Tailoring the Degradation Rates of Thermally Responsive Hydrogels Designed for Injection into the Ventricular Wall after Myocardial Infarction

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Statement of purpose: Pathological remodeling of the ventricular wall following myocardial infarction can ultimately lead to end stage heart failure and death. The injection of hydrogels into and around the infarcted myocardium has been effective in preventing ventricular remodeling and maintaining cardiac function putatively by providing mechanical support[1]. Degradation or dissolution of hydrogels within an appropriate time allows cell infiltration and new tissue growth, which is important in achieving desired therapeutic effects. However, more needs to be known about the influence of duration of hydrogel support on the efficacy of cardiac injection therapy[2]. We previously reported a thermally responsive, bioabsorbable hydrogel (MAPLA Gel), which can be easily injected into the myocardium at low temperature and promptly forms a physical hydrogel[3]. In this study, the degradation rate of MAPLA Gel was modulated by incorporating a 4th monomer, methacrylic acid, as an auto-catalyst for side chain hydrolysis. In addition, thermal transition behavior and mechanical strength are decoupled from degradation rate.

Methods: Hydrogel polymers [poly(NIPAAm-*co*-HEMA-*co*-MAPLA-*co*-MAA)] were synthesized from N-isopropylacrylamide (NIPAAm), 2-hydroxyethyl methacrylate (HEMA), methacrylate-polylactide (MAPLA) and methacrylic acid (MAA). The feed ratios of NIPAAm, HEMA, MAPLA and MAA were 80/(10-j)/10/j, where j = 0, 0.5, 1, 2, 5, 10 (**Fig. 1**). MAA content was measured with NMR and acid-base titration. Hydrogels were prepared from a 15 wt% copolymer PBS solution at 37°C. Hydrolytic degradation was evaluated in PBS. Rheological and uniaxial testing were performed to determine the transition temperature and Young's modulus, respectively.

Results: Copolymer compositions were verified with ^{1}H NMR and MAA content agreed with titration results. Degradation rates dramatically increased with MAA incorporation. Time to 50% weight loss in PBS gradually dropped from 151 days for MAPLA Gel (no MAA) to 55 days (0.5% MAA), 28 days (1% MAA), 6 days (2% MAA) and less than 1 day (5% and 10% MAA) with increase of MAA feed ratio (**Fig. 2**). Rheology tests showed transition temperatures of poly(NIPAAm-*co*-HEMA-*co*-MAPLA-*co*-MAA) do not significantly vary with MAA content or pH, and the hydrogels did not become softer by incorporating MAA. In addition, smooth muscle cell proliferation was not significantly affected by the hydrogel degradation products. **Fig. 3** shows the gross appearance of a rat heart injected with MAPLA Gel, which was similar to those injected with hydrogels with different MAA content.

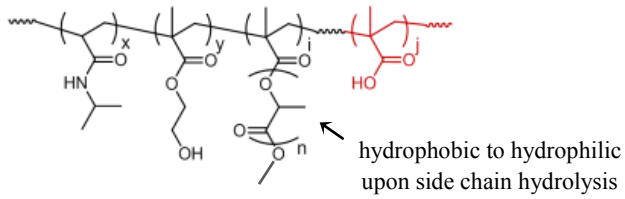

Fig. 1. Chemical structure of poly(NIPAAm-*co*-HEMA-*co*-MAPLA-*co*-MAA).

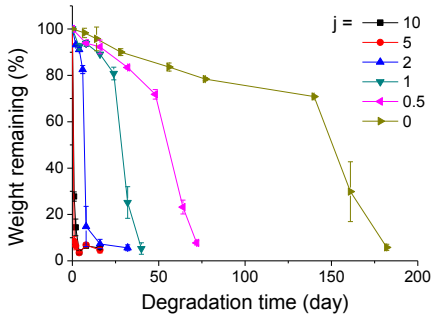

Fig. 2. Degradation curves of poly(NIPAAm-*co*-HEMA-*co*-MAPLA-*co*-MAA) with graded MAA content.

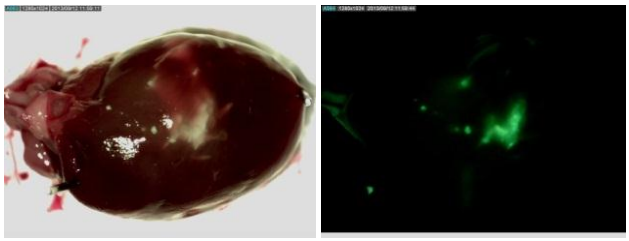

Fig. 3. Rat heart injected with MAPLA gel labeled with a small amount of fluorescent monomer.

Conclusion: By tuning MAA content, the degradation rate of copolymers could be controlled, while the thermal transition behavior and mechanical strength remained steady. These copolymers appear to be suitable candidates for optimizing the efficacy of cardiac injection therapy and potentially for other injectable biomaterial applications.

References:

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