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## Self-Regulated Degradation of Dextran-Based Hydrogels through Polyion Complexation

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A novel concept of closed loop feedback-controlled system was proposed and feasibility of a self-regulated degradation system was confirmed in this study. A pseudo-metabolic cycle as a self degradation system was designed: enzymatic degradation products from a polysaccharide generate oxidants such introduce a cationic charge into the polysaccharide chains, and can form a polyion complex with an anionic polysaccharide. As a model component of such a system, dextran, with nicotinamide substitution, was prepared. Its degradation by dextranase, redox reaction via glucose oxidase-catalysis, and polyion complex formation with carboxymethyl dextran (CMD) were examined.

Polyion complex formation regulated by its enzymatic degradation products was achieved and the regulating factors of the complex formation were evaluated. Nicotinamide-modified dextran (NA-Dex) with nine nicotinamide moieties per 100 glucose units was soluble in PBS and completely oxidized by 100 mM  $\text{H}_2\text{O}_2$ . The oxidized type of NA-Dex was found to form a 1:1 complex with CMD. By the addition of dextranase, isomaltase and glucose oxidase (GOD) to phosphate buffer solution of the reduced type of NA-Dex and CMD, the transmittance of the solution dropped, suggesting polyion complex formation via the oxidation of 1,4-dihydronicotinamide in NA-Dex by  $\text{H}_2\text{O}_2$  generated from GOD-catalytic reaction. NAH-Dex with molecular weight  $> 40000$  formed a complex with CMD ( $M_n = 40000$ ) and the transmittance of the solution dropped. The complex formation was found to proceed stoichiometrically. As the concentration of NAH-Dex and CMD increased, the transmittance value of the solution decreased. On the other hand, as the concentration of  $\text{H}_2\text{O}_2$  increased, the onset time of the transmittance drop decreased. The transmittance value may be dependent on the concentration of  $\text{H}_2\text{O}_2$ , whereas the onset time of the transmittance drop may be dependent on the concentration of NAH-Dex and CMD.

From the above, dextran-based hydrogel containing NAH-Dex and CMD was prepared and inhibition of the enzymatic degradation of the hydrogel by polyion complex formation was achieved. Hydrogel containing NAH-Dex and CMD was prepared and its gel behavior and enzymatic degradation polarity was investigated. The water content of the gel increased with increasing CMD content in the gel. By the addition of  $\text{H}_2\text{O}_2$  to hydrogel in PBS, the water content of the gel decreased with time, suggesting polyion complex formation via the oxidation of NAH-Dex by  $\text{H}_2\text{O}_2$ . Therefore, it is considered that the gel shrinkage is occurred by neutralization of carbanion on CMD. The rate of dextranase-catalyzed degradation of the gel which was oxidized by  $\text{H}_2\text{O}_2$  was slower than that of initial gel. It is suggested that the enzymatic degradation is inhibited by steric hindrance of shrunk gel. Therefore, the mode of enzymatic degradation, i.e., surface vs. bulk degradation can be controlled by slightly volume change via polyion complex formation. These findings are of great importance for designing a self-regulated degradation system aiming at biodegradable and oscillative drug release.