

temperature) and/or host-guest complexations (Mura et al. 2013; Webber et al. 2016; Du et al. 2015b). Another approach takes advantage of locally over-expressed enzymes to help dissociation (following hydrolysis) of the supramolecular nanostructures and subsequently release the drug in the desired location. This approach is of particular importance for anti-cancer therapeutics where enzymes are considered as cancer biomarkers, which is the focus of this section. In this context, there are mainly two routes to deliver a drug from gel matrices; the first is based on drugs, which are covalently conjugated with therapeutics (i.e., pro-drug based materials); the second is based on drugs' encapsulation within the gel matrix.

Pro-drug based hydrogels

There has been a great interest to deliver therapeutics using this route; drugs (or model drugs) are modified in such a way that they have the correct hydrophobic and hydrophilic balance to allow them to self-assemble and form supramolecular structures. The formed structures (i.e., pro-drugs) might then entangle to form a gel. Ideally, this chemical modification should include a covalent conjugation of an enzyme cleavable linker. This allows for specific bond cleavage upon enzymatic exposure, leading to the release of the therapeutic molecule.

Up to this end, Cisplatin (cis-diamminedichloroplatinum II) (a chemotherapeutic agent used in treating different cancers such as testicular, ovarian and bladder cancers, as well as, lymphoma and glioma) was conjugated with a PA (comprising an MMP-2 sensitive derivative GTAGLIGQRGDS) (Kim et al. 2009). The new compound (i.e., pro-drug) was developed so it can self-assemble to form nanofibers that eventually gel (Fig. 6A). Cisplatin derivative release from the pro-drug gel was a consequence of MMP-2 cleavage of the PA (between glycine (G) and leucine (L)). TEM analysis was used (before and after enzymatic treatment) to confirm the hydrolysis process (Fig. 6A). The drug release was found to be dependent on the enzyme concentration. It was also found that the higher the MMP-2 concentration the more drug can be released from the gel matrix (Fig. 6B).

Using a similar approach, Escuder and Miravet have prepared a pro-drug through the conjugation of a low-molecular weight gelator (containing lysine) to model anti-cancer drugs (benzylamine or phenethylamine). The drug and self-assembling units were connected through a self-immolative linker (p-aminobenzoylcarbonyl) which is stable under physiological conditions (Fig. 7A) (Sáez et al. 2010). This pro-drug molecule forms a stable hydrogel with a minimum gelator concentration of 0.1% w/v. Cryo-SEM image showed that the gels have a sponge-like morphology with micrometre sized cavities filled with the solvent (Fig. 7B). Upon trypsin treatment, the amide bond of the molecule is hydrolysed, the amino group of p-aminobenzoylcarbonyl becomes free and undergoes a rapid 1,6-elimination to carbamic acids that are unstable and decompose to release the model drug (Fig. 7C).

Another interesting supramolecular design of a pro-drug conjugate was reported by Gao et al. (Gao et al. 2009). In this work, an anti-cancer drug (taxol) was modified so it can form nanofibers and finally entangled to form a supramolecular hydrogel. Taxol