Journal of Drug Delivery Science and Technology 30 (2015) 352–359

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Hybrid responsive hydrogel carriers for oral delivery of low molecular weight therapeutic agents

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ARTICLE INFO

Article history:
Received 19 May 2015
Received in revised form
28 July 2015
Accepted 28 July 2015
Available online 13 August 2015

Keywords:
Responsive hydrogels
Oral delivery
pH responsive delivery
Poly(methacrylic acid)
Poly(acrylic acid)

ABSTRACT

Hydrogels have been influential in the development of controlled release systems for a wide variety of therapeutic agents. These materials are attractive as carriers for transmucosal and intracellular drug delivery because of their inherent biocompatibility, tunable physicochemical properties, basic synthesis, and ability to be physiologically responsive. Due to their hydrophilic nature, hydrogel-based carrier systems are not always the best systems for delivery of small molecular weight, hydrophobic therapeutic agents. In this work, versatile hydrogel-based carriers composed of copolymers of methyl methacrylate (MMA) and acrylic acid (AA) were designed and synthesized to create formulations for oral delivery of small molecular weight therapeutic agents. Through practical material selection and careful design of copolymer composition and molecular architecture, we engineered systems capable of responding to physiological changes, with tunable physicochemical properties that are optimized to load, protect, and deliver their payloads to their intended site of action. The synthesized carriers' ability to respond to changes in pH, to load and release small molecular weight drugs, and biocompatibility were investigated. Our results suggest these hydrophilic networks have great potential for controlled delivery of small-molecular weight, hydrophobic and hydrophilic agents.

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1. Introduction

Drug delivery systems (DDS) are of utmost importance to the development of new pharmaceutical formulations. With the advent of new, sophisticated, therapeutic agents that can target specific cellular functions, it is vital that these drugs reach the desired diseased cells. Environmentally responsive DDS can accomplish this [1–3]. Synthetic polymer-based hydrogels improve the solubility, bioavailability, and pharmacokinetics of a drug delivered orally. These materials are attractive for transmucosal and intracellular drug delivery because of their straightforward synthesis, their inherent biocompatibility, tunable physicochemical properties, and ability to be physiologically responsive [4].

The oral administration of small molecular weight agents has numerous obstacles that must be circumvented to create an effective delivery system. Compared to intravenous delivery, there is low bioavailability in transportation of the hydrophobic agents from the gastrointestinal (GI) tract to the bloodstream. Design of polymeric carriers must ensure the drug is carried from the GI tract to the bloodstream without it being inactivated. The drug must be protected from the low pH of the stomach, but concurrently the GI tract must be protected by the potential toxicity of these therapeutic agents.

In our laboratory we have developed a class of hydrogels containing an acid backbone composed of acrylic acid (AA) and/or methacrylic acid (MAA) for the development of pH responsive hybrid biomaterials, for oral delivery within the upper small

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http://dx.doi.org/10.1016/j.jddst.2015.07.023
1773-2247/Published by Elsevier B.V.

intestine. Previously we've demonstrated that the physicochemical behavior of these hydrogels can be controlled by the three-dimensional architecture of the polymer networks as well as by their environmental conditions for biomacromolecular delivery [4–19]. Unfortunately, due to their hydrophilic nature, traditional hydrogel-based carrier systems may not be the optimal systems for delivery of small molecular weight, hydrophobic therapeutic agents. Hybrid hydrogel systems that contain hydrophobic components have the potential to overcome this limitation.

Several novel hybrid hydrogel materials have recently been developed to overcome this shortcoming [4,16,17]. In their work, Schoener et al. [16] developed two types of hybrid hydrogels that had hydrophobic domains within the hydrophilic polymer network. The first hybrid hydrogels were amphiphilic interpenetrating networks (IPNs) that had a hydrophobic network composed of poly(*n*-butyl acrylate) (PBA) interwoven within a hydrophilic hydrogel of methacrylic acid grafted with poly(-ethylene glycol) tethers P(MAA-g-EG) [16]. The presence of the PBA rendered the overall network more hydrophobic but it also decreased the swelling of the hydrogel network that could limit the loading efficiency and release of therapeutic agents.

To overcome this limitation, Schoener and colleagues developed a second hydrogel architecture composed of P (MAA-g-EG) hydrogels containing hydrophobic poly(methyl methacrylate) (PMMA) nanoparticles [17]. The presence of PMMA nanoparticles in the hydrogel network altered the swelling behavior, loading efficiency, and release profiles of model hydrophobic drugs. The swelling ratio of nanoparticle-containing hydrogels decreased with increasing nanoparticle content. Also, the presence of the PMMA nanoparticles influenced the physical properties of the hydrogel system. It appeared that the nanoparticles reduced ionic repulsion between the deprotonated carboxyl groups in the P (MAA-g-EG) hydrogel, reduced the free volume for polymer chain movement of the pH responsive network, and reduced water intake.

In the present work, microparticles composed of co-polymer blends of methyl methacrylate/acrylic acid (MMA/AA) were investigated for the development of an oral drug delivery system for small molecular weight drugs. The carriers' ability to load and release diltiazem hydrochloride, a hydrophilic low molecular weight drug and fluorescein, a model hydrophobic low molecular weight drug, was studied. P (AA-co-MMA) copolymers start swelling at pH values near the pKa of acrylic acid (~pH 5). Thus, these hydrogels are expected to remain collapsed in the acidic conditions of the stomach, but swell in the more basic conditions of the small intestine. In addition, the mixture of hydrophobic and hydrophilic monomers will give the polymer unique characteristics that may prove to be beneficial for loading a release of small molecular weight drugs and hydrophobic therapeutics.

It is well known that acrylic acid is hydrophilic whereas methyl methacrylate is more hydrophobic. Therefore, we believe that the hydrophobicity will improve the polymer's ability to load and retain a hydrophobic drug but the hydrophilicity makes aqueous swelling possible and improves the drug's solubility. In acidic conditions, the hydrogel will be collapsed and capable of retaining a small molecular weight drug, but in neutral conditions the hydrogel will swell allowing for release of the drug as the polymer network relaxes and imbibes water.

In vitro characterization of particles' biocompatibility and ability to effectively transport agents across the intestinal lining was investigated using a co-culture model developed by the Peppas Lab [19]. The co-culture model uses HT-29 MTX cells, a mucus-secreting subclone of human carcinoma cells, and Caco-2 cells to model the intestinal epithelial layer. The Caco-2/HT29-MTX co-culture model is a robust human gastrointestinal (GI) tract model. When grown out to confluence for 20 days the cells produces enzymes and mucus, possess tight junctions, and develop microvilli. These features create a GI tract model whose transport of molecules correlates well with *in vivo* absorption [19].

2. Methods

2.1. Materials

All solvents (ethanol, acetone) were from Fisher Sciences. The two agents for delivery were (+)-cis diltiazem hydrochloride and fluorescein sodium were purchased from Sigma Aldrich. Tert-butyl methacrylate (*t*-BMA), tetraethylene glycol dimethacrylate (TEGDMA), acrylic acid (AA), and methyl methacrylate (MMA) were from Sigma Aldrich. The ultraviolet (UV) photoinitiator, 2-hydroxy-1-[4-(hydroxyethoxy) phenyl]-2-methyl-1 propanone (Irgacure 2959) was purchased from Sigma Aldrich. Inhibitor was removed via a basic alumina column from TEGDMA, *t*-BMA, and MMA before being use. All polymer films were made in a Labconco controlled chamber glove box with a Dymax light curing system.

Caco-2 cells were obtained for the American Type Culture Collection (ATCC) and HT29-MTX cells were generously donated by Dr. Thecla Lesuffleur (INSERM, Paris, France). HT29-MTX cells are a sub-population of HT29 cells that were adapted to 10^{-6} M methotrexate (MTX) [20,21]. All cell types were cultured in Dulbecco's Modified Eagle Medium (DMEM) high glucose supplemented with 10% heat-inactivated fetal bovine serum, with 1% streptomycin from Sigma Life Sciences. Dulbecco's Phosphate-Buffered Saline (DPBS) and was also obtained from Sigma Life Sciences. The dimethyl sulfoxide (DMSO) and 10 x Phosphate-Buffered Saline (PBS) was from Fisher BioReagents. The Hank's Buffered Saline Solution (HBSS) used was purchased from HyClone. The fluorescence and Costar UV 96-well plates were acquired from Corning. Cells were maintained in T-75 flask from Corning and Costar Transwell® plates with a polycarbonate membrane were used from transport studies from Fisher Scientific.

2.2. Hydrogel film synthesis

Polymer films of MMA/AA copolymers, henceforth designated as P(AA-co-MMA), were synthesized using UV-initiated free radical polymerization. Copolymers with 10, 20, and 30 mol % of MMA in the total monomer feed were produced. Tetraethylene glycol dimethacrylate (TEGDMA) was used as the crosslinking agent. Irgacure 2959 was used as the photoinitiator. A 1:1 mixture of ethanol and water were used as the solvent during polymerization to ensure complete solubility of the monomer components, crosslinking agent, and photoinitiator.

All components were added to an amber bottle, covered, and sonicated for 15 min. The amber bottle was then placed in a sealed glove box and purged with nitrogen gas for 20 min. The UV light source was set to an intensity of 16–18 mW/cm^2. The solution was transferred between two glass slides separated by a Teflon spacer and placed under the UV light source for 30 min. After polymerization, the hydrogels were removed from the glass slides. Synthesized films were washed for 10 days in deionized water (DIH_2O), with daily water changes and then vacuum dried for 3–5 days. After drying, the film was crushed using a mortar and pestle. The particles were sieved to be between 10 and 40 μm. In this way, we could achieve a more uniform size of microparticles to be used in all characterization studies.

2.3. Characterization of hydrogel samples

2.3.1. FT-IR spectroscopy

Fourier transform infrared (FT-IR) spectroscopy was used to