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Improvement of physicochemical stability of highly-concentrated antibodies using cyclodextrin polypseudorotaxane hydrogels

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Recently, a large number of antibodies have been utilized as biodrugs, and their subcutaneous formulations are required to allow the self-administration. However, because of the lower administration capacity of subcutaneous formulation than intravenous ones, highly-concentrated antibody formulations (>100 mg/mL) are desired. Regretfully, highly-concentrated antibodies often cause aggregation during the long-term storage and transportation, resulting in the loss of pharmacological activity and induction of immunogenicity. On the other hand, we previously reported the potential use of polypseudorotaxane (PPRX) hydrogels consisting of polyethylene glycol (PEG, MW 20,000) and cyclodextrins (CyDs) as sustained release systems for protein drugs such as insulin and lysozyme. Therefore, in the present study, we evaluated the stabilizing effects of CyD PPRX hydrogels on the aggregation of highly-concentrated human immunoglobulin G (IgG) or various antibody preparations [1].

To prepare PPRX hydrogels, α-CyD solution (145 mg/mL) or γ-CyD solution (232 mg/mL) including human IgG (130 mg/mL) or several antibody preparation was mixed with PEG solution (0.02 M, MW 20,000), and the solutions were stood at 4 °C for 12 h. According to the results of powder X-ray diffraction, α-CyD and γ-CyD successfully formed PPRX hydrogels with one PEG chain and two PEG chains, respectively, even in the presence of human IgG (>100 mg/mL) and antibody preparation. In addition, α-CyD and γ-CyDPPRXs including human IgG formed the hexagonal or tetragonal columnar necklace-like inclusion complex, respectively, resulting in physical cross-linking points to form the hydrogels (Fig. 1). The imaging data obtained by Raman spectroscopy indicated that both α-CyD and

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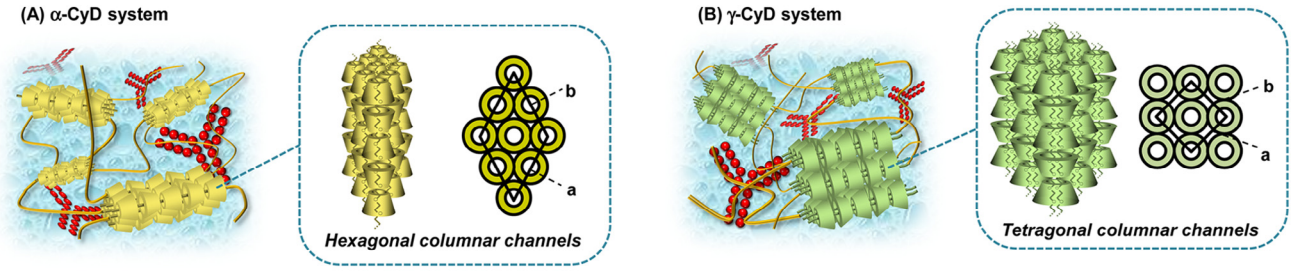

Fig. 1 – Schematic proposed structures of α-CyD and γ-CyD PPRX hydrogels including highly-concentrated human IgG.

γ-CyD were sparsely dispersed in the hydrogels, whereas human IgG was homogeneously distributed. In addition, we evaluated the physicochemical stability of human IgG and various antibody preparations into the PPRX hydrogels after heating (60 °C, 30 min) or shaking (500 rpm, 1 week). Importantly, the thermal stability and shaking stability of human Ig Gen capsulated into PEG/CyD PPRX hydrogels were markedly improved, compared to human IgG alone. Moreover, the shaking stability of various antibody preparations encapsulated into PEG/CyD PPRX hydrogels were improved, compared to antibody preparation alone. These results obtained in the present study suggest that PEG/CyDs PPRX hydrogels could be a promising stabilizing material for highly-concentrated human IgG or antibody preparations.

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