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pH-Sensitive Keratin-Based Polymer Hydrogel and Its Controllable Drug-Release Behavior

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ABSTRACT: Using feather keratin as biocompatible and inexpensive natural biopolymer and methacrylic acid as a functional monomer, we prepared a pH-sensitive feather-keratin-based polymer hydrogel (FKPGel) with grafted copolymerization. The obtained FKPGel was characterized by Fourier transform infrared spectroscopy, thermogravimetric analysis, and scanning electron microscopy. The swelling behavior and pH sensitivity of the FKPGel were investigated. When the small molecule (rhodamine B) and macromolecule (bovine serum albumin) were used as model drug molecules, the FKPGel exhibited controllable release behavior *in vitro,* and the hydrogels had pH sensitivity. For a small molecular drug, the cumulative release rate was 97% in 24 h at pH 8.4. For macromolecular drug, the cumulative release rate reached 89% at pH 7.4. Its release behavior could be controlled by the pH value. In summary, a simple method was found to reuse disused feathers. It is a kind of pH-sensitive hydrogels to be applied in drug-delivery systems.
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INTRODUCTION

During the last 2 decades, significant efforts have been made toward diminishing the impact of human beings on the environment. After this tendency, an attempt was made to replace synthetic polymers derived from petroleum. The exploitation of biomaterials derived from renewable resources is an important approach for solving environmental and resource problems. In this sense, biopolymers are an important alternative. Nevertheless, some properties of biopolymer materials must be improved, so that they can compete with fossil derivatives. Several proteins, such as collagen, albumin, gelatin, fibroin, and keratin, have been investigated for the development of naturally derived biomaterials.[1] Among these proteins, keratin has wide varieties of resources, and its price is very low. Keratin-based materials show promise for revolutionizing the world of biomaterials because of their biocompatibility, biodegradability, and mechanical durability.2 Environmentally sensitive materials are promising candidates in smart bioengineering systems.[3] Among different kinds of stimuli, pH is the most widely used because it is easy to control and has practical advantages both *in vitro* and *in vivo*.[4] As a classic example of such pH-sensitive polymer materials, poly(methacrylic acid) (PMAA) has been studied for diverse biomedical applications because of its biocompatibility.[5] Keratin is a kind of major structural fibrous protein and is the main component in feathers and animal hair; it provides outer coverings, such as hair, wool, feathers, nails, and horns in mammals, reptiles, and birds. It has a high content of cysteine and serine and a large number of hydroxyl amino acids. Keratin contains a certain number of noncovalent interactions, such as electrostatic interactions, hydrogen bonding, and hydrophobic interactions, and covalent interactions (disulfide).[6] Keratin is a good biocompatible material with outstanding properties; this makes extremely valuable in biomedical fields.[7] Because of their degradable properties, attention has been paid to keratin-based materials. Hydrogels are polymeric networks that maintain a three-dimensional structure when they are swollen in water.[8] In this study, the keratin was modified by grafting copolymerization with a functional monomer, methacrylic acid (MAA); this afforded a feather keratin-based polymer hydrogel (FKPGel), a kind of pH-sensitive hydrogel. This was also applied to loading drugs, and its drug-release properties were investigated. In addition, because the protein was used as a natural backbone, we expected that the resulting gels would show more compatibility with human bodies.[9] This will pave the way for further developments in the future.

EXPERIMENTAL

Materials and Reagents

Feather keratin (FK) was extracted from chicken feathers with our published method,[10] and its protein content was 93%. Dithiothreitol (DTT) was obtained from Beyotime Institute of Biotechnology. MAA was produced by Tianjin Guangfu Fine Chemical Research Institute, and it was purified by vacuum

distillation before use. *N,N*-Methylene bisacrylamide [BIS; analytical reagent (AR)] was produced by Tianjin Chemical Reagent Research Institute. Ammonium persulfate (APS; AR) was obtained from Laiyang Both Chemical Reagent Factory and recrystallized before use. Bovine serum albumin (BSA) was obtained from Aladdin. Other reagents, such as rhodamine B (RB), ethanol (EtOH), sodium carbonate (Na_2CO_3), sodium chloride (NaCl), magnesium sulfate ($MgSO_4$), calcium chloride ($CaCl_2$), sodium hydroxide (NaOH), and urea were AR grade and were commercially obtained. Physical saline (Sal), a D-glucose solution (Glu), a urea solution, a synthetic urine solution (Syn Uri), and double-distilled water (DDW) were used to prepare solutions for simulating physiological conditions. The concentration of the phosphate buffer solution (PBS) was 0.2 mol/L.

Instrumental Analysis

All of the samples used were dried in a lyophilizer (FD-1D-50, Beijing Changliu Sci Instruments Co., Ltd. China) for 12 h. Fourier transform infrared (FTIR) spectra were measured on an FTIR spectrometer (FTS 3000) of DigiLAB, The transmittance spectra were collected in the range 4000–400 cm^{-1} at a resolution of 1.93 cm^{-1}. The morphologies of the dried hydrogels structures were studied by scanning electron microscopy (SEM) of Zeiss Ultra Plus. Thermogravimetric analyses (TGAs) of the hydrogels were carried out on a PerkinElmer Pyris Diamond thermogravimetry (TG)/dynamic thermal analyzer at a heating rate of 10°C/min under a nitrogen atmosphere. The UV spectrophotometer (Agilent 8453) were used to measure the release behaviors of RB and BSA in PBS by the calibration curves.

Preparation of the FKPGel

First, 0.25 g of FK was dispersed into 25 mL of urea solution (8 mol/L) with stirring at 65°C for 2 h under an N_2 atmosphere. Then, with the addition of 2 mL of DTT solution (2.59 mmol/L), FK was reduced for 30 min. Second, 2 mL of the MAA solution (50% neutralization degree), 0.25 g of BIS (1.62 mmol/L), and 0.17 g of APS (17.5 mmol/L) were added dropwise with stirring. Then, 0.25 g of $NaHCO_3$ (2.98 mmol/L) was added and continuously stirred until the bubbles disappeared. Third, the mixture was moved into reaction vials and kept at 65°C for 2 h in a water bath; this afforded FKPGel. To remove the homopolymer and unreacted materials, the hydrogel was immersed and washed with EtOH and water separately for 24 h. With freeze drying, the FKPGel was obtained and stored in a desiccator.

Swelling Behaviors of the FKPGel

The swelling ratios (SRs) of the hydrogel were measured in different physiological solutions. First, some solutions, including Sal, Glu, urea, and Syn Uri, were chosen as simulating physiological conditions. The preparations of these solutions were as follows: (I) Sal: 0.9 g of NaCl + 100 mL of DDW, (II) Glu: 5 g of Glu + 100 mL of DDW, (III) Syn Uri: 0.8 g of NaCl + 0.1 g of $MgSO_4$ + 2 g of urea + 0.06 g of $CaCl_2$ + 100 mL of DDW, and (IV) urea: 5 g of urea + 100 mL of DDW. Second, 0.1 g of a dried FKPGel was placed in each glass vial, each of which contained one of the previously discussed simulated physiological solutions at 37°C. After 3 days of soaking, the swollen FKPGels were taken out from the previous solutions. They were carefully washed by DDW and were quickly wiped with blotting paper. Then, the swollen FKPGels were weighed. The SR (g/g) of the FKPGel was calculated according to eq. (1):

$$SR = W_s / W_d \quad (1)$$

where W_s and W_d are the weights of the swollen FKPGel and dried FKPGel samples, respectively. All of the experiments were carried out in triplicate, and the average values were reported. The swelling of the samples was also evaluated in different concentrations of NaCl and $CaCl_2$ salt solutions.

Drug Load and Release Experiments

The FKPGel was saturated in the solution of the model drug, such as RB (1 mg/mL) or BSA (10 mg/mL), at room temperature for 3 days. After swelling equilibrium was reached, the drug-loaded FKPGel was taken out and rinsed with DDW. Then, it was added to 50 mL of PBS for drug release. At predetermined time intervals, 5-mL aliquots were collected from the PBS release media, and another 5 mL of fresh PBS was added to the release media. The released RB (552 nm) or BSA (280 nm) in PBS was monitored with a UV spectrophotometer by a calibration curve. The release experiments were performed in triplicate. The cumulative amount percentages of released RB and BSA were calculated with eq. (2):

$$\text{Cumulative release}\,(\%) = \sum M_t / M_0 \times 100 \quad (2)$$

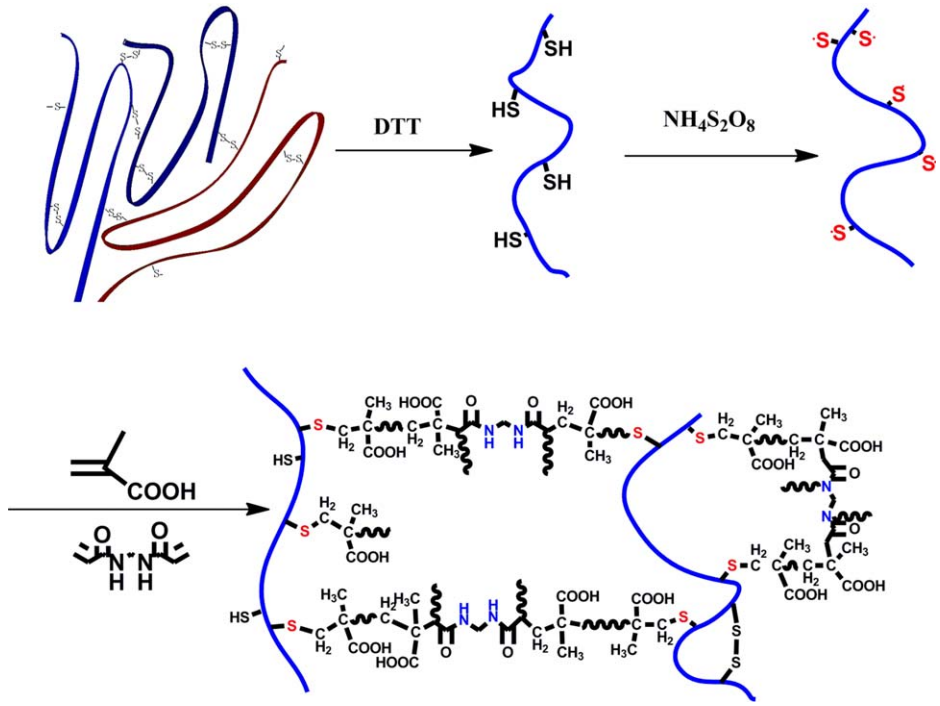
where $\sum M_t$ is the total weight of released drug at time t and M_0 is the total adsorbed drug in the hydrogel.

RESULTS AND DISCUSSION

Preparation of the FKPGel

As a natural polymer, FK is a kind of typical protein extracted from chicken feathers. It contains rich sources of hydrophobic amino acids and disulfide bonds (—S—S—); this increases its stability and stiffness.[11,12] There were many functional groups along the molecular chains of FK, including —OH, —NH_2, —COOH, and —SH. Active sites were formed on these groups where the functional monomers could be grafted.[13,14] In general, FK should be dissolved or dispersed in proper solvents before it is processed into other applications as the dispersant can make the FK chains stretch. Amino, carboxyl, and disulfide bonds will be exposed.[15] Here, the urea solution (8 mol/L) was applied to dissolve FK. Then, the reducing agent (DTT) was used to reduce the disulfide bonds to thiol groups. After the addition of the monomer (MAA) and crosslinker (BIS) and initiation with APS, the PMAA chains were grafted on the thiol group of the FK chains by grafted copolymerization (Scheme 1). PMAA was used as a typical pH-sensitive material to modify the physicochemical properties of FK. It would be helpful to widen the applications of FK and improve the properties of the FKPGel.

The obtained FKPGel was washed by water and EtOH to remove the unreacted materials and impurities.[16] With vacuum freeze drying, the dry FKPGel was obtained. The morphologies of the FKPGel under different conditions are shown in Figure 1. The fresh wet FKPGel with water was nearly transparent (I). After the gel was soaked in EtOH for 24 h, the FKPGel lost moisture and became denser. However, its shape remained (II).



Scheme 1. Reaction mechanism of the PMAA-grafted FK. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Its volume enlarged after it was immersed in DDW. The FKPGel became transparent with swelling (III). After it was washed with EtOH and DDW and lyophilized, the dried FKPGel shrank greatly and formed a porous structure (IV).

The porous structure of the FKPGel was beneficial for drug loading and release. This was been confirmed by Berg et al.'s[17] results, which show that the porous materials could load drugs, such as ketoprofen and cytochalasin D, and provided controllable release. Similarly, the obtained dried FKPGel with a porous structure could be applied in drug-delivery systems as well.

Characterization of the FKPGel

FTIR Analysis. The FTIR spectra of the FKPGel and materials are depicted in Figure 2. The broad peaks of PMAA appeared at 1700 and 1180 cm^{-1} and corresponded to C═O and C—O stretching vibrations, respectively. FK showed characteristic absorption peaks near 1643, 1527, and 1237 cm^{-1} and were assigned to peptide bonds (—CO—NH—), which originated bands known as amide I, amide II, and amide III, respectively. Amide I is useful for the analysis of the secondary structure of the proteins, is mainly related to C═O stretching, and occurs in the range 1700–1600 cm^{-1}. Amide II, which falls in the 1540–1520-cm^{-1} range, is related to N—H bending and C—H stretching vibrations.[18,19] Amide III occurs in the range 1220–1300 cm^{-1}, and it results from C—N stretching vibrations and C═O bending vibrations. The peaks at 990 and 580 cm^{-1} were characteristic absorption peaks of C—S and S—S bonds.[20,21] In a comparison of the FTIR spectra of the FK, FKPGel, and PMAA, the presence of the FKPGel was confirmed by the characteristic peaks at 1665 and 1180 cm^{-1}. The peaks at 1650, 1528, 1232, and 680 cm^{-1} were assigned to the characteristic absorption peaks of the FK amide I, amide II, amide III, and amide IV.[22] The broad band at

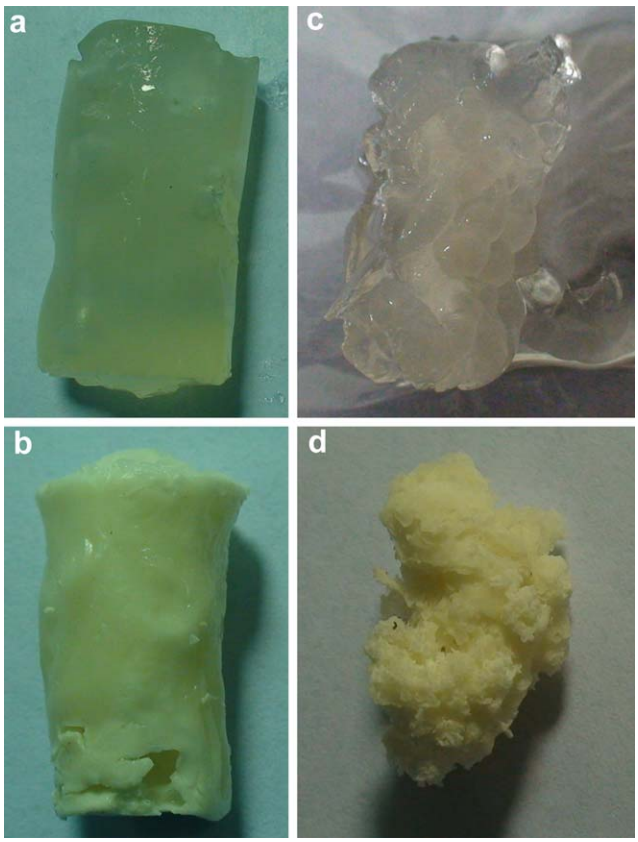


Figure 1. Photographs of the FKPGel under different conditions: (a) fresh FKPGel, (b) swollen FKPGel in EtOH, (c) swollen FKPGel in H_2O, and (d) dried FKPGel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

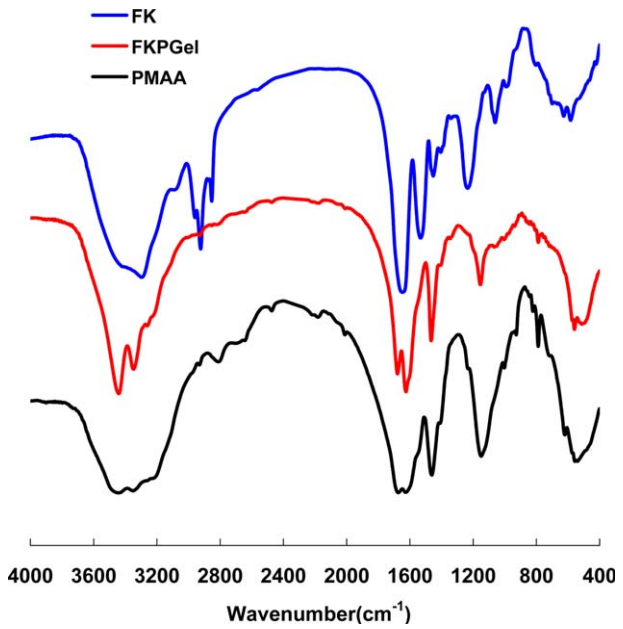


Figure 2. FTIR spectra of the FK, FKPGel, and PMAA polymer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

3200–3600 cm^{-1} was attributed to the stretching vibrations of the —NH and —OH groups of the FKPGel.

TGA. The TG–derivative thermogravimetry curves of the FK and FKPGel are presented in Figure 3. There were three stages in the process of thermal decomposition. The water was lost in the first stage at about 100°C. In the curves of FK, the weightlessness starting from 200°C was mainly caused by the thermal decomposition of FK. It was obvious that the TG–derivative thermogravimetry curves of the FK and FKPGel were quite different. There were two distinct weightlessness regions at 160–250 and 250–350°C for FKPGel; this was primarily due to the degradations of FK and PMAA. That indicated that FK was more stable than FKPGel. After the formation of the gel with PMAA, the skeleton of FK became loose and easily degraded. The decomposition temperature of the FKPGel became lower.

SEM. The SEM images of the dried FKPGel, pure FK, and synthetic polymer (PMAA) are shown in Figure 4. It shows that the surface of FK was compact with small protrusions. The surface morphologies of PMAA showed granular structures with uneven grain sizes. After the formation of the FKPGel, it exhibited a sponge with porous structure. This means that PMAA chains were completely dispersed in keratin chains with grafted copolymerization. Similar results were also reported in the literature.[23,24] Obviously, a denser network was hard to collapse when the FKPGel was subjected to a compression load, and it showed a stronger compression strength.[25,26] Here, the addition of PMAA modified the surface morphology of the FK, and the hydrophilicity of the FK increased. BIS was used to extend the chemical crosslinking. Therefore, after compositing with the PMAA chains, the obtained FKPGel appeared in porous structures.

Swelling Behavior in Different Simulated Physiological Fluids. The SR is a very important parameter because it describes the amount of stored water in hydrogel and water retention. As we know, the swelling behavior of the hydrogel is the result of osmotic pressure and the restoration of elastic pressures. Variations in the pH value always occur at several body sites, including the gastrointestinal tract, vagina, and blood vessels.[27] The appearance of solute in the surrounding aqueous medium is able to tilt this balance; this leads to changes in the swelling behavior of the hydrogel. To widen the application fields of the FKPGel, its swelling phenomena were investigated in simulated biological fluids, including Sal (pH 7.0), Syn Uri (pH 6.5), urea (pH 7.8), and Glu (pH 4.5) solutions (Figure 5). Compared with DDW, the SRs of the FKPGel were appreciably reduced in the biological fluids; this was similar to reported phenomena.[28,29] The SRs of the FKPGel in the Glu and urea solutions were higher than those in Sal or Syn Uri. The SRs decreased as follows: DDW > Glu > Urea > Sal > Syn Uri. The reason was that the FKPGel was pH sensitive, and its swelling properties varied at different pH values. In addition, the SRs of the FKPGel in Sal and Syn Uri were similar to those in the physiological Sal (SR = 45.6 g/g). The reason was that the FKPGel was pH sensitive and salt sensitive. Therefore, its swelling properties varied under different simulated physiological solutions. NaCl is the main component in physiological Sal and makes a primary contribution during the swelling process.[30]

The swelling behavior of the hydrogel in salt solutions is of prime importance in many practical applications, especially the field of medicine. As shown in Figure 6, the FKPGel exhibited low SR in the solutions of NaCl and $CaCl_2$. The reason was as follows. Under neutral conditions, the carboxyl groups of the FKPGel were ionized, and this led to the hydrophilicity of the FKPGel, electrostatic repulsion between the backbones, and a further increase in SR. With addition of NaCl and $CaCl_2$, the repulsion between charged carboxyl groups reduces. Thus, SR decreased with increasing NaCl and $CaCl_2$ concentrations.[31,32] The results hereby were similar to eq. (3), a well-known relationship between the SR and concentration of inorganic salt solutions:[33]

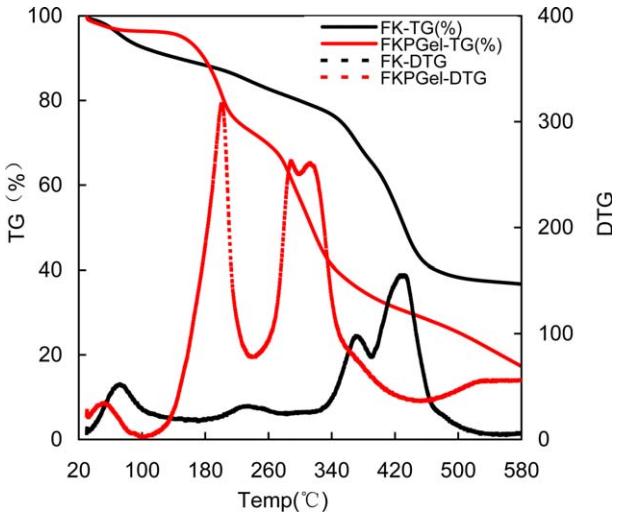


Figure 3. TGA curves of the FK and FKPGel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

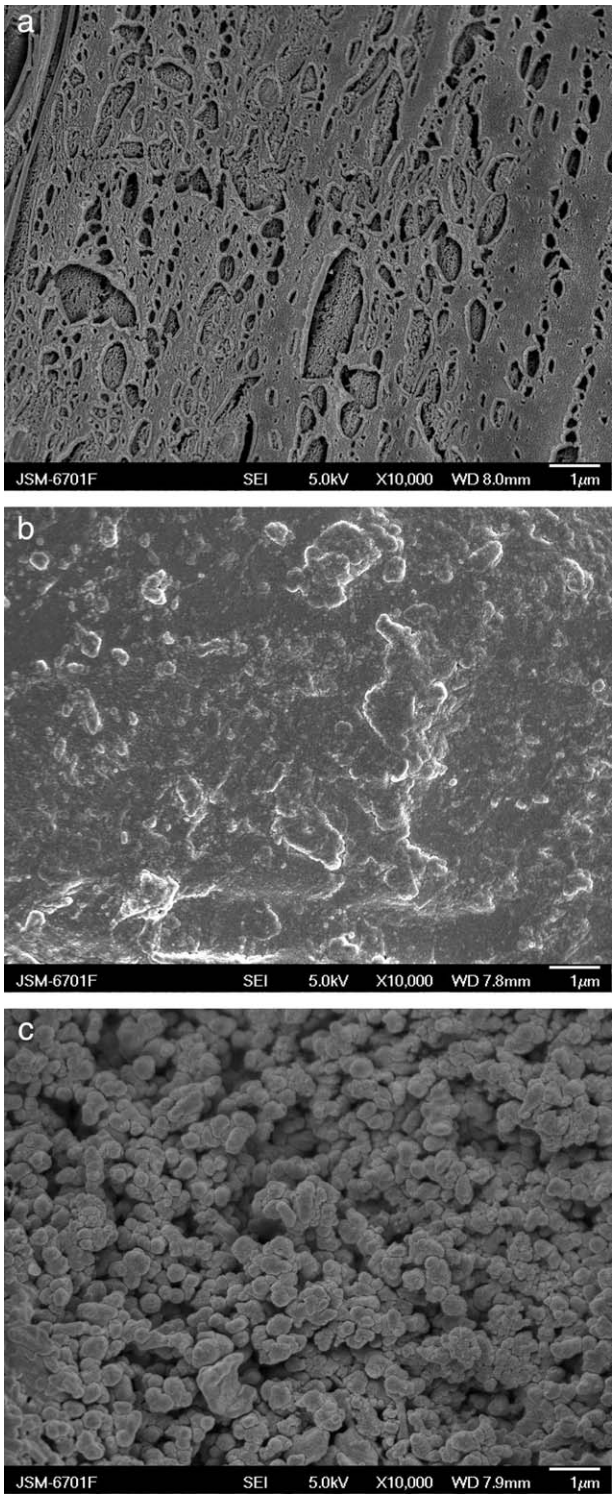


Figure 4. SEM images of the (a) FKPGel, (b) PMAA, and (c) FK.

$$SR = k[salt]^{-n} \quad (3)$$

where k and n are constant values for an individual FKPGel. The k value is the swelling at a high concentration of salt, and the n value is a measure of the salt sensitivity.

FKPGel Dynamics in Salt Solution. Figure 7 shows the deswelling dynamics of the FKPGel in the 0.1 mol/L NaCl solutions.

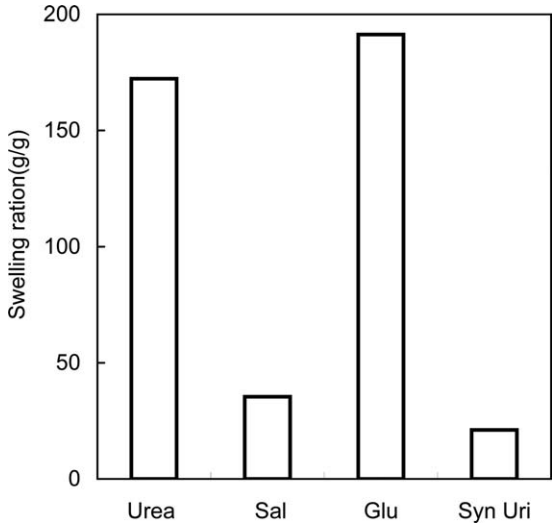


Figure 5. Effects of the simulated biological solutions on the SR of the FKPGel at 37°C.

First, the dried FKPGel was put into DDW and reached swelling equilibrium. Then, it was put into the NaCl solution. The swollen FKPGel gradually shrunk, and water was lost at the same time. The FKPGel volume and weight decreased. The water retention ratios of the FKPGel decreased to 67.4 and 51.9% after 3 and 9 h, separately. This indicated that the polymer chain of the FKPGel stretched in water and then shrunk in Sal. Its water retention ratio gradually decreased and finally reached swelling equilibrium. The water retention ratio reached 44% in 24 h. Accordingly, the shrinkage of the FKPGel was based on the assumption that electrostatic interactions dominated; that is, the binding of the sodium ions to the carboxylate groups was mainly ionic. This suggested that the binding between the FKPGel and the sodium ions was dominated by specific interactions.[34] In conclusion, FKPGel in Sal possessed the smart

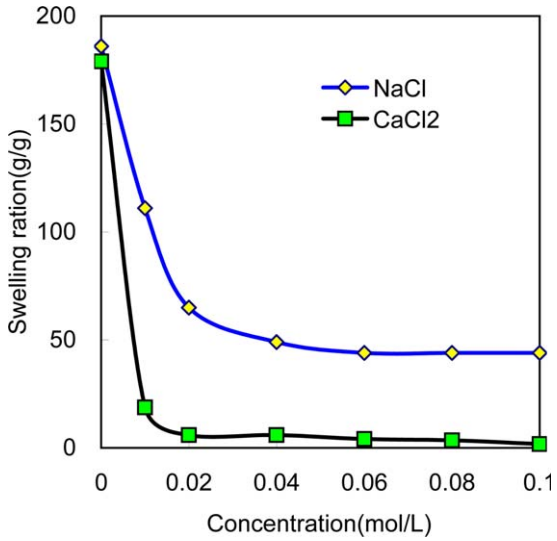


Figure 6. Effects of the salt concentration (NaCl and $CaCl_2$) on the SR of the hydrogel. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

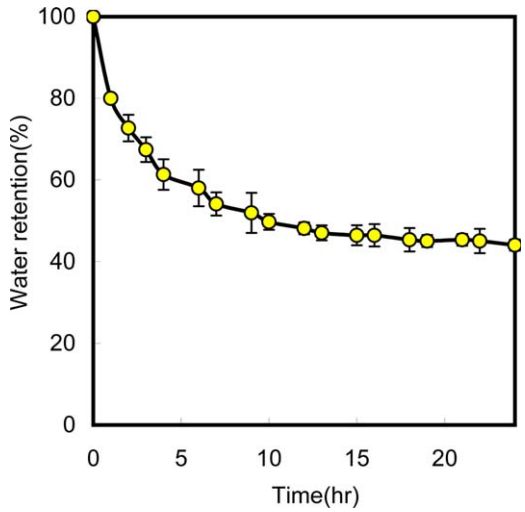


Figure 7. Deswelling kinetics of the FKPGel in a 0.1 mol/L NaCl solution at 37°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

behavior of swelling–deswelling; this played an important role in the application of biomimetic materials.

Controllable Release Behavior of the FKPGel. In the design of oral dosage forms, the formulator must consider that the natural pH environment of the gastrointestinal tract varies from acidic in the stomach to slightly alkaline in the intestine. It is known that the fasting pH of the stomach is about 2.0–6.0, and the pH value in the duodenum is about 6.0–6.5. The pH of the small intestine is about 7.0, with that of the distal part as high as 8.0.[35,36] In the presence of food, the pH values in the stomach and duodenum changes along with food ingestion.[37]

Hydrogels have several advantages, including a simple preparation, efficient drug loading without chemical modification of the parent drug, and controlled drug release. To investigate the controllable behavior of the FKPGel for the drug-release rate *in vitro*, RB and BSA were loaded into the FKPGel. RB was used as a small molecular compound, and BSA was used as a macromolecular model drug.[38]

RB Release from the FKPGel. First, RB, the small molecular compound, was loaded in the FKPGel. The loading efficiency and encapsulation efficiency of the FKPGel were 37.6 and 48.1%, respectively. Then, RB was released at 37°C at different pH values. The relationship between cumulative release ratio (percentage) and time (hours) is shown in Figure 8. In the acidic environment (pH 3), the small molecular drug (RB) released quickly from the FKPGel. However, after 2 h, the cumulative release ratio became very slow. Only 60% of the loaded RB was released after 8 h. The reason was that the FKPGel was easy to shrink in acid solution. Therefore, RB was imprisoned in the FKPGel, and the release ratio decreased quickly. With increasing pH value, the RB cumulative release rate increased. Both in a neutral environment (pH 7.4) and in the alkaline solution (pH 8.4), more than 90% of loaded RB was released after 8 h. As the FKPGel was a pH-sensitive drug carrier, the drug release was controlled by the adjustment of the pH value. With sufficient swelling of the FKPGel, the diffusion of the drug molecules was much easier. So the release in the alkaline solution was much faster than that in the acidic environment.

We found that FK could be extracted from feathers and could be applied to prepare films.[10] The obtained FK films could be applied to load model drugs, such as RB. However, FK could not be used to prepare hydrogels. Here, FKPGel, a pH-sensitive polymer hydrogel, was prepared with graft copolymerization. This pH-sensitive FKPGel could preserve the loaded bioactive molecules in the acidic environment and release the payload rapidly, so FKPGel cannot be used as an oral drug carrier. Therefore, it may be a promising candidate as a topical drug carrier.

BSA Release from the FKPGel. For macromolecular BSA, the FKPGel loading efficiency and encapsulation efficiency were 26.8 and 35.5%, respectively. FKPGel was used for BSA release, and its accumulative release rates at different pH values are shown in Figure 9. The drug burst release period and stagnant release period of the FKPGel were different with changing environments. In the acidic environment (pH 3.0), 40% of BSA was released in the first 2 h. Its initial burst release period was 2 h. After that, only 5% of BSA was released in the following 22 h (stagnant release period). In a neutral environment (pH 7.4), 58% of BSA was released in the initial burst release period (2 h), and 31% of BSA was released in a stagnant release period. The accumulative release rate reached 89% in 24 h. In the alkaline solution (pH 8.4), 40% of BSA was released in the initial burst release period (2 h), but 28% of BSA was released in the stagnant release period, and the accumulative release rate reached 68% in 24 h. The reasons were as follows: First, acting as a macromolecular model drug, BSA encountered more resistance during its release from the FKPGel. Therefore, its release time was longer. Second, BSA was positively charged under acidic conditions (pH 3), and the carboxyl group of the FKPGel played a role of negative charge by electrostatic attraction. BSA was difficult to release from the

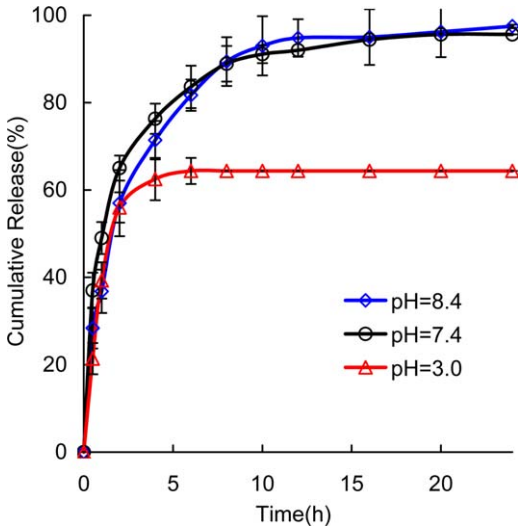


Figure 8. Release of RB from the FKPGel in PBS at 37°C with different pH values *in vitro*. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

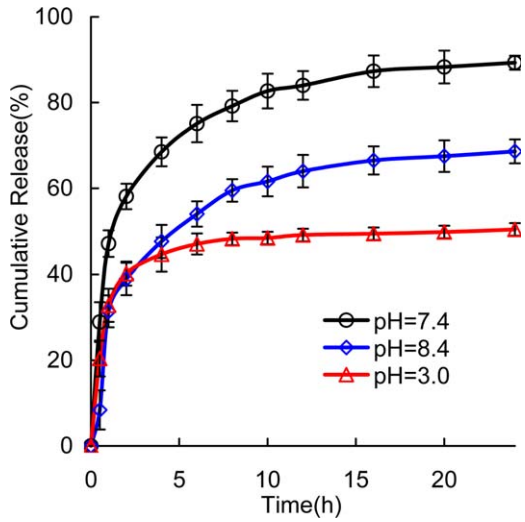


Figure 9. Release BSA behavior of the FKPGel at 37°C under different pH values *in vitro*. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FKPGel. When the pH was higher than its pI (pH > 5), BSA was easy to release from the FKPGel.

It was found that animal and plant proteins could be applied in medicine delivery systems.[39] Soy protein isolate (SPI) and zein could be mixed for preparing microspheres and used as delivery systems for nutraceutical products in functional foods.[40,41] Song and Zhang[42] reported that SPI could be used to prepare SPI gels, which could be used for the loading and release of drugs. However, its accumulative release rates were only about 20% at pH 1.2 and 63% at pH 7.4. On the basis of previous results, the FKPGel release rate was higher. However, BSA could be easily released in neutral and alkaline environments. Clearly, this type of the FKPGel is suitable for short-term drug release, including treatment plans measured in hours or days. Therefore, the FKPGel could be used as a suitable polymeric carrier for topical drugs.

CONCLUSIONS

A novel pH-sensitive hydrogel (FKPGel) was prepared by graft copolymerization and characterized by IR, TGA, and SEM. FKPGel exhibited a high water absorption. The use of small molecules (RB) and macromolecules (BSA) as model drug molecules, the release behaviors of the FKPGel were investigated. For small molecular drugs, its cumulative release rate was 97% in 24 h at pH 8.4. Although for macromolecular drugs, its cumulative release rate reached 89% at pH 7.4. Its release behaviors were controlled by the adjustment of the pH value. Compared with small molecular drugs, the releasing time of the macromolecular drugs was longer, and the controlled behaviors were better. Meanwhile, FKPGel is an attractive candidate in the biomedical field.

ACKNOWLEDGMENTS

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REFERENCES

1. Pritchard, E. M.; Kaplan, D. L. *Expert. Opin. Drug Delivery* **2011**, *8*, 797.
2. Balaji, S.; Kumar, R.; Sripriya, R.; Kakkar, P.; Ramesh, D. V.; Reddy, P.; Sehgal, P. K. *Mater. Sci. Eng.* **2012**, *32*, 975.
3. Qiu, Y.; Park, K. *Adv. Drug Delivery Rev.* **2001**, *53*, 321.
4. He, C. L.; Kim, S. W.; Lee, D. S. *J. Controlled Release* **2008**, *127*, 189.
5. Yoo, H. S.; Kim, T. G.; Park, T. G. *Adv. Drug Delivery Rev.* **2009**, *61*, 1033.
6. Verbeek, C. J. R.; van den Berg, L. E. *Macromol. Mater. Eng.* **2010**, *295*, 10.
7. Meier, C.; Welland, M. E. *Biomacromolecules* **2011**, *12*, 3453.
8. Chen, S. H.; Tsao, C. T.; Chang, C. H.; Lai, Y. T.; Wu, M. F.; Liu, Z. W.; Hsieh, K. H. *Macromol. Mater. Eng.* **2013**, *298*, 429.
9. Pourjavadi, A.; Salimi, H. *Ind. Eng. Chem. Res.* **2008**, *47*, 9206.
10. Yin, X. C.; Li, F. Y.; He, Y. F.; Wang, Y.; Wang, R. M. *Biomater. Sci.* **2013**, *1*, 528.
11. Yang, C.; Song, X.; Sun, C.; Chen, M.; Xu, Y.; Liu, X.; Ni, Z. *J. Appl. Polym. Sci.* **2006**, *102*, 4023.
12. Yuan, Z.; Zhao, X. X.; Zhou, M. H. *Adv. Mater. Res.* **2013**, *647*, 195.
13. Furuzono, T.; Ishihara, K.; Nakabayashi, N.; Tamada, Y. *Biomaterials* **2000**, *21*, 327.
14. Liu, Y.; Zhang, Y.; Liu, Z.; Deng, K. *Eur. Polym. J.* **2002**, *38*, 1619.
15. Nayak, P. L.; Lenka, S.; Pati, N. C. *J. Appl. Polym. Sci.* **1979**, *23*, 1345.
16. Gao, X.; He, C.; Xiao, C.; Zhuang, X.; Chen, X. *Polymer* **2013**, *54*, 7.
17. Berg, M. C.; Zhai, L.; Cohen, R. E.; Rubner, M. F. *Biomacromolecules* **2006**, *7*, 357.
18. Vasconcelos, A.; Freddi, G.; Cavaco-Paulo, A. *Biomacromolecules* **2008**, *9*, 1299.
19. Aluigi, A.; Zoccola, M.; Vineis, C.; Tonin, C.; Ferrero, F.; Canetti, M. *Int. J. Biol. Macromol.* **2007**, *41*, 266.
20. Shao, J.; Zheng, J.; Liu, J.; Carr, C. M. *J. Appl. Polym. Sci.* **2005**, *96*, 1999.
21. Ha, S. W.; Tonelli, A. E.; Hudson, S. M. *Biomacromolecules* **2005**, *6*, 1722.
22. Gobin, A. S.; Froude, V. E.; Mathur, A. B. *J. Polym. Sci. Part B: Polym. Phys.* **2005**, *74*, 465.
23. Keleş, S.; Güçlü, G. *Polym.–Plast. Technol.* **2006**, *45*, 365.
24. Jyothi, A. N.; Sajeev, M. S.; Moorthy, S. N.; Sreekumar, J. *J. Appl. Polym. Sci.* **2010**, *116*, 337.

25. Voepel, J.; Edlund, U.; Albertsson, A. C. *J. Polym. Sci. Part A: Polym. Chem.* **2009**, *47*, 3595.
26. Alonso-Sande, M.; Teijeiro-Osorio, D.; Remuñán-López, C.; Alonso, M. *J. Eur. J. Pharm. Biopharm.* **2009**, *72*, 453.
27. Gupta, P.; Vermani, K.; Garg, S. *Drug Discovery Today* **2002**, *7*, 569.
28. Gil, E. S.; Hudson, S. M. *Biomacromolecules* **2007**, *8*, 258.
29. Zhao, Y.; Kang, J.; Tan, T. *Polymer* **2006**, *47*, 7702.
30. Kim, S. J.; Shin, S. R.; Shin, D. I.; Kim, I. Y.; Kim, S. I. *J. Appl. Polym. Sci.* **2005**, *96*, 86.
31. Hirashima, Y.; Tamanishi, H.; Sato, H.; Saito, K.; Naito, A.; Suzuki, A. *J. Polym. Sci. Part B: Polym. Phys.* **2004**, *42*, 6.
32. Kulkarni, R. V.; Sa, B. *J. Biomater. Sci. Polym. E* **2009**, *20*, 2.
33. Pourjavadi, A.; Salimi, H. *Ind. Eng. Chem. Res.* **2008**, *47*, 23.
34. Konradi, R.; Rühe, J. *Macromolecules* **2005**, *38*, 4345.
35. Chen, S. C.; Wu, Y. C.; Mi, F. L.; Lin, Y. H.; Yu, L. C.; Sung, H. W. *J. Controlled Release* **2004**, *96*, 285.
36. Cummings, D. E.; Overduin, J. *J. Clin. Invest.* **2007**, *117*, 13.
37. Dressman, J. B.; Berardi, R. R.; Dermentzoglou, L. C.; Russell, T. L.; Schmaltz, S. P.; Barnett, J. L.; Jarvenpaa, K. M. *Pharm. Res.* **1990**, *7*, 756.
38. Wang, S.; Zhang, Q.; Tan, B.; Liu, L.; Shi, L. *J. Macromol. Sci. B* **2011**, *50*, 2307.
39. Xu, X. D.; Liang, L.; Chen, C. S.; Lu, B.; Wang, N. L.; Jiang, F. G.; Zhuo, R. X. *ACS Appl. Mater. Int.* **2010**, *2*, 2663.
40. Chen, L.; Subirade, M. *Biomacromolecules* **2009**, *10*, 3327.
41. Luo, Y.; Wang, Q. *J. Appl. Polym. Sci.* **2014**, *131*, 40696.
42. Song, F.; Zhang, L. M. *Eng. Chem. Res.* **2009**, *48*, 7077.