



# Fabrication of 3D porous poly(lactic acid)-based composite scaffolds with tunable biodegradation for bone tissue engineering

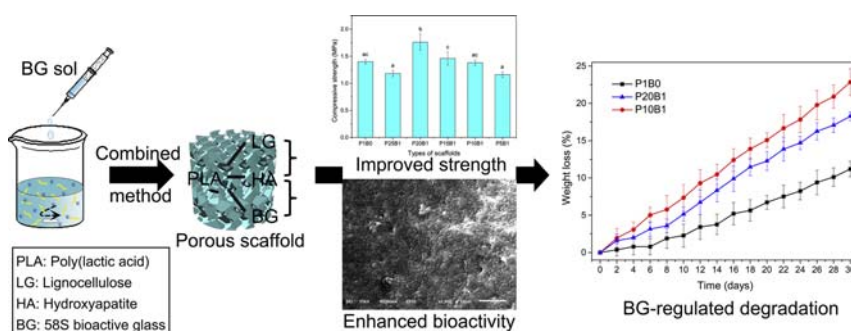
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## HIGHLIGHTS

- The combined method hardly involved any complex and harsh operation, which helped to preserve the polymer properties.
- The scaffold composition was reasonably designed to obtain proper mechanical properties and favorable bioactivity.
- The scaffold exhibited tunable degradation rate, which matched the growth rate of new bone tissue at different sites.
- The scaffold showed good structural integrity during degradation.

## GRAPHICAL ABSTRACT



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## ABSTRACT

Success of biomimetic scaffold relies on the comparability of its microarchitecture and physicochemical properties to the natural bone. However, porous scaffolds which simultaneously possessed excellent mechanical properties, favorable bioactivity and tunable biodegradation were rarely reported. Herein, to integrate the high stiffness of hydroxyapatite (HA), the formability of lignocellulose (LG), the processability of poly(lactic acid) (PLA) and the bioactivity of sol-gel derived 58S bioactive glass (BG), poly(lactic acid) (PLA)-based composite scaffolds were fabricated by a simple technique of combining the solvent casting/particulate leaching and sol-gel method. The resultant scaffolds showed well-defined interconnected porous structure with pore size of 200–400  $\mu\text{m}$  and rough pore wall, which was reported to be potentially beneficial for cell adhesion and ingrowth. In addition, the mechanical properties were obviously improved by the reinforcements of LG, HA, and BG. *In vitro* biomineralization studies indicated the incorporation of BG significantly enhanced the bioactivity of composite scaffolds. Specially, the degradation rate of scaffolds could be easily regulated by adjusting the BG content to match the regeneration of new bone. The developed PLA-based composite scaffolds might have a great potential for bone regeneration.

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## 1. Introduction

The high incidence of bone defects caused by trauma, tumor resection and congenital defects has aroused concern recently [1]. However, bone substitutes are always in short supply for clinical operations. As

the commonly used autologous/allograft bone grafts have failed to meet the increasing demands for surgery, bone tissue engineering (BTE) came into being [2]. Various composite scaffolds have been developed since the proposal of BTE. However, the currently reported biomimetic bone scaffolds showed more or less incompatibility with natural bone, which made them difficult to achieve clinical application. For example, Wen-Chuan Hsieh et al. fabricated a novel poly(vinyl alcohol)-g-curdlan 3D scaffold and found that the 3D scaffold showed excellent

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degradation property and favorable cell proliferation and growth [3]. However, the compression strength of the 3D scaffold was up to only  $8\text{--}16 \times 10^{-3}$  MPa, while the trabecular bone has been reported to have a mechanical strength range of 1–10 MPa [4, 5]. Ting Xu et al. developed a poly(lactic acid)/chitosan composite scaffold with outstanding mineralization ability and cell activity, but the electrospinning process limited the composite to a 2D membrane [6]. Most importantly, most recent studies have ignored a severe challenge: currently available porous composite scaffolds have rarely been studied for controlled degradation performance to match the regeneration of new bone [7]. 3D porous scaffolds with excellent mechanical properties, favorable bioactivity and tunable biodegradation are attracting increasing attention in BTE.

Thus far, a variety of biodegradable polymers have been examined as scaffolding materials, including collagen, gelatin and polycaprolactone, particularly because of their biocompatibility and biodegradability [8, 9]. PLA, an artificial polymer approved by the Food and Drug Administration (FDA) to be widely used in the biomedical field, is considered as one of the most promising candidates because of the excellent degradability, biocompatibility, and good design control property [6]. However, its poor mechanical properties, hydrophobicity, and slow degradation limit its application for BTE. Recently, researchers have modified the PLA-based scaffold to meet the requirements of BTE [10, 11]. However, the modifications that had already been carried out were not comprehensive, and the overall performance of the scaffold had not been improved simultaneously [12]. In this respect, the composite scaffold composed of polymer matrix and various fillers is expected to provide overall improvements in its physicochemical properties and its interaction with cells.

Selection of fillers for a tissue-engineered scaffold is an important factor to determine the properties of the composites. As commonly used bioactive component and reinforced agent, HA improves cell interaction and mechanical properties of the composite scaffold [13]. However, HA displays a slow biodegradation, limiting the absorption of the scaffold and its effect on the cells *in vivo*. On the contrary, BG has been shown to release ions upon dissolution, which can upregulate osteoblast-specific gene expression [14, 15]. Thus, the combination of HA with BG is expected to produce a composite with high bioactivity and mechanical properties, which is suitable for load-bearing bone repair. On the other hand, it is generally known that incorporation of inorganic components into the organic matrix will destroy the integrity of the scaffold. With that in mind, the unique fiber structure of LG is expected to improve the formability of the composite scaffolds [16, 17].

Many methods have been investigated to improve the performances of PLA-based scaffold [9, 11]. Among various fabrication techniques, the solvent casting/particle leaching method has the advantages of cost-efficiency, simplicity and controllability over the others [1]. Furthermore, in sol-gel method, bioactive inorganic phases are directly incorporated into polymer, thus, more closely mimicking the chemical composition of the native bone ECM [14, 18, 19].

Based on the above rationale, PLA/LG/HA/BG composite scaffolds were fabricated through a simple technique of combining solvent casting/particle leaching and sol-gel method. Besides, we attempted to regulate the degradation of the composite scaffolds to match the regeneration of new bone *in vivo*. The pore structure, chemical composition, compressive mechanical properties as well as *in vitro* biomineralization of the as-prepared porous PLA-based scaffolds were studied.

## 2. Materials and methods

### 2.1. Materials

Poly(lactic acid) (PLA 4032D) with 98% L-lactide content was purchased from NatureWorks LLC. Lignocellulose (~1 mm in length) was supplied by Shanghai Yi Sheng construction Mstar Technology Ltd.

Ammonium phosphate ( $(\text{NH}_4)_2\text{HPO}_4$ ,  $\geq 99.0\%$ ) was purchased from Tianjin Beichen Founder Reagent Factory. Triethyl phosphate (TEP,  $\geq 99.5\%$ ) was supplied by Aladdin Reagent (Shanghai) Co., Ltd. Tetraethyl orthosilicate (TEOS,  $\text{SiO}_2$  content  $\geq 28.0\%$ ), calcium nitrate tetrahydrate ( $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ ,  $\geq 99.0\%$ ) and ammonium hydroxide ( $\text{NH}_3 \cdot \text{H}_2\text{O}$ , 25–28%) were obtained from Chengdu Kelong Chemical Reagent Factory. Dichloromethane ( $\text{CH}_2\text{Cl}_2$ ,  $\geq 99.5\%$ ), ethyl alcohol ( $\text{C}_2\text{H}_5\text{OH}$ ,  $\geq 99.7\%$ ), hydrochloric acid (HCl, 36.0–38.0%) and sodium chloride (NaCl,  $\geq 99.5\%$ ) were purchased from Chongqing Chuandong Chemical (Group) Co., Ltd. All the above mentioned reagents were used as received.

### 2.2. Fabrication of HA particles and BG sol

A hydrothermal method using  $(\text{NH}_4)_2\text{HPO}_4$  and  $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$  was used to prepare HA particles as reported in our previous research [20]. The 5S8 ( $60\text{SiO}_2\text{--}36\text{CaO--}4\text{P}_2\text{O}_5$ , mol%) bioactive glass was produced using a sol-gel method [14, 18]. Briefly, TEOS, TEP, and  $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$  was dissolved in a cosolvent made of HCl,  $\text{C}_2\text{H}_5\text{OH}$ , and water with the molar ratio of TEOS:TEP:EtOH: $\text{H}_2\text{O}$ : $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ :1 M HCl = 1:0.133:2:2:0.6:0.03 using magnetic stirring at room temperature. The obtained sol was aged at 40 °C for 2 h and subsequently kept at room temperature for 24 h before being added into the hybrid solution.

### 2.3. Preparation of 3D PLA/HA/LG/BG composite scaffolds

The PLA/LG/HA/BG composite scaffolds were fabricated through solvent casting/particle leaching and sol-gel method. The flowchart of the preparation process is shown in Fig. 1. Predetermined amounts of HA particles and LG were dispersed in  $\text{CH}_2\text{Cl}_2$  by ultrasound and magnetic stirring. PLA was dissolved in the above  $\text{CH}_2\text{Cl}_2$  suspension under vigorous magnetic stirring until a clear solution formed. Subsequently, predetermined amounts of the BG sol (0:1, 1:25, 1:20, 1:15, and 1:10 w:w compared to PLA) was added into the above-mentioned blended polymer solution to obtain hybrid solutions with varying polymer/inorganic component ratios. NaCl particulates (used as porogen) with the size of 200–400  $\mu\text{m}$  were added into the hybrid solutions and stirred for 30 min. The interconnected porous structure was acquired by leaching the NaCl particulates with distilled water for >48 h. The desalted scaffolds were dried at 50 °C and stored in a desiccator until use.

The mechanical properties of the porous composite scaffolds were absolutely optimal when the mass ratio of PLA/LG/HA was 20:1:1 (Table S1–S3). Thus, in consideration of the optimal mechanical properties and the focus of this work, the mass ratio of PLA/LG/HA = 20:1:1 was chosen for further study. On the basis of the designed PLA/BG weight ratios of 1:0, 25:1, 20:1, 15:1, and 10:1, the samples were labeled as P1B0, P25B1, P20B1, P15B1 and P10B1, respectively.

### 2.4. Characterization

The microstructure morphology and elemental analysis of the scaffolds were observed by scanning electron microscopy (SEM; JSM-6510LV, JEOL, Japan) equipped with an X-ray energy dispersive spectrometer (EDS). The functional groups and chemical interactions between polymer and inorganic components were investigated by a Fourier transform infrared spectrophotometer (FTIR, Shimadzu Instruments RF-5301PC, Japan). The phase composition and crystalline of the synthesized scaffolds were examined by an X-ray powder diffractometer (XRD, Beijing Purkinje General Instrument Co., Ltd., Beijing, China) with  $\text{Cu K}\alpha$  radiation at 36 kV, 20 mA with a scanning rate of  $4^\circ \cdot \text{min}^{-1}$ . The thermal stability of the scaffolds was measured via the thermogravimetric analysis (TGA; TA Instruments SDTQ600, USA); the samples were heated from room temperature to 600 °C at a heating rate of  $20^\circ \text{C} \cdot \text{min}^{-1}$  under nitrogen atmosphere. The melting behavior of the samples with ~6 mg was studied using a differential scanning

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