An injectable gelatin derivative hydrogel for controlled release of growth factors

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Introduction

Gelatin, the product of partial hydrolysis of collagen, is widely used as a cell delivery vehicle because of its excellent biodegradability and biocompatibility [1, 2]. However, gelatin itself has limited capability for controlled drug delivery. A variety of proteins, such as extracellular matrix proteins and growth factors, have heparin-binding domains. This property enables the controlled release of the growth factors by incorporating heparin-containing segments into the release system. In this work, a novel injectable gel was successfully synthesized by linking heparin to the main chains of gelatin gels. The releasing study demonstrated that this system is effective for the controlled release of vascular endothelial growth factor for several weeks and accelerated dense vasculature formation in vivo.

Methods

The gelatin derivative hydrogel was synthesized by a two-step cross-linking reaction, in which the carboxyl groups of heparin were cross-linked with the amino groups of gelatin. The heparin content, morphology and properties were examined using Toluidine Blue test, ATR-FTIR, SEM, Table-Top Material Tester and ELISA measurements.

Results and Discussion

Figure 1 shows ATR-FTIR spectra of the synthesized gelatin derivative hydrogel. The appearance of peaks at1456, 1240, 1428 and 1013 cm^{-1} for the modified gelatin indicates that heparin has been successfully conjugated onto the gelatin. This modification made this polymer gellable in the presence of HRP and H_2O_2, and the gelation time could be controlled by varying the concentration of HRP, H_2O_2, and the material composition. The gelation time increased when the concentration of HRP and gelatin decreased and the H_2O_2 increased. The release of VEGF from this hydrogel was then measured by ELISA. The release profile shows that there was a minor burst release, and the slow release of VEGF continued over 4 weeks. For further study, in vivo subcutaneous injection onto the backs of rat was carried out. After injection, the hydrogel was successfully formed in-situ within one minute. Figure 2 shows the histological images of the hydrogel after 2 weeks. Infiltration of the surrounding tissue and newly formed blood vessels were observed in the gel matrix, suggesting that this hydrogel had an excellent biocompatibility and bioactivity in vivo.

Conclusions

The novel injectable gelatin derivative hydrogel has great potential for soft tissue regeneration.

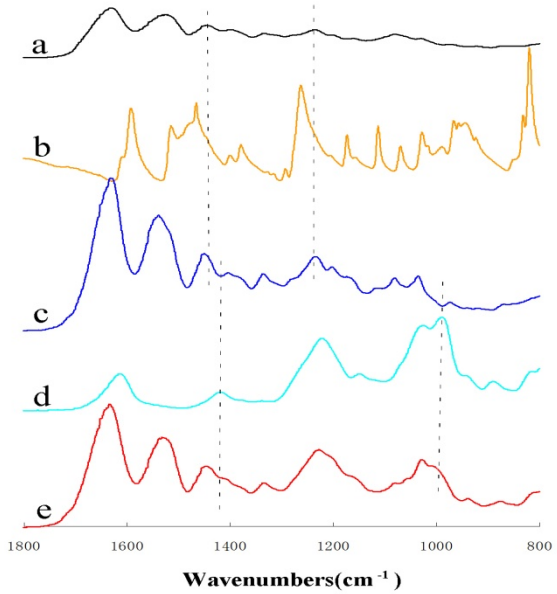

Figure 1. ATR-FTIR spectra of gelatin derivative injectable hyrogels (a) gelatin; (b) tyramine; (c) gelatin/tyramine; (d) heparin, and (e) gelatin derivative hydrogel.

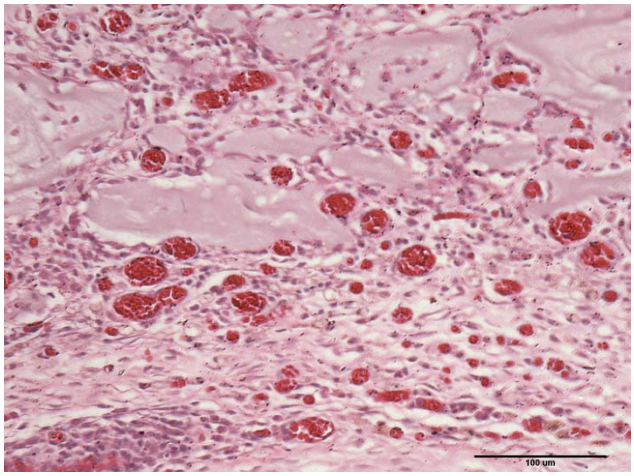

Figure 2. Hematoxylin and eosin staining of a tissue section after subcutaneous implants of a VEGF-loaded gelatin derivative hydrogel for two weeks. The histology showed that controlled release of VEGF from the hydrogel accelerated dense vasculature formation.

Reference:

1. Patel, Z.S., et al., Acta Biomaterialia, 2008. **4**(5): 1126-1138.
2. Liu, X., et al., Biomaterials, 2009. **30**(12): 2252-2258.