released. As the surrounding environment changes, this swelling can be 'turned off' and shrinkage of the device results in a closed structure, through which drug molecules cannot diffuse. This feature can be exploited for application in targeted drug delivery. A relevant example is the delivery of drugs via injections to a site across the blood-brain barrier. Transition between gel and solution can be optimized for the process of administration with subsequent controlled release. Temperature controlled systems are generally composed of co-polymer structures. Pluronics®, which are varying ratios of poly(ethylene oxide) and poly(propylene oxide) are co-polymers defined by low critical solution temperatures (LCST). With the LCST falling close to 37°C, the formulation can undergo a phase transition at body temperature which can subsequently influence drug release as previously stated (Qiu and Park 2012; de Las Heras Alarcon et al. 2005). These SMART formulations are also of particular interest when devising pulsed release systems in an attempt to mimic natural functions of the body, such as insulin secretion or hormone dosing systems (Stubbe et al. 2004). Polymers composed of p(NIPAM) have also been researched in applications for controlled drug delivery exploiting the LCST property. The polymer chains aggregate due to hydrophobic interactions in aqueous media at low temperatures; these polymeric micelles exist in a swollen state within which the drug is entrapped (Ashraf et al. 2016; Schmaljohann 2006). At temperatures above the LCST, hydrophobic interactions cause collapse of the network and subsequent release of drug thereby rendering a responsive device (Jones et al. 2012). The thermoresponsive properties of p(NIPAM) have been confirmed in various research however specific application as a homopolymer is lacking due to the weak tensile properties of the gel (Schmaljohann 2006; Ashraf et al. 2016; Nguyen et al. 2015). Jones et al. have investigated the formation of copolymers with p(NIPAM) and additional hydrophilic and hydrophobic polymers (Jones et al. 2012). This research confirmed that while improving the tensile properties of the material, the stimuli responsive attribute desired was maintained. Application of this technology for controlled drug release purposes, as anti-infective biomaterials, was investigated and proved to be successful technology. The swelling variation is a key feature of the controlling mechanism of release in SMART formulations however other factors are suspected to be involved, all of which are not yet fully understood (Peppas 1997; Qiu and Park 2012; Zhang et al. 2002). A single kinetic model cannot be assigned to the drug delivery from this style of device given that release of this nature can result in multiple phases. Each phase can be individually modelled as previously discussed based on the relaxation, swelling, erosion and subsequent diffusion depending on the rate-limiting step in the release phase.

Chemically controlled drug release

Degradation of the polymer implies a similar outcome to erosion however it is an independent phenomena that is initiated by exploiting specifically designed aspects of the polymer structure using environmental stimuli (Lin and Metters 2006). For degradation to occur, there must be cleavage of specific bonds within the network, which result in disintegration of the structure. The cleavage can be initiated by enzyme presence or changes in swelling and is independently designed for the specific drug. Application of these hydrogels are ideal in the delivery of pro-drugs or proteins as a