Study on Biodegradable Hydrogels for Multi-Stimuli Responsive Drug Delivery

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Abstract

This dissertation describes the design of biodegradable hydrogels for multi-stimuli responsive drug delivery. Biodegradable hydrogels consistin g of oligopeptide-terminated poly(ethylene glycol) (PEG) and dextran (Dex) w ith an interpenetrating polymer network (IPN) structure were prepared as mod els of novel biomaterials exhibiting a dual-stimuli-responsive function. Th e IPN-structured hydrogels were synthesized by sequential crosslinking react ion of N-methacryloyl-glycylglycylglycyl-terminated PEG and Dex. Specific d egradation in the presence of papain and dextranase was observed in the IPN-structured hydrogel with a particular composition of oligopeptide-PEG and De x. This same hydrogel was not degraded by one of the two enzymes.

Second approach for dual-stimuli-responsive degradable hydrogels has been studied by the combination of gelatin (Gtn) and Dex as the constituents of IPN-structured hydrogels. The hydrogels were prepared by sequential cros s-linking reaction below or above the sol-gel transition temperature (Ttrans) of Gtn. IPN-structured hydrogels prepared below Ttrans showed to be homog eneous in terms of phase-contrast microscopic observation and small-angle li ght scattering measurements. In contrast, IPN-structured hydrogels prepared above Ttrans showed a phase-separated structure. The IPN-structured hydroge ls prepared below Ttrans exhibited a specific degradation behavior: the degr adation of the hydrogels by either a-chymotrypsin or dextranase alone was co mpletely hindered whereas the hydrogel degradation proceeded via a surface f ront in the presence of both enzymes. Such a specific feature of enzymatic degradation was not observed for the IPN-structured hydrogels prepared above Ttrans.

To achieve dual-stimuli responsive drug release, IPN-structured hydr ogels of Gtn and Dex were prepared together with lipid microspheres (LMs) as a drug microreservoir, and LM release from these hydrogels was examined in r elation to their dual-stimuli-responsive degradation. The IPN-structured hy drogel prepared below Ttrans exhibited a specific degradation-controlled LM release behavior: LM release from the hydrogel in the presence of either a-c hymotrypsin or dextranase alone was completely hindered whereas LM release

w as observed in the presence of both enzymes.

In order to modulate multi-stimuli-responsive degradation, thermo-re sponsive hydrogels were designed with two different ways. One approach to c ontrol the cross-link density of biodegradable hydrogels is the incorporatio n of thermo-responsive chains into these networks. Hydrogels consisting of poly(N-isopropylacrylamide-co-N, N-dimethylacrylamide-co-butylmethacrylate) and a novel biodegradable cross-linker were prepared. A swelling ratio of t he hydrogels decreased rapidly in proportion to temperature. In vitro degra dation of the hydrogels was examined in buffer solution containing papain at different temperatures. The enzymatic degradation of the hydrogel was obser ved to proceed at 30 ℃, however, the hydrogel was not degraded above 35 ℃.

Another approach was performed by the control of miscibility between thermo-responsive polymers and degradable polymer networks. Dex hydrogels gr afted with poly(N-isopropyl acrylamide -co-N, N-dimethylacrylamide) (poly(IPAA m-co-DMAAm)) chain were prepared. Although swelling ratios for hydrogels we re constant in a wide range of temperature, the transmittance dropped in rel ation to the lower critical solution temperature of poly(IPAAm-co-DMAAm). T emperature-dependent degradation was observed in these hydrogels, dependent upon the molecular weight of the graft chain. Degradation rate of Dex hydro gel grafted with shorter chains was constant in a wide range of temperature. In contrast, degradation rate of Dex hydrogel grafted with higher chains in creased in proportion to temperature.

In conclusion, biodegradable hydrogels can feasibly be used as novel biomaterials for multi-stimuli responsive drug delivery.

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