

host-guest supramolecular hydrogels can be conjugated on water-soluble macromers, thus permitting *in situ* cell encapsulation. These hydrogels, similar to covalently crosslinked mesh-like hydrogels, do not possess fibrillar or porous structures. However, this system offers ‘injectability’ and the supramolecular macromers are increasingly being used as ‘building blocks’ to fabricate cell-compatible hydrogels.

The gelation and stability of physical hydrogels formed by host-guest interactions are governed by the principles of thermodynamics and the kinetics of the affinity binding. The equilibrium binding strengths between the host and guest molecules are determined by the equilibrium dissociation constant (K_D , unit: M), which is the ratio of dissociation (or reverse) rate constant (k_{off} or k_{-1} , unit: sec^{-1}) and association (or forward) rate constant (k_{on} or k_1 , unit: $\text{sec}^{-1}\text{M}^{-1}$). In the formation of supramolecular host-guest hydrogels, it is essential to use multifunctional macromers for both the host and the guest macromers, which increase both the speed of gelation and the stability of the resulting gels in an aqueous environment. The thermodynamic equilibrium of the host-guest binding is determined by the binding affinity, as well as the concentrations and the stoichiometric ratio of the host and guest moieties. Delicate adjustment of the various parameters related to host-guest affinity binding is essential in maintaining a stable hydrogels while allowing cell-mediated reversible bond dissociation.

One example of ‘host’ molecule is amphiphilic cyclodextrins (CD, including α -CD, β -CD, and γ -CD), whose inner hydrophobic cavity is capable of binding with hydrophobic bulky molecules, such as adamantane, azobenzene, ferrocene, and stilbene (Appel et al. 2010; Appel et al. 2012a; Appel et al. 2012b; Webber et al. 2015). Various forms of functionalized CD have been synthesized for creating matrices for in biomaterials, drug delivery, and tissue engineering applications. For example, the Burdick group developed CD and adamantane (Ad) conjugated hyaluronic acid (HA) for forming shear-thinning hydrogels suitable for cell encapsulation (Rodell et al. 2015a; Rodell et al. 2015b). The association between CD and Ad led to gelation but the complexes disassembled upon applying shear force, which leads to gel-sol transition. Upon removing the shear force, the host-guest interaction re-establishes and the hydrogel re-forms. Similar gelling principles are used to create supramolecular hydrogels based on macrocyclic oligomer cucurbit[8]uril and its corresponding guest molecules fabricated in the form of pendant linear macromers (Appel et al. 2010; Appel et al. 2012a; Appel et al. 2012b). Alternatively, transient protein-protein or protein-peptide interactions are exploited for forming affinity-based supramolecular hydrogels (Lu et al. 2012). For example, two-component hydrogels formed by multivalent binding of WW domains and proline-rich peptides have been developed for cell encapsulation (Wong Po Foo et al. 2009; Parisi-Amon et al. 2013).

Covalently crosslinked hydrogels with reversible crosslinks

Covalently adaptable hydrogels describe a class of hydrogels formed by reversible linkage (Wang and Heilshorn 2015). The reactions between the complementary reactive motifs form metastable bonds that can be broken and reformed under certain environmental conditions (e.g., temperature, stress, etc.). Unlike hydrogels crosslinked by pure covalent bonds, these materials typically exhibit viscoelastic properties similar to that found in native tissues (McKinnon et al. 2014a; McKinnon et al. 2014b;