Evaluation of a novel polysaccharide-based drug delivery system

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Key words: Hydrogel, chitosan, drug delivery.

http://dx.doi.org/10.12692/ijb/4.5.123-127 Article published on March 10, 2014

Abstract

The present work focused on the design of drug delivery system (DDS) based on a pH-sensitive hydrogel. The hydrogels were prepared via graft copolymerization of acrylic acid (AA) and N-isopropylacrylamide (NIPAAm) monomers were directly grafted onto chitosan using ammonium persulfate (APS) as an initiator and methylenebisacrylamide (MBA) as a crosslinking agent under an inert atmosphere. The loading and release of cephalexin from these pH-sensitive hydrogels was studied in both simulated gastric and intestinal fluids.

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Introduction

The smart materials are getting ever-increasing interest both because of their unusual properties and because of the growing number of their possible practical applications. Among them an important group of materials are smart or stimuli-responsive polymers (Zhou et al., 2011). They can be defined as polymers, whose properties may change drastically in response to the application or a small change in some stimulus, e.g. temperature, pH, electric field, and magnetic field (Hua et al., 2010; Raghavendra et al., 2010). The possible applications of smart polymers include shape memory materials, intracellular delivery of therapeutic macromolecules, gene delivery, micro-fluidic devices, and polymer-biomolecule conjugates to mention just a few and the list is still rapidly growing (Buchholz et al., 1997).

Hydrogels are hydrophilic three-dimensional polymer networks capable of absorbing a large volume of water or other biological fluid. Hydrogels resemble the natural living tissue more than any other class of synthetic biomaterials. Thus hydrogels have found widespread application in different areas, e.g. as materials for contact lenses and artificial skin, wound dressing, protein separation, membranes for biosensors and devices for the controlled release of drugs (Hoffman, 2002).

Stimuli-sensitive hydrogels have the capability to change their swelling behaviour, permeability or mechanical strength in response to external stimuli, such as small changes in pH, ionic strength, temperature and electromagnetic radiation. The principal requirement of any controlled release system is that the release profile and rate are controlled. Controlled or sustained release drugs provide many advantages in comparison with conventional forms including reduced side effects; drug concentration kept at effective levels in plasma, improved utilization of drug and decreases the dosing times. Drug delivery systems based on hydrogels have been extensively explored to achieve the higher concentration of drugs in the specific region or tissue and the controlled release profile for extended time periods (Po R, 1994). According to the literature survey based on Chemical Abstract Service, a few studies have been reported in the case of polysaccharide-based hydrogels (Zheng et al., 2009; Sokker et al., 2011, Hua et al., 2009). Hence, the target of the current study was to exploit novel pH-sensitive Chitosan-based hydrogels for the effective cephalixin controlled release system. Drug absorption and release capacities of hydrogel systems were also examined.

Experimental

Materials

Chitosan (from Fluka, with MW=22742 and degree of deacetylation of 0.7) was used as received. Acrylic acid (AA, Merck) and N-isopropylacrylamide (NIPAAm) were purchased from Aldrich. Ammonium persulfate (APS) was used without purification. Methylenebisacrylamide (MBA, Fluka) was used as received. The drug cephalixin was purchased from Sigma Inc. The chemical structure of cephalixin is shown in Figure 1. Distilled water was employed for the hydrogel preparation and swelling measurements.

Drug loading on hydrogels

The vacuum dried powdered samples (±0.0001 g), with average particle sizes between 250–350 μm, were accurately weighted and immersed in the aqueous solution of drug (0.5 g dissolved in 50 mL distilled water) at 0°C for 25h to reach the equilibrated state. The swollen hydrogels loaded with drug were placed in a vacuum oven and dried under vacuum at 37°C.

The amount of drug content entrapped in the hydrogels was determined by an indirect method (Kost, 1995). After the gel preparation, the washings were collected, filtered with a 0.45 Millipore filter and tested at λmax 276 nm using UV/VIS spectrophotometer (UV-1201, Shimadzu, Kyoto, Japan).

In vitro drug release of hydrogels

The release of cephalixin was followed as a function of time by measuring the light-absorbance of the
outer aqueous phase at 276 nm using an UV/VIS spectrometer. The samples (0.1±0.0001 g) were immersed into 50 mL of the release medium with different pH values at 37°C with agitation using a magnetic stirrer. The same volume of fresh release medium was used to replace what was removed.

**Results and discussion**

**Swelling in solutions with various pHs**

The equilibrium swelling of the H-Ch-g-poly(AcA-co-NIPAAm) hydrogel samples (F1, F3, and F5) were kept in solutions with various pHs ranging from 1.0 to 10.0 and measured until the equilibrium was reached, as shown in the Fig. 2. No additional ions (through buffer solution) were added to medium for setting pH because absorbency of a superabsorbent is strongly affected by ionic strength. Therefore, stock NaOH (pH 10.0) and HCl (pH 1.0) solutions were diluted with distilled water to reach desired basic and acidic pHs, respectively(Kost,1995; Wu et al., 2010). The pKₐ of the weak polyacrylic acid is about 4.60, their ionization occurs above these values and consequently swelling capacity is increased. According to Fig. 2, the high swelling capacity of the hydrogel at pH 6 can be attributed to high repulsion of COO⁻ groups. At very acidic conditions (pH≤3), most of carboxylate groups are in the form of −COOH and the low swelling values of hydrogels can be attributed to the presence of non-ionic hydrophilic COOH and -OH groups in the chitosan and grafted monomers backbones. With further pH increase (pH>6), the swelling capacity is decreased. Again, the swelling loss is due to the counter ions, i.e. Na⁺, that shield the charge of the carboxylate anions and prevents efficient anion-anion repulsion. As a result, a remarkable decrease in equilibrium swelling is observed(Wu et al., 2010).

**Table 1.** Feed composition for preparation of full-polysaccharide hydrogels (F1-F5).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Chitosan (g)</th>
<th>AcA/NIPAAm (g)</th>
<th>MBA (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F2</td>
<td>2</td>
<td>1/2</td>
<td>3</td>
</tr>
<tr>
<td>F3</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>F4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>F5</td>
<td>1</td>
<td>2/5</td>
<td>3</td>
</tr>
</tbody>
</table>

In addition, Fig. 2 also revealed that at each pH conditions, the swelling ratio depended on the chain conformations and network structures. For instance, at pH 8.0, the swelling ratio of F1, F3, and F5 are 13, 16 and 14, respectively. Of course, these swelling ratios exhibited in pH solutions are quite smaller than those manifested in distilled water, which can be attributed to the charge-screening effect(Brandl et al., 2010).

According to feed compositions shown in Table 1, a series of hydrogels were prepared and their swelling ratios were measured in distilled water at 20°C. The swelling ratios of hydrogels formed with different amounts of MBA are presented in Figure 3.

**Swelling kinetics of hydrogels**

All the samples absorbed water quickly, and equilibrium water uptakes achieved after about 50 min for F1, 60 min for F2, and 65 min for F3. When

![Fig. 1. Chemical structure of cephalaxin.](image)

![Fig. 2. Effect of pH of solutions on the swelling capacity of H-Ch-g-poly(AcA-co-NIPAAm)hydrogel.](image)
the AcA/NIPAAm molar ratio was kept constant, the swelling degree of the hydrogel fell faster with the decreasing MBA content. It was well known that the higher the crosslinker concentration decreased drastic acceleration of shrinking kinetics of hydrogels. This result indicates that it is difficult for water to enter the network because of the rigidity of the network chains formed by the higher concentration of MBA crosslinker (Desai et al., 2005).

**Fig. 3.** Swelling kinetics of H-Ch-g-poly(AcA-co-NIPAAm) hydrogel samples in water solution. Particle size of the dried gel was 250–350 μm.

It was well known that the F1 sample would exhibit improved molecular mobility due to the existence of freely mobile chains, which show rapid dehydration, followed by the higher swelling rate and capacity.

**Fig. 4.** The dependency of the drug loading amount to the crosslinker concentration.

*In vitro cumulative release behavior of hydrogels*

The *in vitro* release profiles of cephalexin encapsulated in the full-polysaccharide hydrogels are shown in Figure 5. The release in simulated gastric fluids (SGF) and simulated intestinal fluids (SIF) displayed pH-sensitivity of these hydrogels. As can be seen from Figure 5, at acidic pH value of SGF, the cumulative release ratio of cephalexin from the hydrogels is below 37% at the end of the experiment (24 h), whereas almost 81% of the loaded drug is released within 16 h in SIF (pH 7.4) medium. This difference of their swelling behavior is responsible for the difference of the drug release ratio with changing pH of the medium. Indeed, the drug in the hydrogel could be released as a result of the hydrogel volume change and interaction between the polymer network and drug. The fractional release is directly proportional to the swelling ratio of the hydrogels. This result indicates that the higher swelling ratios of the hydrogel create larger surface areas to diffuse the drug. In basic solutions (pH 7.4), the electrostatic repulsion between COO- anions of grafted poly(sodium acrylate) on the hydrogel accelerates the release of cephalexin from the hydrogel (Dai et al., 2007; Desai et al., 2005).

**Fig. 5.** Release of cephalexin from hydrogel carrier as a function of pH.

**Conclusion**

In this work a novel sensitive hydrogel based on chitosan was synthesised. Their stimuli-responsive property can be monitored by changing the pH of solution. These pH-sensitive hydrogels have the potential to be used in the controlled drug delivery system. Cephalexin was encapsulated as a model drug an *in vitro* release studies were carried out in SGF and SIF. The model drug encapsulated was slightly fast release in SIF relative to that in SGF. Higher
release rates were also observed for hydrogels with lower crosslink density.

References


