Preparation of PLLA nanocomposites containing magnesium hydroxide for neutralization of an acidic environment in biodegradable polymers

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Introduction: Biodegradable polymers, such as poly(L-lactide) (PLLA), poly(lactide- co-glycolide) (PLGA), and polycaprolactone (PCL) are very useful in many biomedical applications. However, an acidic microenvironment due to the degradation of polyester has been concerned as a factor contributing to inflammation in the body. We hypothesized that soluble base, magnesium hydroxide ($Mg(OH)_2$) nanoparticles, can neutralize acidic species produced during polymer hydrolysis. Moreover, the active hydroxyl groups on particle surface enable L-lactide (LA) directly to graft by ring opening polymerization. In this study, we have synthesized PLLA-grafted $Mg(OH)_2$ nanoparticles, Mg-O-PLLA, and investigated the effect on the neutralization by nanoparticles, the interfacial adhesion between polymer matrix and nanoparticles, and mechanical properties of PLLA/Mg-O-PLLA nanocomposite formed by blending method.

Materials and Methods: Mg-O-PLLA nanoparticles were synthesized by the ring opening polymerization (ROP) in the presence of stannous octoate under vacuum condition at 150 °C for 24 h. After the synthesized product was purified, it was dried in a vacuum oven at 60 °C for 24 h to remove the residual solvent. Mg-O-PLLA nanoparticles synthesized with different ratio of LA and $Mg(OH)_2$ were characterized by FT-IR, thermal gravimetric analysis (TGA), and SEM. Tensile test was carried out on Instron at room temperature and PLLA (Mw: 300K) was used as matrix material. The pH change was also monitored by pH meter. For cytotoxicity by MTT assay and cyclooxygenase 2 (COX-2) expression by western blot analysis, human umbilical vein endothelial cells (HUVECs) were cultured.

Results and Discussion: PLLA-grafted $Mg(OH)_2$ nanoparticles were confirmed by FTIR (Fig. 1(A)). The peaks at 1085, 1750, and 2930 cm^{-1} were attributed to Mg-O-C linkage, carbonyl of ester groups, and C-H stretching in PLLA. The amount of grafted LLA was measured by TGA (Fig. 1(B)). The weight losses of nanoparticles, Mg-O-PLLA20, Mg-O-PLLA50, Mg-O-PLLA70, and Mg-O-PLLA80 were 41.6, 67.9, 80.6, and 89.8%, respectively. The morphology of $Mg(OH)_2$ particles seemed like disk type, as observed by SEM. However, after grafting of PLLA, their shape was changed to needlelike nanoparticles strongly aggregated. It was thought that the nanoparticles had tendency to aggregate due to the interaction of polymers. The relationship between the content of Mg-O-PLLA and mechanical properties was shown in Fig. 2. As the content of Mg-O-PLLA increase, tensile strength also increased linearly from 26.4 to 39.3 MPa as compared to $Mg(OH)_2$ without PLLA chains (Fig. 2(A)). This suggested a good interfacial interaction between pure PLLA matrix and nanocomposites. On the other hand, the strain of all of nanocomposites decreased with increasing the contents of nanoparticles in the same content range (Fig. 2(B)). Meanwhile, it is known that inflammation is associated with up-regulation of COX-2. We found that the expression of COX-2 was increased to a significant level with the concentration of lactic acid by western blot analysis and it was down-regulated above 7.8 mM of lactic acid due to cytotoxicity. However, although lactic acid was very high concentration, cellular inflammation and cytotoxicity were not observed in the presence of Mg-O-PLLA nanocomposites due to pH neutralization.

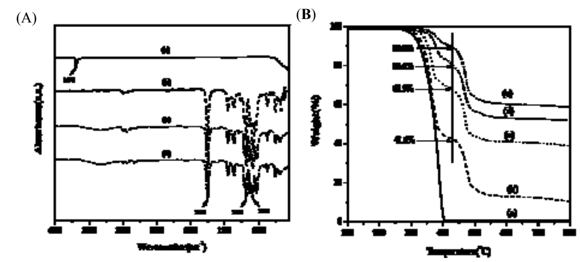

Fig. 1. (A) FT-IR spectra of (a) $Mg(OH)_2$, (b) PLLA (Mw: 300,000), (c) Mg-O-PLLA20, and (d) Mg-O-PLLA50, and (B) TGA curves of (a) control PLLA, (b) Mg-O-PLLA20, (c) Mg-O-PLLA50, (d) Mg-O-PLLA70, and (e) Mg-O-PLLA80.

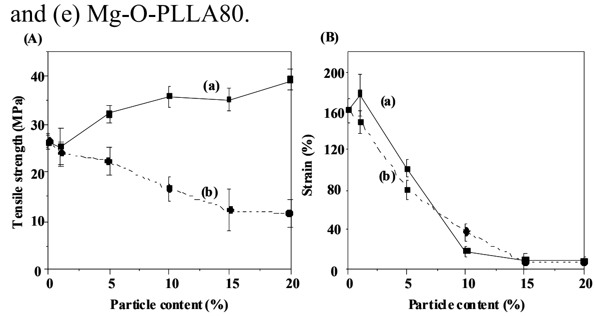

Fig. 2. Dependence of (A) tensile strength and (B) strain on nanoparticles contents within PLLA matrix: (a) Mg-O-PLLA80 and (b) $Mg(OH)_2$ particle.

Summary: PLLA was successfully grafted on the surface of $Mg(OH)_2$ nanoparticles by direct ROP. The PLLA/Mg-O-PLLA nanocomposite exhibited the improvement of biocompatibility as well as mechanical properties and interfacial adhesion. Therefore, we expect that this nanocomposite may have promising medical devices including biodegradable cardiovascular stent.

References:

1. Y. Li. et al. Biomacromolecules, 11, 1847 (2010).

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