

Title	多刺激応答型薬物放出のための生分解性ヒドロゲルに関する研究
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Citation	
Issue Date	1998-03
Type	Thesis or Dissertation
Text version	none
URL	http://hdl.handle.net/10119/2048
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Description	Supervisor: 由井 伸彦, 材料科学研究科, 博士

Study on Biodegradable Hydrogels for Multi-Stimuli Responsive Drug Delivery

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Keywords: Multi-stimuli responsive drug delivery, Interpenetrating polymer network, Biodegradable Hydrogels, Modulated degradation

Abstract

This dissertation describes the design of biodegradable hydrogels for multi-stimuli responsive drug delivery. Biodegradable hydrogels consisting of oligopeptide-terminated poly(ethylene glycol) (PEG) and dextran (Dex) with an interpenetrating polymer network (IPN) structure were prepared as models of novel biomaterials exhibiting a dual-stimuli-responsive function. The IPN-structured hydrogels were synthesized by sequential crosslinking reaction of N-methacryloyl-glycylglycylglycyl-terminated PEG and Dex. Specific degradation in the presence of papain and dextranase was observed in the IPN-structured hydrogel with a particular composition of oligopeptide-PEG and Dex. 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 cross-linking reaction below or above the sol-gel transition temperature (T_{trans}) of Gtn. IPN-structured hydrogels prepared below T_{trans} showed to be homogeneous in terms of phase-contrast microscopic observation and small-angle light scattering measurements. In contrast, IPN-structured hydrogels prepared above T_{trans} showed a phase-separated structure. The IPN-structured hydrogels prepared below T_{trans} exhibited a specific degradation behavior: the degradation of the hydrogels by either α -chymotrypsin or dextranase alone was completely hindered whereas the hydrogel degradation proceeded via a surface front in the presence of both enzymes. Such a specific feature of enzymatic degradation was not observed for the IPN-structured hydrogels prepared above T_{trans} .

To achieve dual-stimuli responsive drug release, IPN-structured hydrogels of Gtn and Dex were prepared together with lipid microspheres (LMs) as a drug microreservoir, and LM release from these hydrogels was examined in relation to their dual-stimuli-responsive degradation. The IPN-structured hydrogel prepared below T_{trans} exhibited a specific degradation-controlled LM release behavior: LM release from the hydrogel in the presence of either α -chymotrypsin or dextranase alone was completely hindered whereas LM release

was observed in the presence of both enzymes.

In order to modulate multi-stimuli-responsive degradation, thermo-responsive hydrogels were designed with two different ways. One approach to control the cross-link density of biodegradable hydrogels is the incorporation 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 the hydrogels decreased rapidly in proportion to temperature. In vitro degradation of the hydrogels was examined in buffer solution containing papain at different temperatures. The enzymatic degradation of the hydrogel was observed to proceed at 30 °C, however, the hydrogel was not degraded above 35 °C.

Another approach was performed by the control of miscibility between thermo-responsive polymers and degradable polymer networks. Dex hydrogels grafted with poly(N-isopropylacrylamide-co-N, N-dimethylacrylamide) (poly(IPAAm-co-DMAAm)) chains were prepared. Although swelling ratios for hydrogels were constant in a wide range of temperature, the transmittance dropped in relation to the lower critical solution temperature of poly(IPAAm-co-DMAAm). Temperature-dependent degradation was observed in these hydrogels, dependent upon the molecular weight of the graft chain. Degradation rate of Dex hydrogel grafted with shorter chains was constant in a wide range of temperature. In contrast, degradation rate of Dex hydrogel grafted with higher chains increased 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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February 13, 1998

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