scaffold should possess characteristics of biocompatibility, osteoconductivity, osteoinductivity, biodegradability, appropriate pore size and porosity, and mechanical strength (Bose, Roy, & Bandyopadhyay, 2012). It is difficult for a single material to meet all the requirements above. Therefore, researchers usually imitate the composition and structural characteristics of natural bone to prepare biomimetic inorganic/organic hybrid scaffolds.

Among the various degradable polymers, poly(lactic acid) (PLA) is highlighted by its excellent mechanical properties, biocompatibility, and biodegradability (Esquirol, Sarazin, & Virgilio, 2014; Persson, Lorite, Cho, Tuukkanen, & Skrifvars, 2013). However, the hydrophobicity, brittleness, acidic degradation products and high cost of PLA restrict its application. Siqueira et al. produced a PDLLA/superhydrophilic vertically aligned carbon nanotubes: hydroxyapatite (PDLLA/VACNT-O: nHAp) scaffold to improve the hydrophilicity of PLA (Siqueira et al., 2015). In order to obtain scaffolds with excellent properties, researchers have combined biodegradable polymers with cellulose or its derivatives (Naseri, Deepa, Mathew, Oksman, & Girandon, 2016). For example, Oliveira Barud et al. reported a bacterial cellulose (BC)/silk fibroin (SF) nanocomposite with good cellular activity (Oliveira Barud et al., 2015). However, its two-dimensional structure and poor mechanical properties make it unsuitable for implantation *in vivo*. As an artificially modified cellulose, the excellent mechanical properties, low cost and renewability of ethyl cellulose (EC) make it one of the most widely used cellulose derivatives (Chen, Wang, Yin, Tam, & Wu, 2017; Delgado, Quinchia, Spikes, & Gallegos, 2017). Especially in tissue engineering, the study on the blend system of poly(lactic acid) and cellulose ether is rare. In addition, it is necessary to incorporate hydroxyapatite (HA) into the composite to impart scaffolds bioactivity, since HA is the main inorganic component for human hard tissue. It has been proved that HA contributes to osteogenesis and load-bearing (Sanaei-Rad, Jafarzadeh Kashi, Seyedjafari, & Soleimani, 2016).

At present, the preparation methods of the scaffold mainly include solvent casting-particulate leaching method (Ding et al., 2015), thermally induced phase separation (Zhang, Liu, Yang, & Zhu, 2015), freeze-drying (Pei et al., 2015), gas-foaming process (Moghadam, Hassanajili, Esmaeilzadeh, Ayatollahi, & Ahmadi, 2017), rapid-

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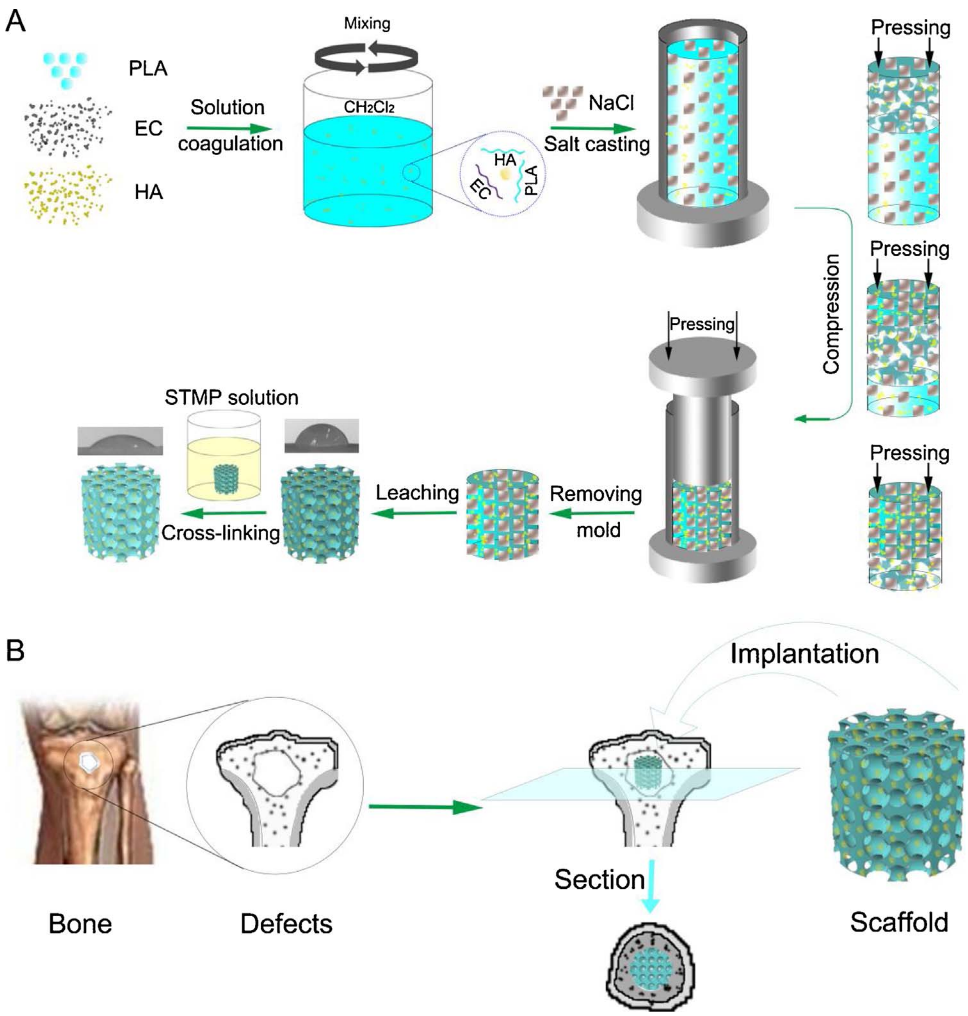

Fig. 1. Schematic illustration of preparation (A) and bone grafting (B) of PLA/EC/HA porous scaffolds.

prototyping techniques (Martínez-Vázquez, Cabañas, Paris, Lozano, & Vallet-Regí, 2015) and so on. Among them, solvent casting-particulate leaching method prepares a scaffold with high porosity and good connectivity easily. Especially, the pore size and porosity of the scaffold can be easily regulated by size and amount of porogen particulate. However, the method requires the concentration of the polymer solution to be low enough to diffuse between the porogen particulates, resulting in insufficient mechanical properties. To address the deficiency, the newly-developed high pressure compression molding method has aroused people's interest. It increases the density of scaffold by external force, so as to improve the performance of scaffold (Zhang, Liu et al., 2016; Zhang, Yang, Ding, & Li, 2016). However, the method usually requires a high temperature above 150 °C during fabrication of the material, which leads to undesired side effects for the heat-sensitivity components. Furthermore, the composition homogeneity can't be guaranteed by the melt blending of different polymers. Therefore, it implied that the combination between compression molding and high concentration solvent casting-particulate leaching may lead to a desired result.

Besides, the surface hydrophilicity of bone scaffold is a prerequisite for its interaction with biological fluid and cells. Surface modification of materials is a traditional and effective method to improve hydrophilicity. Among various modifiers, sodium trimetaphosphate (STMP) has the advantage of non-toxicity, which is usually used as a starch modifier in the food industry (Irit Gliko-Kabir, Boris Yagen, Adel Penhasi, & Rubinstein, 2000). Amrita et al. reported the use of STMP as a cross-linker for pullulan-based composite scaffolds (Amrita, Arora, Sharma, & Katti, 2015).

Aiming to improve the hydrophilicity and mechanical properties of bone scaffold, a combined method of high concentration solvent casting, particulate leaching, room temperature compression molding is used to prepare the PLA/EC/HA composite scaffolds in the present work. The alteration of mechanical properties with different PLLA/PLGA ratios was monitored and the corresponding phase transition was elucidated. The effect of the concentration of HA on the properties of the scaffolds was also studied. On the whole, the compact interpenetrating network structure and enhanced mechanical properties caused by the combined method will make the porous scaffold a promising candidate for bone tissue engineering.

2. Materials and methods

2.1. Materials

Poly(lactic acid) (PLA 4032D) with 98% L-lactide content was purchased from NatureWorks LLC. Ethyl cellulose (EC, 18–22 mPa s, 5% methylbenzene/isopropanol 80:20) was obtained from Aladdin Reagent (Shanghai) Co., Ltd. Ammonium phosphate ($(NH_4)_2HPO_4$, Tianjin Beichen Founder Reagent Factory), calcium nitrate tetrahydrate ($Ca(NO_3)_2 \cdot 4H_2O$, Chengdu Kelong Chemical Reagent Factory), ammonium hydroxide ($NH_3 \cdot H_2O$, Chongqing Yubei chemical plant), were used as received. Dichloromethane (CH_2Cl_2), sodium hydroxide (NaOH), and sodium chloride (NaCl) particulates sieved in a specific range from 150 to 250 μm were supplied by Chongqing Chuandong Chemical Ltd.