pH neutralization and inflammation prevention by RA and PLLA-grafted magnesium hydroxide nanoparticles

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Introduction: Although biodegradable polymers, such as poly(L-lactide) (PLLA) and poly(lactide-co-glycolide) (PLGA) have been popularly used in many biomedical applications, the degradation of these polyesters has induced the acidic environment resulting in increased inflammatory response in human body. In order to avoid inflammatory response by the polymer degradation, magnesium hydroxide, $Mg(OH)_2$ was modified to the biodegradable polymers. As the soluble base, $Mg(OH)_2$ nanoparticles can neutralize acidic species produced by the polymer hydrolysis. In addition, the active hydroxyl groups on particle surface can be used as an initiator for ring-opening polymerization (ROP) of lactide. In the present study, we have synthesized ricinoleic acid (RA)-grafted and further lactide (LA)-grafted $Mg(OH)_2$ nanoparticles (RA-Mg-OLA), and then fabricated the nanoparticles-reinforced PLLA nanocomposites. RA was utilized for making nano-sized $Mg(OH)_2$. The effect of RA-Mg-OLA nanoparticles on the pH neutralization and mechanical properties of PLGA nanocomposite films was investigated.

Materials and Methods: RA-Mg-OLA 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. RA-Mg-OLA 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 and PLGA was used as matrix materials. The pH change was also monitored by pH meter. For cell viability and IL-6 by ELISA, human umbilical vein endothelial cells (HUVECs) were cultured.

Results and Discussion: The chemical structure of OLA-grafted magnesium hydroxide nanoparticles was characterized by FTIR. The peaks at 1085, 1750, and 2930 cm^{-1} were attributed to Mg-O-C linkage, ester groups, and C-H stretching in PLLA, respectively. From the result of TGA, it was also confirmed that OLA was successfully grafted on the surface of magnesium hydroxide (Fig. 1(A)). The amount of grafted OLA was measured by TGA (Fig. 1(B)). It is known that the thermal decomposition of PLLA starts from below 300 °C and completed at around 400 °C, that a similar pattern was observed in this study. However, the weight loss of RA-Mg-OLA showed different patterns. The weight loss started at 280 and 400 °C. The first weight loss indicates the decomposition of OLA chains that were grafted on the surface of magnesium hydroxide because pure PLLA decomposes at 270~280 °C. Thus, the grafting ratio of OLA on magnesium hydroxide could be determined. Mechanical properties of PLLA films containing RA-Mg-OLA or magnesium hydroxide were investigated. RA-Mg-OLA made significantly different mechanical changes to PLLA film than magnesium hydroxide. With increasing RA-Mg-OLA content up to 10 wt%, tensile strength gradually increased. The morphology of $Mg(OH)_2$ particles seemed like disk type, as observed by SEM. Figure 2 shows pH changes of PLGA, RA-Mg-OLA, and their composites for 21 days. The decreased pH is due to the generation of lactic acid during degradation. At the same condition, all RA-Mg-OLA presented higher pH levels than PLGA only, and the pH values depend on the content of magnesium hydroxide. The effect of RA-Mg-OLA on inflammation caused by degradation of PLLA was examined. During HUVEC culture, the expression level of IL-6, an inflammatory marker, was determined by ELISA analysis. An experiment was performed to confirm the correlation between IL-6 expression level and L-LA amount. The more RA-Mg-OLA amount, the less inflammation by pH neutralization.

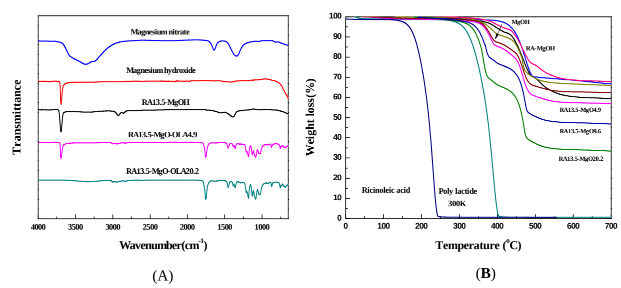

Fig. 1. (A) FTIR spectra of Mg $(OH)_2$, RA13.5-Mg-OH, RA13.5-Mg-OLA4.9, and RA13.5-Mg-OLA20.2, and (B) TGA curves of control PLLA, RA13.5-Mg-OH, RA13.5-Mg-OLA4.9, and RA13.5-Mg-OLA20.2.

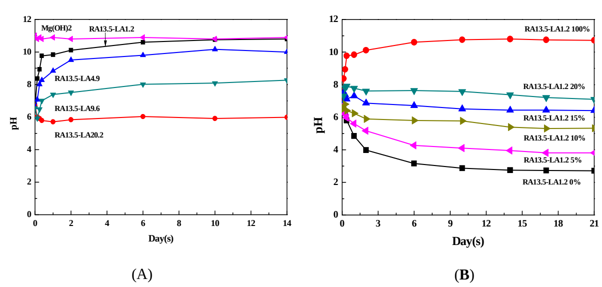

Fig. 2. pH change of (A) RA13.5-Mg-OH, RA13.5-Mg-OLA4.9, and RA13.5-Mg-OLA20.2, and (B) amounts of RA13.5-Mg-OLA4.9 in PLGA composite.