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Notes

Drug Release Characteristics of Modified PHEMA Hydrogel Containing Tethered PEG Sulfonate

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Introduction

Hydrogels are highly biocompatible on account of their low surface tension, similar hydrodynamic properties to those of natural biological gels and tissues, and minimal mechanical irritation in the soft and rubbery state. Currently, a wide variety of clinically important hydrogels are being employed as short and long term materials in kidney dialyzers, blood oxygenators, heart valves, vascular grafts, contact lenses, etc. Increasing interest has been devoted to the preparation and novel application of polymeric hydrogels based on poly(hydroxyethyl methacrylate) (PHEMA) in a variety of medical and biological applications.[1-4] PHEMA is one of the most well-studied synthetic hydrogel polymers which is nontoxic and biocompatible. By the bulk polymerization of HEMA, a glassy and transparent polymer is produced, which is hard like poly(methyl methacrylate). When PHEMA is immersed in water, it swells and becomes soft and flexible. Although it allows the transfer of swelling agents and some low molecular weight solutes, this kind of PHEMA is considered non-porous.

Recently, there has been increasing interest in the use of scaffolds for tissue and organ reconstruction and substitution.[5] Hydrogel polymers are particularly appealing candidates for the design of highly functional tissue engineering scaffolds and also as supports for delivery of bioactive agents (drugs) either locally or systemically.[2,6] In both broad application areas, the rate of transport of both small and large molecules, and indeed cells, through the polymer network, critically determines their efficacy. Here the porous nature of scaffold materials is one of important factor that influence the delivery of bioactive molecules and cell-scaffold interaction.[7,8]

PEG has a wide range of beneficial properties for biomedical applications, including low toxicity and non-thrombogenic.[2,9,10] PEG has been widely used to provide a non-fouling surface in different molecular forms for various biomedical applications in contact with the blood or tissue. A variety of strategies for tailoring the surfaces of materials with PEG-grafts have been developed.[11,12]

In our previous study, we have prepared modified PHEMA hydrogels with PEG or SPEG (PEG with sulfonate end-group) graft and investigated the effects of PEG tether on the swelling and morphology of the resulting gels along with their cytotoxicity evaluation.[13] In this short note, we report the study of drug loading and release behavior from the SPEG-modified PHEMA hydrogel using different types of model compounds to elucidate the effect of SPEG tether within the gel matrix.

Experimental

Chemicals and Measurements. A methacryloyl PEG macromer with a sulfonate end group, MA-PEG-SO_3H, (with average MW of ca. 1,200) was prepared using the method previously reported elsewhere.[14-17] 2-Hydroxyethyl methacrylate (HEMA) was purchased from Aldrich Chem. Co. and passed through an alumina column to remove the polymerization inhibitor prior to use. Ammonium peroxodisulfate (APS, Aldrich, 99%) was used without further purification. Biphenyl acetic acid (BPAA), methylene blue (MB), and methyl orange (MO) as model drugs were purchased from Aldrich Chem. Co. Doubly distilled water was used as the reaction medium.

The IR spectra were obtained using a Perkin Elmer FT-IR spectrometer (Model SPECTRUM 2000). The morphology of the prepared gel scaffolds was observed by SEM (FESEM Model JSM6700F, JEOL Inc.). UV-vis spectrometer (Biochrom Libra S22) was used for the quantitative analysis of drug concentration in aqueous medium.

Gel Preparation.

Radical Crosslinking Polymerization of HEMA in the Presence of SPEG Macromer and Model Drug Compound: HEMA and the copolymer hydrogels can be prepared either on a Teflon mold or in a small reaction ampoule. Typically, a predetermined amount of MA-PEG-SO_3H (0, 5, 10, 15 wt% of HEMA) and HEMA were added to the flame-dried vial and stirred to obtain a clear solution. No additional dimethacrylate compound was added to this gel preparation. The reagent grade HEMA contains dimethacrylate compound in itself and forms a crosslinked gel by addition of radical initiator. The vial was capped with a rubber septum, and the atmosphere was replaced by

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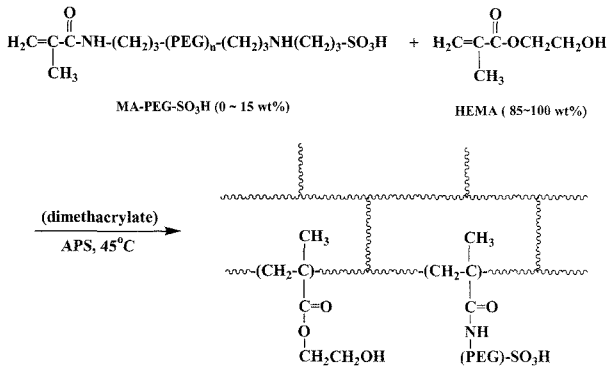
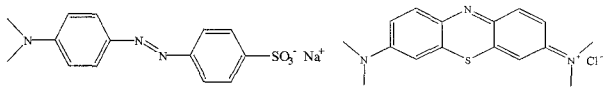


Scheme I. Preparation of PHEMA hydrogel with sulfonated PEG.

repeated vacuum and nitrogen purging through a three-way stopcock. The initiator APS solution was added to the above using a microsyringe, and the mixture was allowed to react at 45 °C for 20 h, where it transformed into a transparent solid gel. The prepared gel product was washed in distilled water for two days and freeze-dried to obtain the gel specimen.

Drug Loading and Release Behavior. Hydrogel samples containing a model drug were prepared to study their release behavior. To a solution of HEMA, with or without SPEG-macromer, 4 mg of model drug was added and degassed several times before initiator solution was injected by microsyringe. The solution was poured onto a Teflon mold and reacted for 20 h at 45 °C under nitrogen atmosphere. The final drug-loaded gel block was placed in a closed steel mesh, and the release experiment was carried out in 200 mL of phosphate buffer saline (PBS) solution at 37 °C in water bath. At periodic intervals, 4 mL aliquots were withdrawn and the absorbance spectrum was obtained on a UV-visible spectrometer. From the pre-prepared calibration curves for each different drug compound (λ_{max} 252 nm for BPAA; 640 nm for MB, and 466 nm for MO, respectively), the cumulative concentration of released drug was determined.



MO **MB**

Results and Discussion

Preparation and Swelling of PHEMA-SPEG Hydrogel. A sulfonated-PEG(SPEG) macromer, MA-PEG-SO_3H, was introduced to the HEMA gel preparation in bulk with different compositions to provide modified gels with tethered SPEG as the procedure are described in the experimental part. All the gel samples were obtained in transparent solid disks by using an open Teflon mold. Figure 1 shows the swelling behaviors of SPEG containing PHEMA gels at 37 °C in different pH conditions. All the samples showed fast swelling for the initial 2 h, after that the swelling gradually increased and reach equilibrium in approximately 8-10 h. The swelling degrees of SPEG containing gels were higher than that of homo PHEMA and the swelling ratio increased gradually with the increasing SPEG content. A more hydrophilic PEG component would result in a higher swelling capacity of the composite system. The swollen gel became more soft and flexible in proportional to the swelling capacity, i.e. the amount of SPEG introduced. As are investigated from our previous study, the PEG graft raised the swelling capacity of PHEMA gel, induced the development of microporocity within the gel matrix. From the swelling measurement in three different pHs of solution, the equilibrium swelling degrees in pH 4 and pH 10 were higher than that in neutral pH 7.4, probably due to the partial ionization of pendent groups in both slightly acidic and basic media.

Release Behavior of Drug-Loaded PHEMA-SPEG Hydrogel. To study the effect of tethered SPEG on the release behavior of this composite hydrogel, we incorporated three different model drugs into the gels and the release behavior was investigated. All three compounds are similar in their molecular size, but possessing different characteristics. BPAA is non-ionic neutral compound, while MB and MO are charged molecules containing cationic and anionic groups, respectively. Figure 2 show the release curves of a BPAA, an anti-inflammatory and analgesic drug. Compared to homo PHEMA, the initial release rate and the level of released drug in a given time were higher in

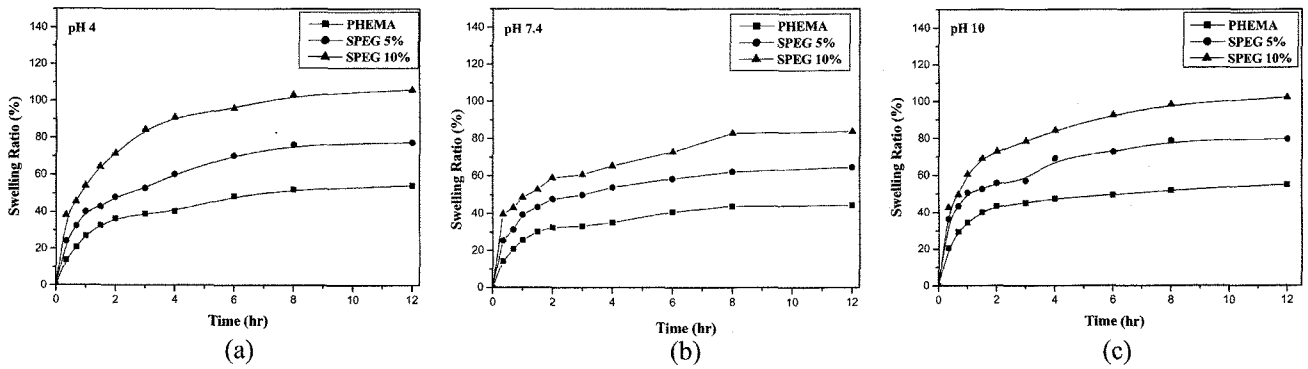


Figure 1. The swelling curves of sulfonated PEG modified PHEMA gels with pH at 37 °C. (a), pH 4, (b) pH 7.4, and (c) pH 10.

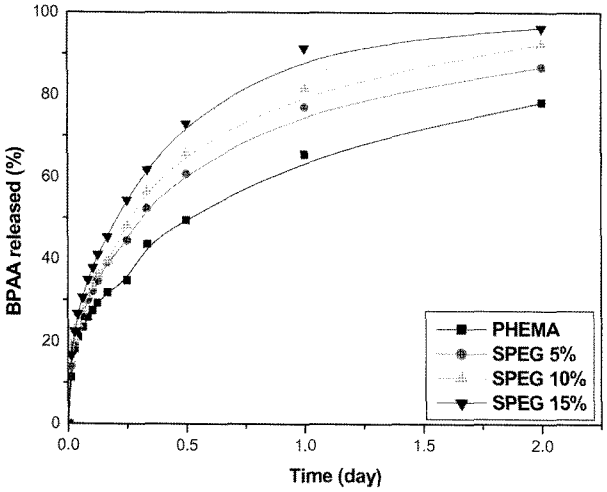


Figure 2. The release of BPAA from SPEG-modified PHEMA hydrogel.

SPEG-graft PHEMA hydrogels, and the release rate of drug tended to increase in proportion to the PEG content. Overall the release seemed to be governed by simple diffusion reflecting the increased swelling of the SPEG modified hydrogels in this release behavior of a small neutral molecule.

It was interesting to incorporate ionic compounds as model drugs and study the release behavior in this modified PHEMA hydrogel because the PEG tethers possess anionic sulfonate moiety on the chain end. The specific interactions between matrix and drug molecules are expected to influence the drug release behavior, especially when the drug molecules are charged in aqueous solution. In Figures 3 and 4, the release curves of cationic MB and anionic MO are represented, respectively. As shown in Figure 3, the release rate was slower in SPEG modified gels and the release was more retarded at higher SPEG content in all different pHs. Interestingly, this result is totally the reverse of swelling degree, suggesting a strong interaction between the gel matrix and drug molecules. The retarding effect which surpass the increased pore volumes within the gel network are thought to be originated from electrostatic interaction between cationically charged MB molecule and anionic sulfonate moiety on the PEG tether within the hydrogel matrix. The strong binding between groups with opposite charge should be responsible for this lowered release rate and retention of drugs inside gels. On the contrary, the release behavior of anionic MO exhibited normal pattern with increased release rate from the SPEG containing gels (Figure 4). At the higher SPEG content, the release was accelerated and seemed to reach an off-constant value rather early compared to the case of MB release. In addition this tendency was more pronounced in alkaline medium of pH 10.

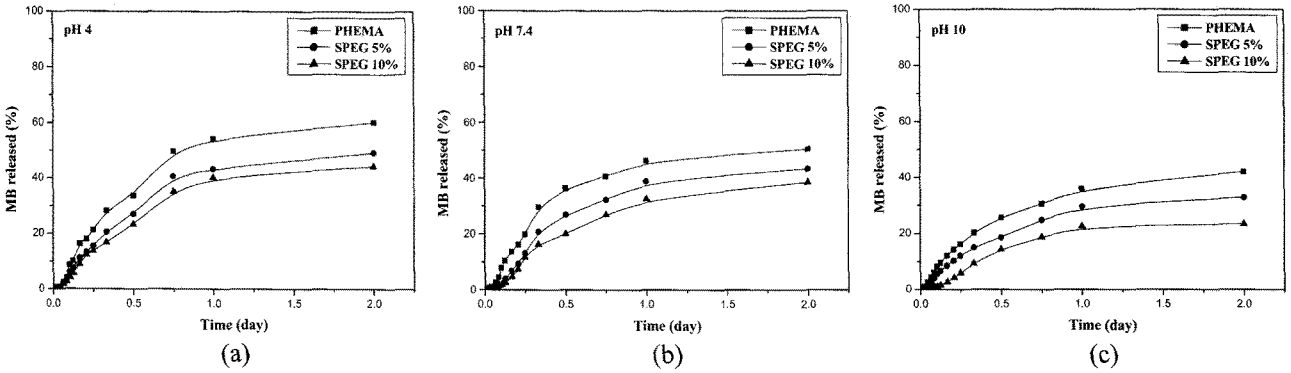


Figure 3. Release behavior of MB from the SPEG modified PHEMA hydrogels in different pH at 37 °C. (a) pH 4, (b) pH 7.4, and (c) pH 10.

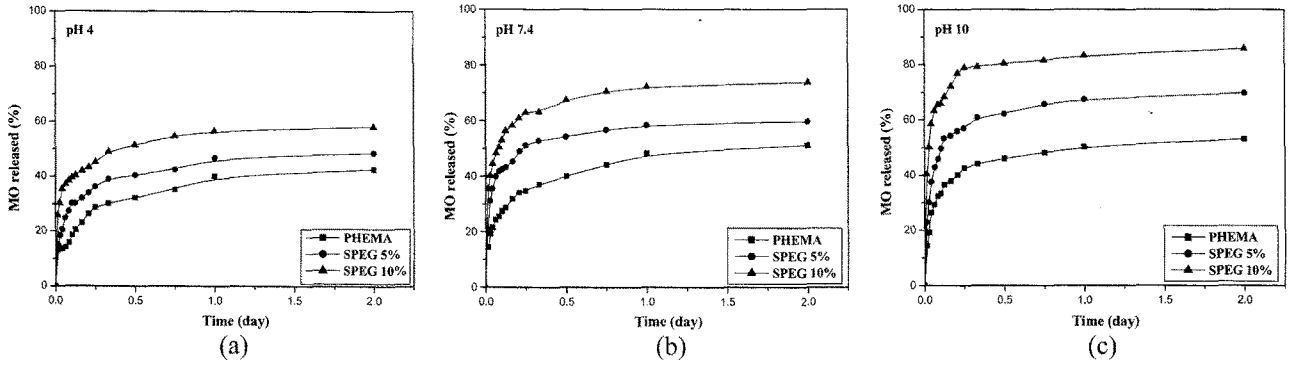


Figure 4. Release behavior of MO from the SPEG modified PHEMA hydrogels in different pH at 37 °C. (a) pH 4, (b) pH 7.4, and (c) pH 10.

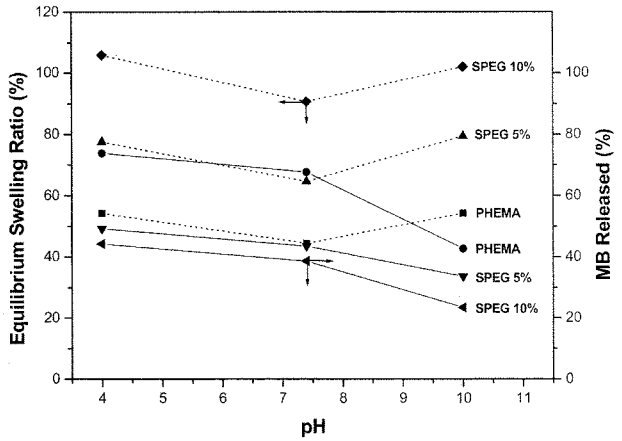


Figure 5. Equilibrium swelling and the release amount of MB in different pH at 37 °C.

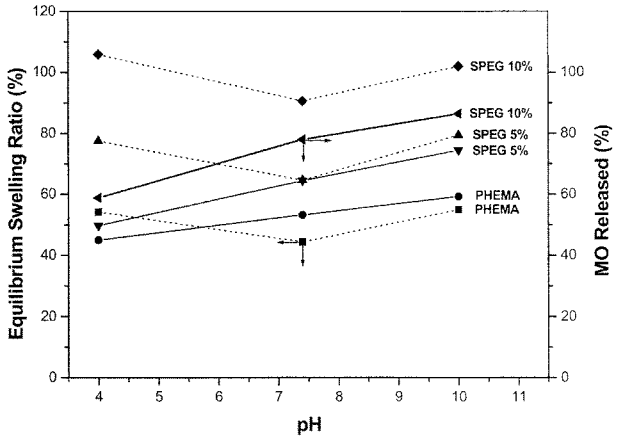


Figure 6. Equilibrium swelling and the released amount of MO in different pH at 37 °C.

Presumably the release of anionic MO molecule increase parallel with swelling degree as expected, however, some electrostatic repulsion between the same charges of molecules may contribute to enhance the release rate in this system. The influence of pH to the release behavior was discussed further below.

Figures 5 and 6 showed the total amount of drug released until the release rate reached to approximately zero in different pH of solution for the compound MB and MO, respectively. As shown in Figure 5, the percentage release of MB decreased as the SPEG content. As discussed earlier, this result might be due to the electrostatic attraction between cationically charged MB molecule and anionic sulfonate moiety on the PEG within the hydrogel matrix. On the other hand, the percentage of MB release gradually decreased as the pH of solution increased from pH 4 to pH 10. Much lowered values at pH 10 in the released amount of MB are in contrast to the higher swelling degrees of gels when the properties are compared each other with those at pH 7.4. At higher pH of medium, the partial dissociation of hydroxyl

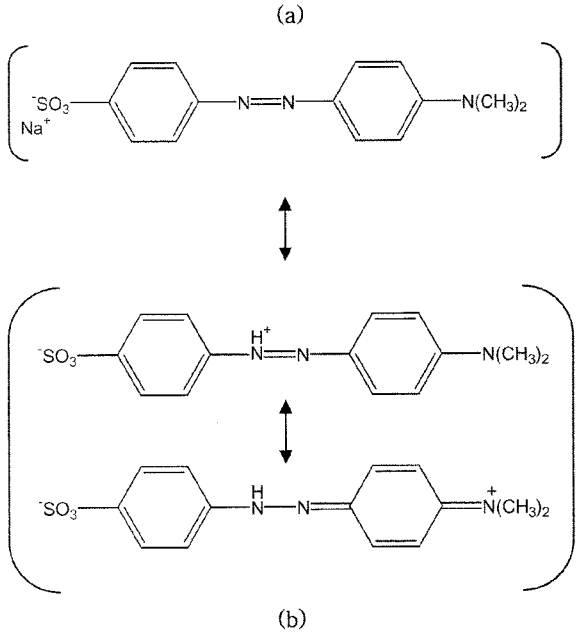


Figure 7. The molecular structures assumed by MO depending on pH of medium.

groups on the polymer backbone should increase the attractive interaction with the cationic MB molecules, resulting in the retarded release of drugs.

In case of MO molecule as the results are plotted in Figure 6, the release amount of MO was increased monotonously as the pH increased. In contrast to the release behavior of MB, the release at pH 7.4 was higher than that of pH 4 in spite of the lower swelling degree. This result might be attributed to the equilibrium structure of MO molecule existing in different pH, which can alter the molecular interaction with substrate. At lower pH the equilibrium shift from structure (a) to structure (b), resulting in the increased electrostatic interaction with anionic pendent groups on the gel matrix (see Figure 7).

In summary, the release behaviors of MO and MB, as ionic charged molecules, are strongly influenced by the electrostatic interactions due to the sulfonate pendant group within the gel network in addition to the effects of swelling degree of gels and pH of the aqueous solution.

Conclusions

The modified PHEMA hydrogel containing sulfonated PEG tether was prepared and the drug incorporation and release behavior was investigated to elucidate the effect of swelling and the ionic sulfonate groups on the PEG chain end. By using the model drugs including biphenyl acetic acid (BPAA), cationic methylene blue (MB), and anionic methyl orange (MO), it was found that the drug release behavior was significantly influenced by the electrostatic

interactions between drug molecules and the inner surface nature of gel matrix to modulate the capacity and release rate of drugs.

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