Abstract

Invasive techniques such as sutures and staples are used to join wounds, but have drawbacks such as secondary tissue damage. A promising and attractive option to mitigate this disadvantage and to close and connect tissues is the use of tissue adhesives. Tissue adhesives are not only used as an adjunct during suturing in surgery, but also function as hemostatic agents, sealants, and tissue adhesives that firmly join and secure two surfaces. However, clinically used tissue adhesives do not fully meet the required properties such as low adhesion under wet conditions and low cytocompatibility, and research and development of new tissue adhesives are being actively conducted worldwide.

Our group has also developed a self-degradable dextran-based medical adhesive, LYDEX, with high adhesive performance and flexibility, low toxicity, and no risk of viral infection, to meet the requirements for an ideal tissue adhesive. LYDEX is a hydrogel composed of aldehyde-functionalized dextran (AD) and succinic anhydride-treated ε-poly-L-lysine (SAPL). This hydrogel is being considered for a wide range of medical applications, including hemostatic agents, sealants, and anti-adhesion materials. However, to apply LYDEX as a medical material, it is necessary to elucidate the mechanism of degradation as much as possible, since it is a degradable and absorbable material and a novel substance.

After gelation and adhesion of LYDEX by Schiff base bond formation between the aldehyde group of AD and the amino group of SAPL, molecular degradation associated with the Maillard reaction begins, but the detailed degradation mechanism was unknown. Here, I elucidated the degradation mechanism of LYDEX by analyzing the major degradation products under typical *in vitro* solution conditions. Degradation of LYDEX gels with sodium periodate/dextran content of 2.5/20 was observed using gel permeation high-performance liquid chromatography and infrared and ^{1}H NMR spectroscopy; the AD ratio in the AD-SAPL mixture increased with decreasing molecular weight as degradation time progressed. The discovery of the self-degradability of LYDEX is valuable for elucidating the degradation mechanism of other polysaccharide hydrogels and for the use of LYDEX in medical applications such as hemostatic and sealant materials.

LYDEX applications are being considered for a wide range of medical fields as described above, and its unique potential to control the *in vivo* degradation rate depending on its composition has been confirmed for anti-adhesion applications. The thickness of the gel also plays an important role in determining the degradation rate, but this issue has not been fully explored in previous studies. Therefore, in this study, the optimal LYDEX dose (film thickness) to maximize the performance of anti-adhesion materials was tested using a rabbit colon model, and it was confirmed that gel film thickness affects the degradation period and anti-adhesion efficacy. The results obtained suggest the possibility of designing LYDEX materials applicable to a wider range of *in vivo* treatment sites, which would be extremely beneficial for the development and use of novel anti-adhesion materials with adequate hemostatic and sealing performance.

In conclusion, the elucidation of the degradation mechanism of LYDEX and the investigation of maximizing its anti-adhesion performance obtained in this study will not only enhance the applicability of LYDEX as a polymeric material for medical use, but also contribute to the research and development of polymeric compounds as a whole, for which the degradation mechanism is complex to understand. Specifically, combining the degradation mechanism of polysaccharide hydrogels (polymer compounds) with methods to control degradation by oxidation is expected to contribute to the development of new materials.

Keywords: hydrogel, LYDEX, degradation, dextran, poly-L-lysine, Maillard reaction, anti-adhesion.