Study on Controlled Release from Biodegradable Hydrogels with Microdomain structures

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Abstract

This dissertation describes the design of biodegradable hydrogels with microdomain structures for controlled drug release which were formulated as advanced drug delivery materials. Firstly, biodegradable dextran hydrogels containing poly(ethylene glycol) (PEG) were prepared as a model of heterogeneous-structured devices composed of drug reservoirs and degradable matrices, and insulin release during their enzymatic degradation was investigated. Specific distribution of bioactive peptides has been well known in a combination of PEG and dextran as an aqueous polymer two-phase system. Insulin was preferentially loaded into PEG phase when methacrylic dextran was crosslinked in the presence of PEG and insulin. The degradation of both crosslinked dextran hydrogels containing PEG (PEG/Dex hydrogels) and crosslinked dextran hydrogel (Dex hydrogel) by dextranase were found to proceed from the surface front. However, release profiles of insulin from PEG/Dex hydrogels were different from that of Dex hydrogel: insulin release from PEG/Dex hydrogels was regulated by the surface degradation of PEG/Dex microdomain-structured matrix whereas diffusion was dominant factor in insulin release from Dex hydrogel. These PEG/Dex hydrogels with different water content were prepared in next step of this study in order to regulate the phase-separated structures, degradability, and drug release profiles. When the water content was lower below 83 percent, the hydrogels were not degraded in the presence of dextranase. From the results of microscopic and thermal analysis, the water content and crosslink density affected to the phase-separated structures of PEG/Dex hydrogels, i.e., higher crosslink density correlated with exhibiting lower phase separability and forming smaller PEG domains in PEG/Dex hydrogels because of phase mixing between PEG and dextran. The difference in the insulin leakage from the hydrogels is affected by the crosslink density of the hydrogels. However, the mode of insulin release from the hydrogels during their enzymatic degradation was quite different. Insulin release from PEG/Dex hydrogel was found to be degradation-controlled release, whereas the diffusion through the matrix was dominant factor of release from Dex hydrogels. Concerned from the results in above, multi-layered hydrogel formulations

consisting of PEG-grafted Dex (PEG-g-Dex) and ungrafted Dex were investigated as a model of pulsatile drug release formulation. In these formulations, it is considered that the grafted PEG domains act as a drug reservoir dispersed in the Dex matrix based on aqueous polymer two phase systems. The formulations exhibited surface-controlled degradation by dextranase, and insulin release was observed in a pulsatile manner because of the multi-layered structure; PEG-g-Dex hydrogel layers containing insulin and insulin-free Dex hydrogel layers. Thus, it is suggested that the multi-layered hydrogel formulations using PEG-g-Dex and Dex are feasible for chronopharmacological drug delivery systems. In the final stage of this study, hyaluronic acids (HA) grafted with PEG (PEG-g-HA) were synthesized. The materials characterization, enzymatic degradability and peptide (insulin) release from solutions of the copolymers were examined. Insulin was preferentially partitioned into the PEG phase in a PEG/HA solution system. Enzymatic degradation of the copolymers was strongly dependent on the PEG content. Thermal analysis revealed that PEG-g-HA exhibited a variation in phase-separated structures depending on the PEG content. The solution of PEG-g-HA enabled insulin to remain in the PEG moieties dispersed in the HA matrix. Leakage of insulin from the copolymers was dependent upon the PEG content. A dramatic increase in leakage rate occurred when the PEG content was increased to greater than 39 percent by weight. It is considered that the loaded insulin was partitioned into the PEG moieties and became entangled with the PEG chains. The conformational change of insulin was effectively prevented in PEG-g-HA solutions, although insulin was denatured in storage of both phosphate buffered solution and HA solution. Such a heterogeneous-structured polymeric solution may be advantageous as an injectable therapeutic formulation for ophthalmic or arthritis treatment. Conclusively, degradation-controlled drug release from biodegradable matrices with aqueous media was developed in this study. The microdomain structures constructed in the matrices acted as drug reservoirs. This heterogeneous structure was based upon phase separation method; aqueous polymer two-phase systems. It is a quite new finding that the conformational change and denaturation of loaded peptide drug were prevented by using PEG-containing polysaccharide hydrogels and solutions.

Publication list

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