Thermoreversible PLGA-g-PEG hydrogels containing hydroxyapatite for potential lipid growth factor delivery

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Introduction

We have synthesized thermoreversible PLGA-g-PEG hydrogels and hydrogel composites containing hydroxyapatite (HA) that are sols at low temperature and gels at body temperature. These hydrogels are designed for controlled delivery of lysophosphatidic acid (LPA), a lipid growth factor which has biological effects that we postulate will foster bone regeneration [1,2]. In this preliminary study, a lipophilic dye with a molecular weight comparable to that of LPA was used to probe the release profiles from these hydrogels as a surrogate for amphipathic lipid growth factors. In addition, hydrogel mechanical properties were evaluated by rheological measurements.

Method

PLGA-g-PEG hydrogels synthesis and rheological measurements were performed as reported previously [3]. Lipophilic dye FM® 2-10 was purchased from Invitrogen. PLGA-g-PEG hydrogel-HA composites were prepared by mixing appropriate amount of HA with PLGA-g-PEG followed by sonication and vortexing. Sol-gel transitions of the hydrogels were demonstrated by test-tube inversion method. The dye was mixed with the hydrogel at 4°C. Release studies were performed at 37°C in a 20 ml vial containing 1.1 ml of hydrogel or hydrogel-HA composite with 3 ml of PBS buffer placed on top. At the times indicated, the 3 ml PBS buffer was collected and replaced with fresh 3 ml 37°C PBS buffer. The concentration of eluted dye in PBS buffer was determined by spectroscopy at wavelength 490 nm.

Results

Figure 1 illustrates the sol-gel transition change of the hydrogel-HA composite when the environmental temperature was increased from 4°C to 37°C. This sol-gel behavior was also observed for hydrogels without HA.

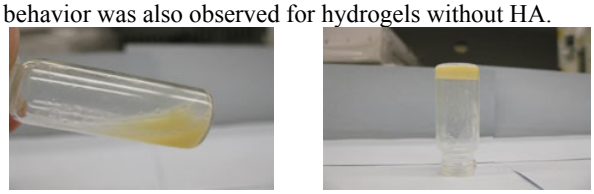

Fig.1. 30wt% hydrogel-HA composite containing 10wt% HA was sol at 4°C (left) and gel at 37°C (right).

Figure 2 shows the release profiles of the lipophilic dye from the thermoreversible hydrogels and hydrogel composites. The graph shows that the dye release was sustained for at least 10 days. Figure 3 shows the storage modulus (G') of the hydrogel as a function of temperature. It was noted that maximum G' of the hydrogels increases with increasing amount of HA. This mechanical reinforcement by HA is probably due to hydrogen bonding formation between HA and PLGA-g-PEG.

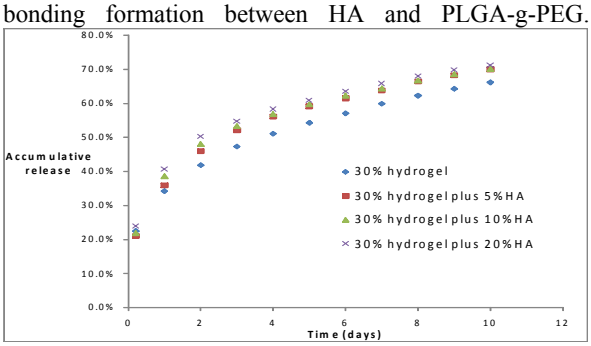

Fig.2. Release profiles of lipophilic dye from hydrogels and hydrogel composites containing 5%, 10% and 20wt% HA.

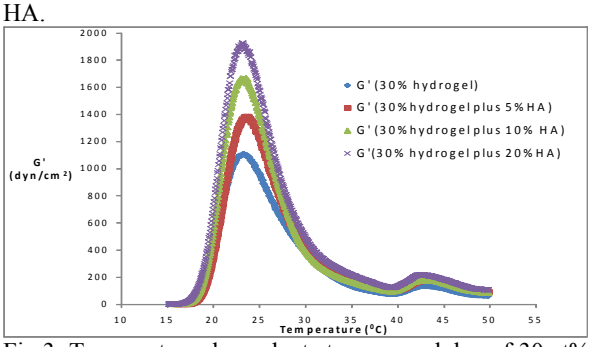

Fig.3. Temperature-dependent storage modulus of 30wt% hydrogels and respective hydrogel-HA composites.

Conclusions

Based on the data presented, several conclusions can be reached. First, the sol-gel transition behavior of PLGA-g-PEG was preserved after incorporation of HA. Secondly, all PLGA-g-PEG hydrogels and composites containing HA achieved a sustained release of lipophilic dye for at least 10 days. Also, hydrogel mechanical properties were strengthened by hydroxyapatite in a content-dependent manner. It should be noted that the current study employed a lipophilic dye to obtain the dye release profiles, which are not necessarily representative of LPA release behavior. Efforts are underway to measure LPA release directly from these hydrogels using methods such as mass spectrometry or tritium labeled LPA. Animal studies will be performed in the future to evaluate the efficacy of LPA for the stimulation of bone repair.

References

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