Metal ion-reinforced injectable hydrogel systems for therapeutic applications

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Injectable hydrogel systems can offer several benefits such as minimal invasiveness (pain relief), delivery of multiple drug cargos (small chemicals, peptides, proteins, and nucleic acids), and direct application to the target site. However, naive hydrogel network mainly based on natural or synthetic polymers may have poor mechanical properties and they may elevate the dosing frequency, inducing inconvenience to the patients. Therefore, rheological tuning approaches have been tried to modulate the therapeutic efficacies following their injection. Among numerous gel crosslinking methods, metal ion-catechol coordination and polydopamine linkage have been selected in our previous studies and they provided suitable rheological features for local injection which can lead to low biodegradation rate and programmed drug delivery. Specifically, crosslinked hydrogel systems were fabricated by using hyaluronic acid (HA) derivative. Although HA has biocompatibility and biodegradability, naive HA hydrogel has poor physicochemical and mechanical properties as a delivery platform for local injection. Amine group of dopamine was reacted with carboxylic acid group of HA for amide bond formation and that HA-dopamine conjugate has been used as a gel matrix to make crosslinked hydrogel systems with several metal salts (*e.g.,* $FeSO_4$, $CuSO_4$, Na_2SeO_3, $HAuCl_4$ etc.). The coordination bond between metal ion and catechol residue (of HA-dopamine) and polydopamine linkage by pH adjustment elevated the viscoelastic properties of hydrogels. Designed hydrogel systems possess injectable capability mainly based on the shear-thinning behavior, slow biodegradation pattern for low dosing frequency, controlled drug cargo release, and prolonged therapeutic actions. Drug cargos with different physicochemical properties can be incorporated into these hydrogel systems and metal ions can serve as pharmacologically active modalities for chemodynamic therapy and several cell death induction. Herein, the physicochemical/rheological features of metal ion-crosslinked catechol-functionalized HA hydrogel systems and their biomedical applications will be introduced.