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The control of cargo release from physically crosslinked hydrogels by crosslink dynamics

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ABSTRACT

Controlled release of drugs and other cargo from hydrogels has been an important target for the development of next generation therapies. Despite the increasingly strong focus in this area of research, very little of the published literature has sought to develop a fundamental understanding of the role of molecular parameters in determining the mechanism and rate of cargo release. Herein, a series of physically crosslinked hydrogels have been prepared utilizing host-guest binding interactions of cucurbit [8]uril that are identical in strength (plateau modulus), concentration and structure, yet exhibit varying network dynamics on account of the use of different guests for supramolecular crosslinking. The diffusion of molecular cargo through the hydrogel matrix and the release characteristics from these hydrogels were investigated. It was determined that the release processes of the hydrogels could be directly correlated with the dynamics of the physical interactions responsible for crosslinking and corresponding time-dependent mesh size. These observations highlight that network dynamics play an indispensable role in determining the release mechanism of therapeutic cargo from a hydrogel, identifying that fine-tuning of the release characteristics can be gained through rational design of the molecular processes responsible for crosslinking in the carrier hydrogels.

1. Introduction

Hydrogels are an important class of biomaterial that have received much attention for controlled drug-delivery applications on account of their similarity to soft biological tissue and highly variable mechanical properties [1–6]. Modeling of the controlled release of drugs and other cargo from these polymeric devices has been a subject of considerable research and many reviews have been published to address the principles of modelling diffusional release [7–9]. Many models in the past have focused on Fickian diffusion [10] however, Peppas and coworkers [11–13], have derived an important and exceedingly simple exponential relationship to describe the general release behavior of cargo from a controlled release polymeric device:

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

The equation relates both a release constant (k) and a diffusional exponent (n), which is characteristic of the release mechanism. While pure Fickian diffusion from such a polymeric device yields an n value of 0.50, values above this limit occur in systems that display some amount of anomalous release. Indeed, greater deviation from $n = 0.50$ signifies a greater contribution of anomalous release to the overall release mechanism. This equation has been applied in a wide variety of instances to describe drug-delivery phenomena including pH-swellable devices [14] and highly swellable polymers [15].

Although the work by Peppas et al. focused primarily on chemically crosslinked hydrogels, the simple mathematical relationship has been utilized in describing delivery of cargo from a wide variety of physically crosslinked hydrogels [4,16–18]. Physical crosslinking arises from entanglements between macromolecular species where specific and dynamic non-covalent interactions are used as the structural crosslinks between polymer chains, thereby coupling many of the exceptional qualities of polymer-based hydrogels with the diversity and orthogonality of supramolecular chemistry [19–22]. These hydrogels are particularly interesting on account of their dynamic nature, which can be regarded as an advantageous characteristic as it is the basis for both shear-thinning (viscous flow under shear stress) and self-healing (recovery after network damage) properties, two desirable characteristics for a variety of important applications [6,23,24]. These types of materials

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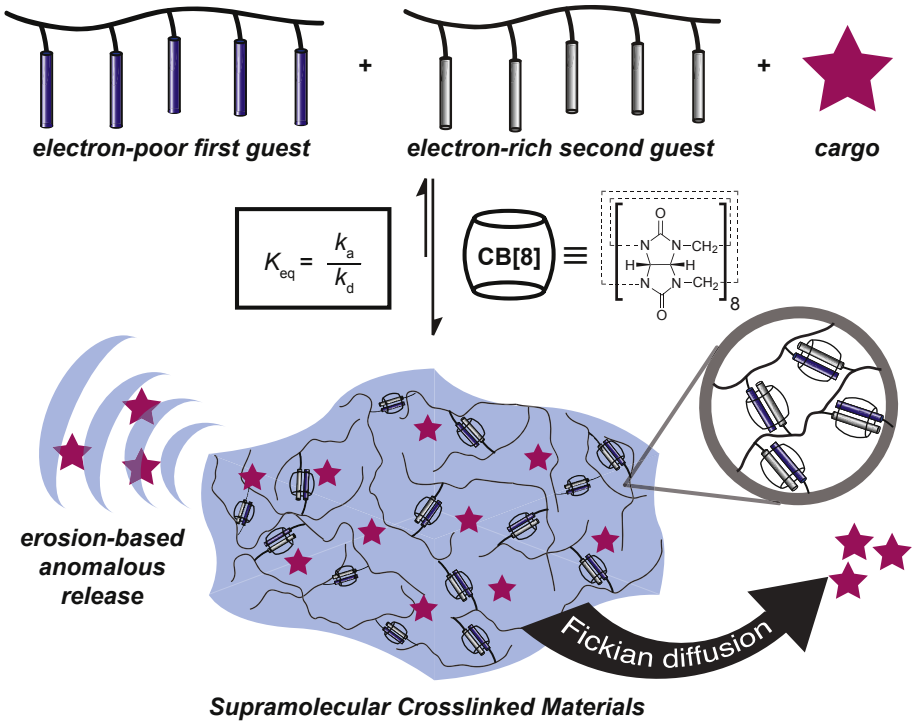

Fig. 1. Schematic representation of the preparation of dynamically crosslinked hydrogels utilizing cucurbit[8]uril host-guest chemistry. Physical crosslink dynamics, arising from the CB[8] ternary complex, play an important role in determining the release mechanism (a combination of erosion-based and Fickian diffusional release) of a model drug from the materials.

have displayed exceptional utility within the field of biomedicine, in part on account of the fact that they do not require surgical procedures since they can be pre-formed *ex vivo* and then delivered in a minimally invasive manner *in vivo* by applying shear stress when injected through a syringe. This method for implantation has been demonstrated to provide a more uniform distribution of cells or other therapeutic cargo in the injected gel [25] and greater control over placement of the material *in vivo* [26].

The release characteristics of cargo from these physically crosslinked materials, however, is conceivably more complex than chemically crosslinked materials on account of their ability to erode from the surface, thereby giving rise to a different mechanism for anomalous release from the device. In these systems, therefore, the diffusional exponent (n) can be utilized to characterize the contribution of erosion to the overall release profile of the cargo. Moreover, it is well known that the physical characteristics of such hydrogels, including their erosion behavior and rheology, arise from a combination of two fundamental characteristics: (a) supramolecular interactions responsible for the dynamic crosslinking and (b) conventional polymer physics describing polymer interactions within the material [2,3]. Elucidation of the role of the fundamental parameters of supramolecular crosslinking in determining the macroscopic behavior of these materials has only recently been achieved [27–29]. As an enormous array of supramolecular units have been utilized in the preparation of physically crosslinked materials over the past two decades, the ability to discern their specific role in determining the controlled release behavior from these polymeric devices is paramount for designing the next generation of such systems.

Our laboratory has previously demonstrated the preparation of physically crosslinked hydrogels based on the strong and highly specific hetero-ternary complex formation of the macrocyclic host cucurbit[8]uril (CB[8]) [30–33]. Cucurbit[n]uril ($n = 5$–8, 10; CB[n]) are a family of macrocyclic host molecules that are oligomers of glycoluril, which exhibit a symmetric 'barrel' shape with two identical portal regions laced by ureido-carbonyl oxygens. The number of glycoluril units determines the size of the cucurbituril cavity without affecting the height of the molecular container (approximately 0.9 nm), similar to the cyclodextrin (CD) family. While smaller homologs of the CB[n] family (*i.e.* CB[5], CB[6] and CB[7]) are capable of binding single guests (typically cationic amines, metal or imidazolium ions) [34–37], CB[8] has a larger cavity volume and can simultaneously accommodate two guests (Fig. 1) [38]. An electron-deficient first guest, such as methyl viologen (MV), and an electron-rich second guest, typically flat aromatic compounds such as naphthyl derivatives, form a stable 1:1:1 ternary complex with CB[8] through multiple non-covalent interactions acting synergistically, resulting in exceptionally high equilibrium binding affinities (K_{eq} up to 10^{14} M^{-2}) [39]. This motif has been utilized previously in the preparation of supramolecular polymeric hydrogels [30–33] and other crosslinked polymeric materials [40] using naphthalene derivatives as the electron-rich second guest. Recently, we have developed a series of ternary complexes whereby the binding of the second-guest moieties display a range of associative and dissociative rate constants (k_a and k_d, respectively) and activation energies for the associative and dissociative processes (Ea_a and Ea_d, respectively) while exhibiting identical thermodynamic equilibrium constants (K_{eq}) [29]. Utilizing these guests for the preparation of physically crosslinked hydrogels has given rise to a series of materials with identical plateau storage moduli (G′; on account their identical K_{eq} values) and structure, yet exhibiting varying network dynamics on account of the different molecular kinetics governing supramolecular crosslinking [29]. The varying dynamics of the second-guest binding, therefore, yield physical crosslinks with varying lifetimes arising from the differences in the energy required to convert an 'active' (bound) crosslink to and 'inactive' (un-bound) species.

Herein, we report the encapsulation and *in vitro* release of Rhodamine-B by these hydrogels (Fig. 1). Rhodamine-B is a