Control of properties of hyaluronate-based terpolymeric hydrogel for biomedical applications

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INTRODUCTION

Hyaluronic acid(HA) is is a biopolymer composed by repeating units of D-glucoronic acid and N-acetyl-D-glucosamine and has advantageous biological properties[1] in its applications to biomaterials in divers forms such as hydrogel and scaffolds for drug delivery and tissue engineering. Even though it has been fabricated as a hydrogel for long time, but its applications have been still limited due to its inherent physico-chemical properties.[2,3] A new HA-based hydrogel with both higher mechanical and biological properties has been requested in medical society. We here report a synthesis of new hydrogel by graft-polymerization of 2-hydroxyethyl acrylate (2-HEA) and either poly(ethylene glycol) diacrylate (PEGDA) or bioactive polymers by the mechanism of radical polymerization for its potential applications to druge delivery and tissue engineering.[4,5]

METHODS

To obtain hydrophobicity and elasticity, 2-HEA was graft-polymerized onto hydroxyl groups of HA side chains, and then crosslinked using different amounts of PEG-DA or methacrylated polymers to obtain sufficient mechanical strength and porous morphologies of hydrogel (HA-g-p(2-HEA)-x-PEGDA). While chemical analyses were performed by FTIR, 1H HR-MAS-NMR, and TGA, physical analyses were done by TGA, swelling measurement and rheologies as well as drug delivery of tetracycline, bovine serum and dimethyloxalylglycine from hydrogel over acidic and basic medium at 37 °C. Diverse biological analyses of hydrogels were done *in vitro* and *in vivo* by implanting subcutaneously in rats for 3 weeks. Diverse histological analyses such as hematoxylin and eosin Y (H&E), and Masson's trichrome (MT) staining and others were done. All data were stated as mean ± standard deviation. Statistical significance was evaluated with one-way and multi-way ANOVA by using the SPSS 18.0 program. The comparisons between two groups were performed by t-test and significant difference has been reported when $p < 0.05$.

RESULTS AND DISCUSSION

The chemcial structure and compositions of the fabricated HA-g-p(2-HEA)-x-PEGDA polymer was verified by the methids of FTIR, 1H HR-MAS-NMR, and TGA analyses, indicating hydrogel formation. The SEM images indicate that the terpolymer contains interconnected porous network structures. The measurement of equilibrium swelling ratio showed physco-chemcial properties depending different pHs, and elastic modulus (G') value in rheology study confirmed the viscoelastic properties of HA-g-p(2-HEA)-x-PEGDA hydrogel in water at 37 °C. The polymeric gel demonstrated pH-dependent release behaviros of bioactive molecules such as tetracycline, bovine serum albumin and dimethyloxalylglycine at 37 °C. The *in vitro* cell study indicated that the hydrogel supported outstanding adhesion, proliferation, and viability of osteoblastic MC3T3 cells as well as cell compatibility. The H&E and MT *in vitro* stains demonstrated that the native gel itself was excellent substrate for the bone tissue regeneration of extracellular matrix and collagen, respecitively, in absence of any extra growth factors after 3 weeks. *In vivo* evaluationa are underway of stainings after explanting the gel samples from rats. Currently we are under processing of its applications to the tissue regeneration scaffolds, which have been fabricated by 3D printing technology.

CONCLUSION

The results demonstrated that the synthesized HA-based hydrogel could be obtained by controlling a secondary polymer as biomateirals for both drug delivery and tissue engineering applications.

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