Enzymatically crosslinked Tetronic-Tyramine Hydrogels for Injectable Intraocular Lens

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Introduction: Although foldable lenses for substituting natural lens of cataract patient have been improving by far, there is still a search for lenses that can be placed through an even smaller incision and maintain accommodation. Lens filling is a new concept to solve the problem by maintaining the natural ability of accommodation. By this technique, the capsular bag is evacuated through an even smaller capsular opening then refilled with a liquid material and cured. An emerging approach for *in-situ* formation of hydrogels is based on enzyme-catalyzed crosslinking reactions. In this study, we report *in-situ* forming Tetronic-tyramine (Tet-TA) hydrogels via enzymatic crosslinking using horseradish peroxidase (HRP) as a catalyst and hydrogen peroxide (H_2O_2) as an oxidant. Two Tet-TA conjugates, i.e. conjugates with Tet1107 and Tet904 having different HLB, were prepared. The hydrogels were characterized in terms of their rheological, swelling and cell adhesion properties.

Methods: Tet-TA conjugates were synthesized in two steps by first reacting Tetronic with epichlorohydrin following by a reaction with TA and then they formed hydrogel in the presence of HRP and H_2O_2. The structure of Tet-TA conjugates were confirmed by ^{1}H-NMR. Rheological experiments were conducted with a rheometer (Gemini, Malvern Instruments, UK) at 37 ℃ in an oscillatory mode to evaluate gelation kinetics and mechanical properties. The gelation time, mechanical properties and swelling were evaluated. *In vitro* cell study is now in progress.

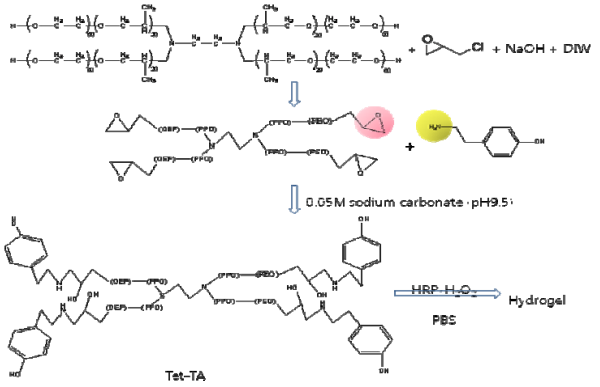

Figure 1. Synthesis of Tet-TA conjugates and hydrogels

Results: From the ^{1}H-NMR spectrum of Tet-TA conjugate, methyl protons of the polypropylene group (δ=1.12 ppm) and the aromatic protons of TA substituent (δ=6.8-7.1 ppm) were observed. Tet-TA hydrogels were formed under physiological conditions by the oxidative coupling reaction of phenol moieties in Tet-TA conjugates in PBS. The gelation time was determined by the vial tilting method. Figure 2 shows the dependence of the gelation time on the concentration of catalysts (H_2O_2 and HRP). The gelation time increased as the H_2O_2 concentration increased (Fig 2a). On the other hand, the gelation time decreased as the concentration of HRP increased (Fig 2b). The kinetics of hydrogel formation was followed by monitoring the storage modulus (G') and loss modulus (G") in time. The gel point was observed after ca. 3 min (Fig 3). At a higher HRP/TA ratio, an immediate gelation after injection was observed. The swelling ratios varied depending on crosslinking densities and Young's modulus decreased ca. 80% of the initial hydrogel after swelling.

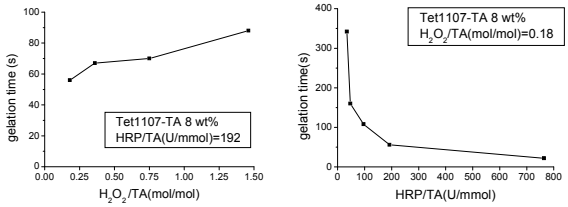

Figure 2. Dependence of gelation time of Tet-TA hydrogels on catalyst concentrations. (a) Effect of H_2O_2 with 192 U/mmol of HRP/TA; (b) effect of HRP with 0.18 mol/mol H_2O_2/TA.

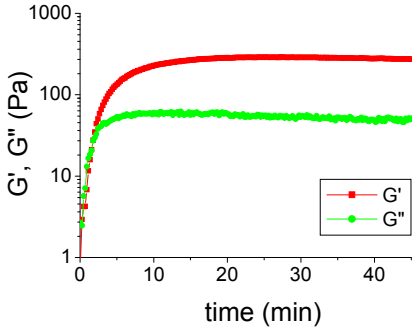

Figure 3. Typical evolution of the G' and G" of Tet-TA hydrogel formed with 96 U/mmol of HRP/TA and 1.5 mol/mol H_2O_2/TA.

Conclusions: Injectable Tet-TA hydrogels were formed by the oxidative coupling reaction of H_2O_2 and HRP. The characteristics of Tet-TA hydrogels such as fast gelation, tunable mechanical strength and proper swelling suggest that Tet-TA hydrogels have great potential as injectable IOL material.

References:

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