Ring-opening Bulk Polymerization of L-Lactide in Porous Hydroxyapatite

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Poly(L-lactide) (PLLA) has been synthesized by ring-opening bulk polymerization of L-lactide in porous hydroxyapatite (HAp) matrix without any additional catalyst, and this hybridizing process directly provided artificial bone materials. The obtained PLLA/HAp composites had enough mechanical properties with a bending strength of 53.7 MPa, which was 2.3 times stronger than porous HAp, and showed excellent biocompatibility for clinical applications.

Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$; HAp] has been widely used in clinical applications because the chemical structure and components are similar to those of natural bones and show biocompatibility to human tissues.[1] Pure HAp materials are only suitable to the non-load-bearing applications because of their fragility, low bending strength, easy rupture, and high Young's modulus. HAp composites with polymers have also attracted much attention for improving the mechanical properties of HAp.[2,3] For artificial bone applications, the polymers should have osteocompatibility, osteoconductivity, and biodegradability. Poly(L-lactide) (PLLA) is one of the best candidates to be selected as a biodegradable polymer because of the excellent metabolic function. Furthermore, it has already been reported that PLLA affects the remodeling process of bone that surrounds implant materials, as well as being an osteocompatible and nontoxic material.[4] Although there are some reports about the PLLA/HAp composites for such a purpose,[5,6] the hybridizing processes have not been simplified and optimized yet.

In general, organometallic compounds have been used as chemical catalysts to synthesize PLLA with high molecular weights, but their toxicity is still unclear for biomedical applications. Thus, the metal-free-catalyzed polymerizations have been desired as a new green chemical methodology.[7] Single site calcium compounds such as $[(THF)Ca(tmhd)]_2[^{\mu}N(SiMe_3)_2]$-$(^{\mu}tmhd)$ and $[(THF)Ca(tmhd)]_2[^{\mu}OCH(Me)Ph](^{\mu}tmhd)$ containing chelating tmhd (H-tmhd = 2,2,6,6-tetramethylheptane-3,5-dione) ligands have been investigated as initiator for ring-opening polymerization of L-lactide.[8] Moreover, HAp and cation- or anion-substituted HAp are reported as effective heterogeneous catalysts for organic reactions.[9,10] In this study, we first attempted to polymerize L-lactide in porous HAp without additional catalysts or solvent with an aim to fabricate the PLLA/HAp composites for artificial bone materials.

Fibrous HAps with the Ca/P ratio of 1.67 were prepared by the homogeneous precipitation method[11,12] and were uniaxially compressed into pellets at 30 MPa, and then were sintered for 5 h at 1200 °C. The PLLA/HAp composites were prepared by the bulk polymerization of L-lactide in a porous HAp pellet via the following three steps. i) Porous HAp was immersed in melted L-lactide at 130 °C. ii) The porous HAp containing L-lactide was freeze–thaw degassed three times. iii) The bulk polymerization was carried out under N_2 at 130 °C for 7 days. After the polymerization, the surface of PLLA/HAp composite was polished and was washed by ultra-sonication with ethanol.

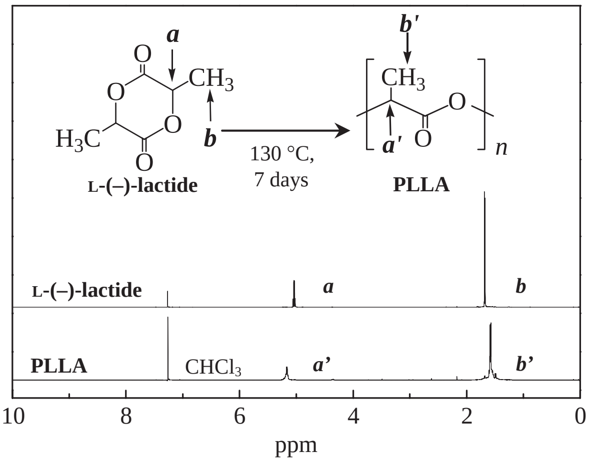

Figure 1. ^{1}H NMR spectra in $CDCl_3$ of L-lactide and PLLA that was prepared by the bulk polymerization in HAp pellets.

The PLLA/HAp composites were characterized by means of ^{1}H NMR, FT-IR, SEM, GPC, TOF-MS, and TG-DTA. Figure 1 shows ^{1}H NMR spectra of L-lactide and PLLA that was eluted from crushed PLLA/HAp composites with chloroform. While L-lactide showed two chemical shifts at 5.02 and 1.67 ppm, which were assigned to proton *a* and *b*, the PLLA showed two chemical shifts at 5.17 and 1.57 ppm. The FT-IR spectrum of the PLLA/HAp composite showed some new absorption peaks that the porous HAp pellet did not show. These peaks at 3000 and 2950, 1755, and 1380 cm^{-1} are assigned to C–H stretching, C=O stretching, and C–H deformation vibration, respectively. The C=O stretching of the PLLA slightly shifted from 1760 to 1755 cm^{-1} possibly owing to the interaction between HAp and PLLA (see Supporting Information).[14]

The PLLA was also extracted with tetrahydrofuran from the crushed PLLA/HAp composites for GPC measurements. The M_n, M_w, and M_w/M_n of the PLLA were 20,200, 24,600, and 1.22, respectively. In addition, the TOF-MS spectrum of the polymer showed $m/z = 1000$–3000 and 72 interval peaks, which are assigned to the L-lactic acid unit. These results revealed that PLLA was synthesized without any additional catalysts in porous HAp.

The porosity of HAp pellets was measured as 43.3% by picnometer method and decreased to 3.91% after the in situ polymerization of L-lactide. As shown in Figure 2, porous morphology was observed with microscale holes on both the surfaces and the cross sections of a porous HAp pellet. On the other hand, the

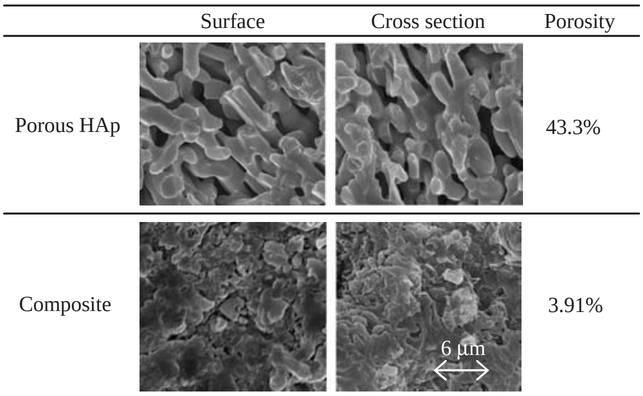

Figure 2. SEM images of porous HAp and PLLA/HAp composite and porosity calculated from relative density by using a picnometer.

Table 1. Characteristics of PLLA polymerized with HAp powder

Conc. of HAp powder /wt %	Monomer conversion /%[a]	Yield/%[b]	Molecular weight[c]	
			M_w	M_w/M_n
0	11.7	0.00	1,130	1.24
5	83.5	22.6	5,680	1.21
25	92.2	45.6	11,200	1.36
50	95.6	56.3	12,700	1.29

[a] Determined by ^{1}H NMR. [b] Yielded as purified PLLA. [c] Determined by GPC with polystyrene standard.

surface of the PLLA/HAp composite was relatively smooth, showing that HAp was filled up with PLLA. This result is also supported by TG-DTA measurements of the PLLA/HAp composite, which indicated that 20 wt % PLLA was present in the PLLA/HAp composites (see Supporting Information).[14]

In order to confirm the polymerization mechanism of L-lactide in porous HAp without catalyst, we polymerized L-lactide (2.00 g) with HAp powder at various concentrations from 0 to 50 wt % (from 0 to 2.00 g). Under N_2 gas atmosphere, HAp powder was dispersed in melted L-lactide, and then the mixture was stirred at 130 °C for 3 days. Table 1 summarizes monomer conversion, yield, and M_w of the PLLA. Both monomer conversion and yield increased with increasing the HAp concentration. Under the presence of HAp, the monomer conversions estimated by ^{1}H NMR spectra were above 80%, and the yield of the PLLA reached 50% at HAp powder 50 wt %. The M_w of the PLLA also increased with increasing the HAp content. When the concentration of HAp powder was above 25 wt %, the M_w of the PLLA reached 10,000, which was 10 times higher than that of the PLLA synthesized with no HAp powder. These results clearly show that HAp functions as the catalyst for the ring-opening polymerization of L-lactide.

Sandner et al.[13] reported that D,L-lactide was polymerized in the presence of HAp and stannous(II) octoate. In that system, HAp acts as an initiator for the polymerization, and stannous(II) octoate promotes the chain growing reaction. In our new system, HAp also acts as the catalyst for the ring-opening polymerization of L-lactide, and much higher molecular weight PLLA was obtained. This difference was not precise, but might be based on different Ca/P ratio and the unique spatial reaction field. Therefore, the Ca/P ratios might be responsible for the difference in the polymerization behavior. The polymerization mechanism of L-lactide in porous HAp will be reported in detail elsewhere.

In this work, we succeeded to fabricate the PLLA/HAp composites by the bulk polymerization of L-lactide in porous HAp without any additional catalyst. It is a very simple process to hybrid two different materials and to directly fabricate artificial bone materials. The mechanical properties of HAp were obviously improved by the hybridization with PLLA. The bending strength, fracture toughness, and Young's modulus of the PLLA/HAp composite were 53.7 MPa, 0.52 MPa m$^{1/2}$, and 20.3–32.3 GPa, respectively, while the values of porous HAp were 23.1 MPa, 0.42 MPa m$^{1/2}$, and 86–110 GPa, respectively. In addition, the biocompatible test was carried out by using osteoblast MC3T3-E1 cells. We confirmed that the cell growth on the PLLA/HAp composites that were synthesized with 2 wt % lipase CA or without catalyst showed a different behavior. The adhesion and growing of the cells on the PLLA/HAp composites without catalyst were superior to those on the composites with catalyst. This difference is quite useful to reduce the risk of implantation materials in the human body.

In our new method, HAp acts not only as an excellent matrix but also as the catalyst. Such composites are quite suitable for artificial bone materials. The polymerization mechanism of L-lactide in porous HAp will be reported in detail elsewhere.

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14 Supporting Information is available electronically on the CSJ-Journal web site, http://www.csj.jp/journals/chem-lett/.