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Advanced molecular design of biopolymers for transmucosal and intracellular delivery of chemotherapeutic agents and biological therapeutics

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ABSTRACT

Hydrogels have been instrumental in the development of polymeric systems for controlled release of therapeutic agents. These materials are attractive for transmucosal and intracellular drug delivery because of their facile synthesis, inherent biocompatibility, tunable physicochemical properties, and capacity to respond to various physiological stimuli. In this contribution, we outline a multifaceted hydrogel-based approach for expanding the range of therapeutics in oral formulations from classical small-molecule drugs to include proteins, chemotherapeutics, and nucleic acids. Through judicious material selection and careful design of copolymer composition and molecular architecture, we can engineer systems capable of responding to distinct physiological cues, with tunable physicochemical properties that are optimized to load, protect, and deliver valuable macromolecular payloads to their intended site of action. These hydrogel carriers, including complexation hydrogels, tethered hydrogels, interpenetrating networks, nanoscale hydrogels, and hydrogels with decorated structures are investigated for their ability to respond to changes in pH, to load and release insulin and fluorescein, and remain non-toxic to Caco-2 cells. Our results suggest these novel hydrogel networks have great potential for controlled delivery of proteins, chemotherapeutics, and nucleic acids.

1. Introduction

The development of molecularly engineered biomaterials has been motivated by the challenges of controlled transmucosal and intracellular delivery of both hydrophobic drugs and macromolecular biotherapeutics, such as proteins and nucleic acids. Intelligent materials that can sense and respond to physiological and biological cues, as shown in Fig. 1, demonstrate promise in helping engineers and scientists overcome the significant challenges of achieving efficient oral administration of fragile therapeutics [1]. For these applications, researchers in our laboratory have developed a new class of crosslinked hydrogels composed of poly(ethylene glycol) (PEG)-containing grafted copolymers of acrylic acid (AA), methacrylic acid (MAA) or 2-diethylaminoethyl methacrylate (DEAEMA), containing functional compounds such as carbohydrate-binding proteins [2], polysaccharides, and targeting ligands [3]. In our recent work, we have shown that biomacromolecular delivery from these hydrogels can be controlled by their three-dimensional network structure as well as the conditions of the surrounding environment as these systems exhibit reversible hydrogen bonding and interpolymer complexation/decomplexation [4,5].

Promising new studies indicate that this class of hydrogel carriers, including complexation hydrogels, tethered hydrogels, nanoscale hydrogels, and hydrogels with decorated structures, can be used for delivery of hydrophobic drugs or biomacromolecules such as proteins and small interfering RNA (siRNA) [6,7].

A molecular understanding of how these hydrogels interact with and respond to biological environments is fundamental to continued development of transmucosal and intracellular drug delivery systems. For example, understanding the mucoadhesive behavior of PEG-containing carriers in contact with the intestinal mucosa is of utmost importance in local protein delivery, especially in the upper small intestine [8]. An important contributor to successful transmucosal delivery is adhesion to the intestinal mucosa through the presence of molecular adhesion promoters such as PEG chains grafted to cross-linked networks, lectins attached to hydrogels [2], and novel hydrogel structures decorated with carbohydrates [9].

In recent years, our laboratory has demonstrated great success in polymer-mediated delivery of fragile biomacromolecules such as insulin [10], calcitonin [11], and interferon β [12]. We now turn our attention to expanding the suite of fragile therapeutics available via oral administration. Through rational molecular design of novel polysaccharide-modified complexation hydrogels, we aim to improve

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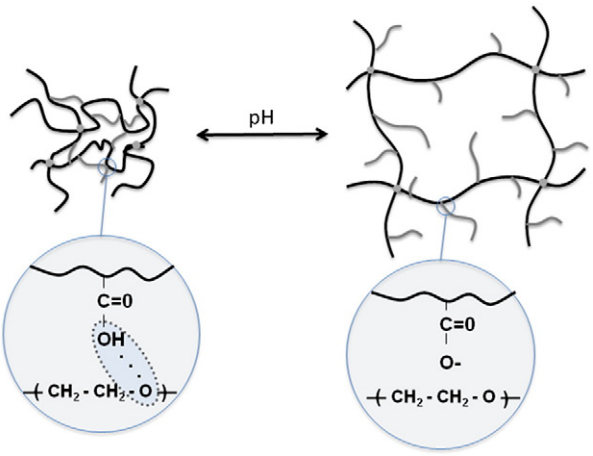

Fig. 1. Schematic of pH responsive hydrogels and the effect of complexation on the correlation length (pore size) ξ for pH responsive hydrogels.

bioavailability of therapeutic proteins by enhanced biophysical interaction with intestinal mucosa. Increased understanding of transport phenomena in tumor environments and the behavior of biomaterials in physiological environments are paramount to our goal of developing highly efficient oral delivery systems for chemotherapeutic drugs. New therapeutic modalities, such as RNA interference, have given researchers a host of new tools with which to treat previously intractable diseases. To this end, we are exploring nanoscale hydrogel carriers as siRNA delivery vehicles to disease targets along the GI tract [9,13–18].

1.1. Tethered carriers and protein delivery

One particular structural modification of interest is the decoration of micro- and nanoparticle surfaces with chains containing specific flexibility and functional groups. Specifically, our laboratory has studied PEG-tethered complexation hydrogels for controlled oral delivery of proteins. A central aim of our work has been protection of the protein bioactivity and to ensure therapeutic bioavailability. The seminal work of Lowman et al. [10,19–22] demonstrated that three-dimensional network structure could be used to control diffusion of proteins in gastric fluids. Promising studies from other groups [23] showed that erodible polyanhydride polymers displayed strong interactions with the mucosa of the gastrointestinal tract, suggesting that these microparticles could be used for delivery of insulin and plasmid DNA. Subsequent studies by our laboratory have focused on tailoring the structures of complexation hydrogels to address the major challenge to oral delivery of protein drugs—low bioavailability. Low bioavailability is attributed [24] to protein drugs' chemical instability in the gastrointestinal (GI) tract, susceptibility to proteolysis, and reduced ability to traverse biological barriers due to size [25].

One unique attribute of poly(methacrylic acid)-grafted-poly (ethylene glycol) (P(MAA-g-EG)) complexation hydrogels is their ability to protect protein drugs from enzymatic and chemical degradation upon exposure to intestinal fluids [26]. Several studies in our laboratory have shown that the structure of P(MAA-g-EG) hydrogels in acidic conditions as well as chemical composition contribute to this phenomenon. At low pH, the formation of physical crosslinks due to hydrogen bond formation between the poly(methacrylic acid) (PMAA) backbone and the PEG tethers limits diffusion into and out of the gel. Using insulin-loaded P(MAA-g-EG) microparticles, Wood et al. demonstrated limited release (<10%) of insulin during a 60 min incubation in simulated gastric conditions [2]. Following a step change in pH from pH 3.2 to pH 7.0, 80% of encapsulated insulin was released within 30 min. The theoretical distance between these adjacent crosslinks, or mesh size, ζ, can be calculated by well-known techniques [27]. We have also shown that PMAA can bind Ca^{2+} thereby inhibiting Ca^{2+}-dependent proteases [26,28]. For insulin and hemoglobin, Lehr and coworkers reported inhibition of proteolytic degradation in the presence of adhesive poly(acrylic acid)-based hydrogels [29,30].

Bioadhesive drug delivery systems capable of concentrating release at the absorption site are one strategy for improving protein drug absorption and increasing bioavailability [18]. The residence time of the carrier at the site of absorption, the upper small intestine, is an important contributing factor to the bioavailability of orally administered protein drug delivery systems. If the residence time of the carrier is extended in the upper small intestine, there is a longer window for protein drug absorption as well as higher concentration gradients at the absorption site. Our design of bioadhesive drug delivery systems relies on a fundamental understanding of how hydrogels interact with mucosal membranes and biological tissues. Serra et al. [8,31,32] have carried out molecular and structural studies to analyze the nature of the adhesive interactions. Thomas et al. [17,33,34] have used these studies to develop a new class of PEG-containing adhesive carriers. Moreover, to take advantage of mucoadhesion due to chain interpenetration, our laboratory has proposed adding adhesion promoters composed of long, linear polymer tethers extending from the hydrogel surface [18,31,35]. A number of studies have demonstrated hydrogels with PEG tethers are mucoadhesive and have increased residence time in the upper small intestine [8,32,34,36]. More recently, we have focused on biomolecules to promote adhesion, with an effort to develop a mechanistic understanding of molecular adhesion. The primary goal of bioadhesive controlled drug delivery is to localize a delivery device within the body to enhance the drug absorption process in a site-specific manner. Wheat germ agglutinin-functionalized P(MAA-g-EG) gels [2] have shown promising results in vitro and in vivo. In this work, we have modified P(MAA-g-EG) hydrogels with neutral polysaccharide tethers of dextran and pullulan to form P(MAA-g-EG-Dextran) and P(MAA-g-EG-Pullulan) hydrogels.

1.2. Nanoscale hydrogels in drug delivery

Several recent efforts have explored the utility of responsive nanoscale hydrogel carriers in drug delivery [3,37–39], demonstrating release of biological therapeutics such as insulin and imaging agents such as gold. Nanoscale hydrogels are increasingly attractive as drug delivery agents owing to their facile manufacture, tunable physicochemical characteristics, and repeatable release. Furthermore, their covalent crosslinking endows them with mechanical integrity not available in their self-assembled counterparts.

1.2.1. Applications in cancer treatment

Significant advancements have been made in our fundamental understanding of cancer; but unfortunately these developments have not yet been fully translated into effective clinical treatments of cancer [40]. A major reason is our inability to administer therapeutic agents selectively to the targeted sites while avoiding adverse effects on healthy tissue. Current therapeutic strategies for most cancers involve a combination of surgical resection, radiation therapy, and chemotherapy. These therapies are associated with significant morbidity and mortality primarily due to their non-specific effects on “normal” cells. The increase in efficacy of a therapeutic formulation is directly correlated to its ability to selectively target diseased tissue, overcome biological barriers, and intelligently respond to the disease environment to release therapeutic agents.

Nanotechnology coupled with advanced cancer biology offers great potential for addressing these challenges [41]. In recent years, outstanding progress has been made using nanovectors, liposomes, and polymer-mediated delivery strategies to increase localized