Study on Biodegradable Hydrogels with Stimuli-Responsive Polymers for Pharmaceutical Applications

（薬剤学的応用を目指した刺激応答型高分子を利用した生体内分解性ヒドロゲルに関する研究）

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This dissertation describes the biodegradable hydrogels in synchronization with temperature for pharmaceutical applications. Dextran graft copolymers containing thermo-responsive polymers, [poly(*N*-isopropylacrylamide-*co*-*N,N*- dimethylacrylamide)s, poly(NIPAAm-*co*-DMAAm)s] were prepared for the development of novel multi-stimuli-polymeric systems. Various kinds of graft copolymers with different graft length and number could be obtained by the coupling reaction between modified dextran and semitelechelic poly(NIPAAm-*co*-DMAAm)s. The resulting graft copolymers exhibited lower critical solution temperatures (LCSTs) due to thermo-sensitivity of their grafts. The degradation of graft copolymers and their hydrogels by dextranase was found to be synchronized with a temperature change, which induces the hydration-dehydration of freely mobile poly(NIPAAm-*co*-DMAAm) graft chains. Release of model proteins from hydrogels containing dextran graft copolymers was evaluated. It is considered that the rate of release depended on the concentration of dextranase as well as the diffusion release. Moreover, a semi-interpenetrating polymer network (semi-IPN) hydrogels consisting of dextran grafted with poly(NIPAAm) homopolymer (lower LCST) and cross-linked poly(NIPAAm-*co*-DMAAm) matrix (higher LCST) was synthesized. The enzymatic degradation of the semi-IPN hydrogel could proceed between the lower LCST and above the higher LCST. This result suggests that both of the effects of steric hindrance (grafts) and swelling-deswelling (network) of thermo-responsive polymer can be controlled to enzymatic accessibility at the same time. Further, novel dextran hydrogels consisting of dextran graft copolymers and poly(NIPAAm-*co*-DMAAm) that is cross-linked with the dextran backbone were prepared. The water contents of these hydrogels slightly decreased with increasing temperature, and the change of the water content was depended on the amount of the cross-linker. The enzymatic degradation of the hydrogel containing lower amount of the cross-linker could proceed between both the LCST regions, the hydrogels containing a large amount of crosslinker prevented dextranase from approaching the hydrogel surface. It was considered that coil-globule transition of the graft chain and a small amount of thermo-responsive cross-linker was very effective for controlling the enzymatic degradation at specific temperature range. These hydrogels are expected to be available for biomedical applications such as drug release device which can release in synchronized with body temperature.

Key Words: Biodegradable hydrogel, Thermo-responsive polymer, Modulated enzymatic degradation, Protein release.