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Degradation behavior of hydroxyapatite/poly(lactic-co-glycolic) acid nanocomposite in simulated body fluid

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ABSTRACT

To investigate the effect of hydroxyapatite(HA) on the degradation behavior of hydroxyapatite/poly(lactic-co-glycolic) acid (HA/PLGA) nanocomposite, the degradation experiment of n-HA/PLGA composite and pure PLGA were carried out by soaking in simulated body fluid(SBF) at 37 °C for 1, 2, 4 and 6 months. The change of intrinsic viscosity, thermal properties, inner structure, bending strength reduction, surface morphology and the surface deposit of n-HA/PLGA composite and pure PLGA with respect to the soaking time were investigated by means of UbbeloHde Viscometer, differential scanning calorimeter (DSC), scanning electron microscope(SEM), electromechanical universal tester, a conventional camera and X-ray diffraction (XRD). The results showed that n-HA played an important role in improving the degradation behavior of n-HA/PLGA composite, which can accelerate the degradation PLGA and endow it with bioactivity, after n-HA was detached from PLGA during the degradation, so that n-HA/PLGA composite may have a more promising prospect of the clinical application than pure PLGA as bone fracture internal fixation materials.

1. Introduction

Poly(lactic-co-glycolic) acid (PLGA) has been extensively used in various fields of biomedical applications, due to its good biocompatiblity, biodegradability, processability [1–4]. Especially, PLGA has recently been used as bone fracture internal fixation devices, such as plates, screws, pins and rods. However, there are some inherent drawbacks for PLGA in clinical practice application, such as relatively poor mechanical property, the lack of osteogenic activity and the slowly degradation rate for PLGA with higher LA content [5–9]. To overcome the above shortcomings of PLGA, researchers focus on adding inorganic nanoparticles into PLGA to develop nanocomposite, so as to obtain an ideal bone fracture internal fixation material [10–13].

Nano-hydroxyapatite(n-HA), an inorganic component of natural bone, has good bioactivity and osteoconductivity, so it has become an attractive topic to incorporate n-HA into PLGA [14–17], which is expected to enhance the mechanical properties, improve the degradation rate and endow it with bioactivity. In our recent study, we have made many efforts to study n-HA/PLGA composite. For example, we have systematically studied the effect of many factors on the mechanical property of n-HA/PLGA composite, including different new surface modification methods and different particle sizes for n-HA, different component ratios of n-HA and PLGA, different precipitation methods and different annealing conditions for preparing n-HA/PLGA composite, so we have concluded that the incorporation of n-HA into PLGA significantly increased the mechanical property of PLGA [18,19], so that n-HA/PLGA composite could meet the original mechanical property requirement as bone fracture internal fixation materials. However, it is well known that degradation behavior is of crucial importance for bioabsorbable bone fracture internal fixation materials, and undesirable degradation rate might directly interfere the later bone fracture healing procession, even cause unpredictable trouble. In our study, the copolymer composition of PLGA is 95:05 (LA and GA), whose degradation rate might be as slowly as PLLA, owing to the high ratio of LA [20], so the degradation rate is expected to be improved by incorporation of n-HA into PLGA. Therefore, it is very necessary to investigate the degradation behavior of n-HA/PLGA composite to value the feasibility for end bone fracture fixation applications.

Generally speaking, degradation rate *in vitro* is a little slower than *in vivo* [21]. However, we can predict the degradation rate *in vivo* according to the result of degradation *in vitro*, so degradation *in vitro* experiment, being a simpler and more economic experiment method in comparison with degradation *in vivo* experiment, has been widely accepted [22–25]. Accordingly, the pH-compensation effect of HA on the acidic degradation products

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of the PLGA was investigated by soaking in phosphate buffered saline (PBS) for 8 weeks [26], the results only showed that incorporation of HA into PLGA accelerated the degradation rate of PLGA. However, for n-HA/PLGA composite prepared in our group, there was good interfacial adhesion between n-HA and PLGA owing to the better surface-modified n-HA, so the effect of n-HA on degradation of n-HA/PLGA composite might be different from other HA/PLGA composites in literatures. Moreover, as bone fracture internal fixation materials, the bioactivity *in vitro* in simulated body fluid (SBF) is also worth evaluating. Furthermore, soaking time is also one of important factors to value the degradation behavior of n-HA/PLGA composite. Unluckily, in most of literatures, the degradation *in vitro* experiment was carried out by soaking for only 3 months even shorter. Moreover, it was unavoidable for the difference between the bone fracture healing time *in vivo* and the degradation behavior *in vitro* for PLGA-based composite. Therefore, in our study, being a successive study for the new n-HA/PLGA composite, the degradation *in vitro* experiment should be carried out in SBF for a longer time, so as to predict the degradation behavior of n-HA/PLGA composite *in vivo* more realistically.

Based on the above consideration, in the present work, we initiated a systematic study for the degradation behavior of n-HA/PLGA composite and pure PLGA *in vitro* by investigating the change of intrinsic viscosity, thermal properties, inner structure, bending strength reduction, surface morphology and the surface deposits after soaking in SBF for 6 months. The main purpose is to investigate comprehensively whether n-HA/PLGA composite had more ideal degradation behavior and bioactivity *in vitro* than pure PLGA, owing to the incorporation of HA into PLGA, which would be expected to provide reference significance to predict the degradation *in vivo* and biological properties of n-HA/PLGA composite as bone fracture fixation applications.

2. Experimental procedure

2.1. Materials

PLGA, whose copolymer composition (LA:GA) is 95:05 (mol:mol) and intrinsic viscosity is 4.2–4.5, was prepared in our laboratory. Surface-modified n-HA with mean size of 120 nm in length and 30 nm in width was also prepared in our laboratory. All other agents were analytical grade.

2.2. Preparation of n-HA/PLGA composite

First, the n-HA/PLGA composite containing about 3 wt% surface-modified n-HA was prepared by solution mixing method [18]. Then, the n-HA/PLGA composite was pressed into bars of 4 mm × 6 mm × 60 mm. Finally, the sample was annealed at 110 °C for 30 min in a vacuum oven, and pure PLGA was treated according to the same procedure as a control.

2.3. In vitro *soaking*

The SBF was prepared by dissolving reagent-grade NaCl, $NaHCO_3$, KCl, $K_2HPO_4{\cdot}3H_2O$, $MgCl_2{\cdot}6H_2O$, $CaCl_2$, and Na_2SO_4 in deionized water. The mixture fluid was buffered to physiological pH 7.40 at 37 °C with tri-(hydroxymethyl) aminomethane ($(CH_2OH)_3CNH_2$) and 0.1 mol/l HCl. The ion concentrations of SBF here were similar to those of human blood plasma [27]. The specimens of n-HA/PLGA composite and pure PLGA were immersed in inert plastic test tubes containing 20 ml of SBF for 1, 2, 4, and 6 months that were placed in a rocking water bath at 37 °C. After soaking, the specimens were removed from SBF at the interval time, gently rinsed with deionized water for several times, absorbed the water on the surface with filter paper, and dried completely in a vacuum oven at 40 °C.

The change of n-HA/PLGA composite and pure PLGA were both tested before and after soaking, respectively, including intrinsic viscosity, thermal properties, inner structure, bending strength and surface morphology. The intrinsic viscosity was tested in accordance with GB/T 10247 after been dissolved in chloroform. The thermal properties were measured with a differential scanning calorimetric (DSC) analyzer (Q20, TA Instruments-Waters, USA) under nitrogen atmosphere with the gas feed rate of 20 ml/min, and about 4–10 mg sample was heated from room temperature to 190 °Cat a rate of 10 °C/min. The bending strength was measured by an electromechanical universal testing machine (CMT6000, Sans, China) in accordance with GB/T6569-1986, at a crosshead speed of 20 mm/min at 19 °C. The fracture surfaces of samples were observed by scanning electron microscope (SEM) (KYKY-2800 KYKY, China), after being uniformly sputtered with a gold layer. The surface morphologies were taken photographs with a conventional camera. The surface deposits were characterized by analyzed using X-ray diffraction (XRD) (XRD, Philips, X' Pert Pro, Cu Kα). A scan axis of 2θ was used to obtain diffraction patterns of a scan range between 10° and 60°. The voltage was 40 kV and the current was 45 mA.

3. Results and discussion

3.1. Intrinsic viscosity

Fig. 1 shows the intrinsic viscosity of the samples of n-HA/PLGA composite and pure PLGA before and after soaking for different time. It is found that the intrinsic viscosity of samples decreased with respect to the soaking time. However, the intrinsic viscosity reduction for the n-HA/PLGA composite was larger than that of pure PLGA, suggesting n-HA/PLGA composite had a faster degradation rate than pure PLGA, which may be resulted from the cavity caused by the dissolution of n-HA from PLGA, and the cavity accelerated the hydrolysis of PLGA, which is similar to the phenomenon of other inorganic/PLGA nonacomposites degradation *in vitro* [28–30].

3.2. Differential scanning calorimetry (DSC)

DSC thermograms curves of the samples of n-HA/PLGA composite and pure PLGA before and after soaking for different time are given in Fig. 2. According to Fig. 2, it is clear that no change of the glass transition temperature (T_g) for pure PLGA was detected during the soaking, and there was no melting peak all the time, which indicated that pure PLGA had a very slowly degradation rate, and suggested that pure PLGA crystallization was not promoted during the soaking. On the contrary, there was a greater effect of *in vitro* soaking on the thermal properties of n-HA/PLGA composite.

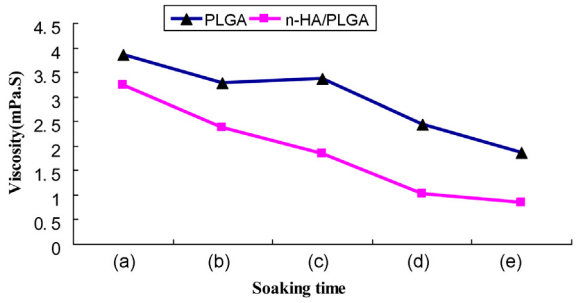

Fig. 1. The viscosity [η] of pure PLGA and n-HA/PLGA composite before and after soaking for different time. (a) Before soaking, (b) 1 month, (c) 2 months, (d) 4 months and (e) 6 months.