Preparation and Properties of pH-sensitive Acrylic acid-grafted Polyvinylpyrrolidone Hydrogels by γ-ray Irradiation

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감마선 조사에 의한 아크릴산이グラフト된 pH 민감성 폴리비닐피플리돈 하이드로겔의 제조와 특성

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Abstract

pH-sensitive hydrogels were studied as a drug carrier for the protection of insulin from the acidic environment of the stomach before releasing it in the small intestine. In this study, hydrogels based on polyvinylpyrrolidone (PVP) networks grafted with acrylic acid (AAc) was prepared via a two-step process. PVP hydrogels were prepared by γ-ray irradiation (radiation dose: 25kGy, dose rate: 5.36kGy/h), and then grafting by AAc monomers onto the PVP hydrogels with subsequent irradiation (radiation dose: 10kGy, dose rate: 3.0kGy/h). These grafted hydrogels showed a pH-sensitive swelling behavior in various pH.

1. Introduction

Hydrogels are hydrophilic polymer networks that are capable of imbibing large amounts of water, yet are insoluble because of the presence of physical or chemical crosslinks, entanglements or crystalline regions. Because of the presence of certain functional groups along the polymer chains, hydrogels are often sensitive to the conditions of the surrounding environment. This environmentally sensitive behavior has led to the extensive use of hydrogels in controlled drug delivery systems1-4 and in membrane separations5, where they can respond to changes in the environment and, thus, regulate drug release or solute diffusion.
Irradiation, especially if combined with simultaneous sterilization of the product, is a very convenient tool for the synthesis of hydrogels. Radiation processing has many advantages over other conventional methods. In radiation processing, no catalysts or additives are needed to initiate the reaction. The advantages of radiation methods are that they are relatively simple, and the degree of crosslinking, which strongly determines the extent of swelling of hydrogels, can be controlled easily by varying the radiation dose. Therefore, these methods are found to be very useful in preparing hydrogels for medical applications, where even a small contamination is undesirable.

Oral delivery of peptides and proteins to the gastrointestinal (GI) tract is one of the most challenging issues. There are many hurdles, including protein inactivation by digestive enzymes in the GI tract, mainly in the stomach, and poor epithelial permeability of these drugs. However, certain hydrogels may overcome some of these problems by appropriate molecular design or formulation approaches. In this work, we have used pH-responsive hydrogels, prepared by gamma radiation grafting, as oral delivery carrier for insulin in order to protect the insulin from the acidic environment of the stomach. We investigated the swelling behavior in various pH.

2. Experimental

Materials

Polyvinylpyrrolidone (PVP) (Mw ca. $3.6 \times 10^5$ and $1.3 \times 10^6$) was purchased from Aldrich Co. (Milwaukee, U.S.A.). Acrylic acid (AAc) monomer obtained from Junsei Chemical Co. (Tokyo, Japan), was purified by an inhibitor removal column packed with aluminum oxide Junsei Chemical Co. (Tokyo, Japan). Ferrous ammonium sulfate ($\text{FeSO}_4(\text{NH}_4)_2\text{SO}_4\cdot6\text{H}_2\text{O}$, Mohr's salt) was purchased from the Wako Pure Chemical Industries Ltd. (Osaka, Japan).

Preparation of hydrogels

An aqueous solution of PVP was prepared by dissolving PVP in distilled water at room temperature with a stirrer. In order to crosslink the PVP solution, irradiation was carried out by a $^{60}\text{Co}$ source. The dose rate was 5.36 kGy/hr. After irradiation, the crosslinked PVP hydrogel was dried and weighted. Then, the hydrogel was kept in deionized water for 48 hr at room temperature and was occasionally shaken. The insoluble part of the hydrogel made up of only the crosslinked hydrogel, was dried and weighed. The gel content is defined as

$$\text{Gel content(%) } = \frac{W_d}{W_i} \times 100 \quad (1)$$

where $W_i$ is the initial weight of dried hydrogel after irradiation and $W_d$ is the weight of the dried insoluble part after agitation with water.
The various concentration of AAc which contain 0.01M of FeSO₄(NH₄)₂SO₄·6H₂O (Mohr’s salt) were prepared. The grafting experiments were performed by the mutual irradiation method for the PVP hydrogel swollen with these monomer solutions in a capped vial. The AAc-grafted PVP hydrogels were washed in deionized water and dried in air. The degree of grafting is defined as

\[
\text{Degree of grafting(\%)} = \frac{(W_g - W_o)}{W_o} \times 100
\]  
(2)

Where \(W_g\) and \(W_o\) denote the weights of the grafted and the ungrafted PVP hydrogel, respectively.

3. Results and discussion

Figure 1 shows the gel content of the PVP hydrogel as a function of PVP polymer solution concentration. The gel content is similar regardless of the concentration of PVP.

[Figure 1: Gel content of PVP hydrogel as a function of PVP concentration (radiation dose: 25 kGy)]

Figure 2 shows the degree of grafting onto PVP as a function of AAc concentration. The higher molecular weight (Mw) of PVP exhibits higher degree of grafting, because higher Mw PVP has more grafting site. As a AAc concentration increase, the degree of grafting is influenced by Mw of PVP slightly.

[Figure 2: Degree of grafting as a function of AAc concentration]
Figure 3 and 4 show the typical swelling behavior of the grafted hydrogels at several different pH values. It is obvious that the weight swelling ratios of the hydrogels are significantly higher at a pH above 6.8 compared to the lower pH media. At a low pH, when the complexation occurred, both the swelling rate and ratio were low. Complex formation results from the formation of temporary physical crosslinks due to hydrogen bonding between the PVP and PAAc pendent groups. This hydrogen-bonded complex causes the polymer network to be less hydrophilic because the carboxyl groups in the PAAc graft chain participate in the complex formation. As the pH increases, complexation does not occur resulting in both a faster swelling rate and higher swelling ratio. In a higher pH media, the complexes are broken and the carboxylic acid groups in the PAAc become progressively more ionized. In these cases, the hydrogels swell more rapidly due to a large swelling force created by electrostatic repulsion between the ionized carboxylate groups. In the transition region of a pH between 4.8 and 5.8, the swelling is governed by the ionic interactions as well as interpolymer complexation. The weight swelling ratio of the AAc grafted lower Mw PVP is superior to higher one.

![Graph 1: Weight swelling ratio of AAc grafted PVP hydrogel as a function of time (PVP Mw: 3.6x10^5, Degree of grafting: 99%).]

![Graph 2: Weight swelling ratio of AAc grafted PVP hydrogel as a function of time (PVP Mw: 1.3x10^5, Degree of grafting: 109%).]

References


