SWELLING AND DRUG RELEASE OF POLY(VINYL ALCOHOL)/GELATIN COMPOSITE HYDROGEL

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Poly (vinyl alcohol)/gelatin (PVA/Gel) composite hydrogel was prepared by freezing-thawing and morphology of the hydrogel was characterized by scanning electron microscope (SEM). The swelling behavior in different pH buffer solutions was studied. With salicylic acid as model drug, the drug releasing process of the hydrogel was investigated. It was found that the polyvinyl alcohol/gelatin composite hydrogel has porous structure. The swelling rate and equilibrium swelling degree increases with the increase of gelatin content in it. The PVA/Gel hydrogel behaves sensitive to the temperature and pH. At the pH of 7.4, the drug release is the fast.

Keywords: poly (vinyl alcohol), gelatin, composite hydrogel

INTRODUCTION

Hydrogel is a kind of functional polymer materials with moderate crosslinking and three-dimensional network. It is insoluble in water, but can significantly swell in water by absorbing a lot of water. So it is good in water holding. The swelling is the most basic and important performance of hydrogel. It has found applications in many fields including biomedical materials and bio-engineering (Gan and Nong, 2010).

Polyvinyl alcohol hydrogel (PVA) has been widely used, mostly because of its biocompatibility, mechanical properties, film forming, non-toxic, and no side-effects. Its application has extended to medicine, food, environmental protection etc (Yoshida *et al.*, 1991; Woerly, 1997). However, the mechanical properties of PVA hydrogel is poor at room temperature, and it is not easy to control the biodegradation, resulting in less commercial value (You *et al.*, 2007). Prepared by the hydrolysis of collagen, gelatin is good in biocompatibility and biodegradability. With gelatin as raw material to prepare hydrogel, the utilization rate of the medicine may be greatly improved with a decreased side-effect and prolonged drug duration. However, pure gelatin is easily soluble in water, hard and brittle when dried. It is poor in mechanical properties too. When the two materials are blended to prepare hydrogel, it is expected to yield hydrogel with the combined advantages, biological activity, and different required swelling degree. Few studys are reported on the drug releasing hydrogels with PVA and gelatin.

The PVA/gelatin composite hydrogel was prepared by freezing-thawing. The swelling behavior at the pHs of both simulated gastric acid and normal human blood was studied, as well as the drug releasing process of the composite hydrogel with salicylic acid as the model drug.

MATERIALS AND METHODS

Main Materials and Reagents

Polyvinyl alcohol(PVA), analytical reagent, was from Tianjin Fengchuan Chemical Reagent Co., Ltd., China; Gelatin and Ortho-hydroxybenzoic acid were all analytical reagent and made by Tianjin Kemi'ou Chemical Reagent Co., Ltd., China.

Preparation of Pva/ Gelatin Hydrogels

PVA was dissolved in deionized water at 90°C and cooled to 60°C for subsequent use. Gelatin was dissolved in distilled water at 60°C to obtain gelatin solution. Both the solutions of PVA and gelatin were mixed at 60°C for 2h. After being ultrasonic de-gased, the mixture was poured in a self-made mold and frozen at -20°C for 22 hours, and then, completely thawed at room temperature. That is a freeze-thaw cycle. The process was repeated four times to obtain the PVA/gelatin hydrogels. According to the amounts of gelatin in the hydrogels, the samples were labeled as PVA/G5, PVA/G10, PVA/G15, PVA/G20, indicating the mass fraction of gelatin in the hydrogel of 5%, 10%, 15% and 20%, respectively.

Morphological Characterization of PVA/Gelatin Hydrogels

After being freeze-dried, a loose porous hydrogel was prepared. The dry hydrogel samples were gold sprayed and the surface morphology was observed by SEM.

Swelling Behavior of PVA/Gelatin Hydrogels

After being vacuum dried, the hydrogels were weighed, noted as m_0. The samples were then soaked in deionized water at 27°C and 37°C, respectively. The swelling ratio was calculated by equation (1):

$$\text{Swelling rate}=\frac{m_t-m_0}{m_0}\times 100\% \quad (1)$$

where m_t is the weight of the hydrogel sample at the soaking moment of t, and m_0 is the weight of the dry sample.

Swelling Kinetics of PVA/ Gelatin Hydrogels

In order to know the diffusion behavior of water molecules in the hydrogel, equation (2) and equation (3) were used (Rathna and Chatterji 2001):

$$F=\frac{m_t-m_0}{m_e-m_0}=kt^n \quad (2)$$

$$\ln F=\ln k+n\ln t \quad (3)$$

where m_e is the equibrium weight of the hydrogel, k is the swelling parameters, and n is the swelling index. When n is not more than 0.5, the swelling is Fick's diffusion process, and when is between 0.5 and 1.0, the swelling is non-Fick's diffusion process.

Drug Loading Behavior of PVA/ Gelatin Hydrogels

After the temperature of the PVA/gelatin solution was lowered from 60°C to 40°C, 4wt% salicylic acid solution was added and the mixture was stirred for at 40°C for 1h. After being ultrasonic degased, the mixture was poured in a self-made mold, followed with four freeze-thaw cycles, yielding the drug-loaded PVA/ gelatin hydrogels.

The Drug Releasing Curve of the Composite Hydrogel

At 37°C, hydrogel samples were added in 150mL buffering solution at pH 1.0 and stirred at 100rpm. 5mL solution was picked out and another 5mL same buffering solution was added. After 30min, the absorbance at 290nm was determined with UV-VIS spectrophotometer. Equation (4) was used to obtain the cumulative drug releasing amount at time *t*.

$$Q = 150C_t + \sum_{i=1}^{t-1} 5C_i \tag{4}$$

where *Q* is the cumulative drug releasing amount, *Ct* is the drug concentration obtained at the moment of *t*. The drug releasing curve of samples at pH 7.4, 37°C was obtained in the same way.

RESULTS AND DISCUSSION

After being dried, the PVA/gelatin hydrogels appear milky white and loose. The images observed with SEM were as shown in Figure 1.

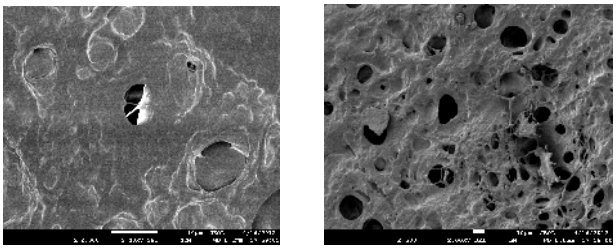

Figure 1. SEM images of PVA (left) and PVA/gelatin (right) hydrogel

In Figure 1, with the introduction of gelatin, the porous of the hydrogel became more abundant, and the structure became looser. There are plenty of such hydrophilic groups as amino and carboxyl in gelatin. When gelatin is blended with PVA, more water will be absorbed. When being frozen and vacuum dried, the water in the hydrogel will escape from the hydrogel while gelatin and PVA were still in a frozen state, resulting in the pore or holes in the samples. Besides, the difference in contraction coefficients of PVA and gelatin may be another reason for the porous structure.

In Figure 2, for the hydrogels with different gelatin contents, the swelling behavior is different. With increasing the gelatin content from 5% to 20%, both the swelling rate and the equilibrium swelling degree of the hydrogel increase. The molecular chain of pure PVA is well-structured, a crystalline polymer. Even after a freeze-thawing, the compact aggregation structure is kept. When gelatin is introduced in the system, gelatin will diffuse in the network of PVA to form a semi-interpenetrating network (Lin et al. 2010). New hydrogen bonding between, gelatin-PVA will be formed, and the original structure of pure PVA will be destroyed. As a result, the structure changed looser, making it easier for water to diffuse in swelling process. Besides, gelatin is a hydrophilic polymer, and the introduction of gelatin will increase the water absorption. So the swelling rate and equilibrium swelling degree are increased.

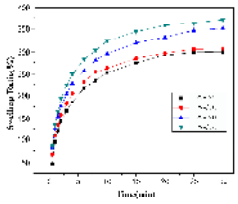

Figure 2. Swelling curves of PVA/ gelatin hydrogel at 37°C, pH1.0

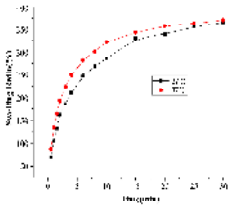

Figure 3. Swelling curves of PVA/G20 hydrogel at different temperatures

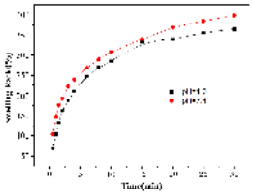

Figure 4. Swelling curves of PVA/G20 hydrogels at 37°C

Figure 3 shows the swelling curves of PVA/G20 hydrogel at pH 1.0 and different temperatures. At higher temperatures, it exhibited higher equilibrium swelling degree and greater swelling rate, indicating temperature sensitivity. With increasing the temperature, the molecules move faster, making the water diffusion easier. On the other hand, increasing the temperature will accelerate the movement of side groups in the system, also help increasing the binding and transferring of water molecules.

Figure 4 is the swelling curves of PVA/G20 hydrogels at different pHs. The swelling rate and equilibrium swelling degree at pH 7.4 are higher than those at pH 1.0. As a hydrolysate of collagen, gelatin contains plenty of carboxyl and amino groups to behave amphoteric electrolyte. At higher pH, carboxyl will dissociate to show $-COO^-$, and amino is in the form of $-NH_2$. At a lower pH, amino $-NH^{3+}$ will be formed, and the carboxyl group is in the form of -COOH. The isoelectric point of gelatin is about 6. At different pHs, the interaction force between the molecules is different. As a result, the aggregation structure and swelling degree of the hydrogel are different.

According to the swelling kinetics equation, the corresponding *lnF* and *lnT* were calculated, and *lnF-lnt* curves were obtained as shown in Figure 5 and Figure 6. The swelling index *n* was got by the linear-fitting the lines in the figures.

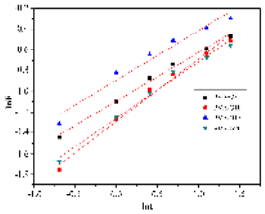

Figure 5. lnF-lnt of PVA/ gelatin hydrogels with various gelatin content at pH 1.0, 37°C

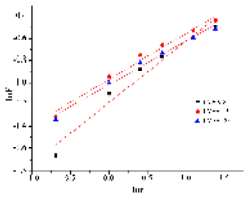

Figure 6. lnF-lnt of the PVA/ gelatin hydrogels with various gelatin content at pH 7.4, 37°C

Table 1. Swelling kinetics parameters of the hydrogel

	pH=1.0		pH=7.4	
	N	R2	N	R2
PVA/G5	0.4792	0.9924	0.3973	0.9596
PVA/G10	0.5476	0.9868	——	——
PVA/G15	0.5571	0.9670	0.5182	0.9813
PVA/G20	0.6042	0.9859	0.5302	0.9846

The swelling index *n* was shown in Table 1. At the gelatin content in the hydrogel of 5%, the *n* is less than 0.5, indicating a Fick's diffusion (Lin *et al.*, 2010). The water absorption is mainly by the hydrophilic interaction, and the water diffusion into the hydrogel is freely. The gelatin in the hydrogel is very little, and not much groups may be dissociated. So the interaction between the molecules in the hydrogel does not affect the water diffusion greatly. At the gelatin content of more than 10%, the *n* is between 0.5-1.0, showing a non-Fickian diffusion. With the addition of gelatin in the system, crosslinking sites are increased, and the chain segments between crosslinking sites turn smaller, which may slow down the relaxation rate of the macromolecules. Therefore, with increasing the gelatin content in the hydrogels, both the water diffusion and the relaxation behaviors in the swelling process may be affected. On the other hand, from the *n*, we know the at a higher gelatin content, there is less difference between the water diffusion rate and molecular chain relaxation rate (Nugent and Higginbotham, 2007).

The *n* at the pH of 1.0 is higher than that at 7.4. As an amphoteric electrolyte, at acidic condition, gelatin is positive-charged, which will react with PVA to slow down the relaxation rate, affecting the water diffusion. At pH 7.4, near the isoelectric point of gelatin, less reaction between gelatin and PVA takes place, the relaxation is less affected, yielding a decreased *n*.

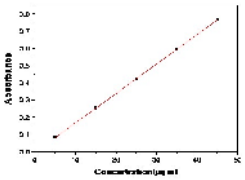

Figure 7. Standard curve of salicylic acid at pH 1.0

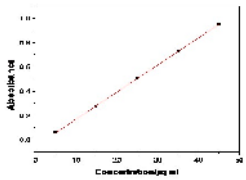

Figure 8. Standard curve of salicylic acid at pH 7.4

The standard curves of hydrochloric acid at the pH of 1.0 and 7.4 are shown in Figure 7 and Figure 8, indicating a linear relationship between the UV absorbance at 290nm and the drug concentration. So we may measure the salicylic acid content of a solution with unknown salicylic acid concentration by it.

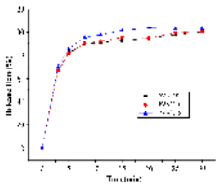

Figure 9. Drug releasing curves of the hydrogel with various gelatin content at pH1.0, 37°C

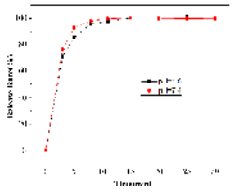

Figure 10. Drug releasing curves of PVA/G15 at different pHs, 37°C

The drug releasing curves of the hydrogels with different gelatin contents at pH 1.0 were shown in Figure 9. The drug-loaded hydrogels exhibited excellent drug releasing. The drug releasing curve may be roughly divided into three such stages as burst release, stable release and complete release. With increasing the gelatin content in the hydrogels, the drug releasing rate increases slightly, which agrees with the results of swelling rate. There are carboxyl and phenolic hydroxyl groups on salicylic acid, and gelatin contains plenty of amino, hydroxyl. With the addition of gelatin, the combining sites of drug on hydrogel is more, and much more pores are provided as shown in the SEM images in Figure 1. So with increasing the gelatin content, the drug releasing capacity is increased. In the present study, the pore affects the drug releasing more. Figure 10 shows the drug releasing curves of PVA/G15 hydrogel at indifferent pHs. The drug releasing of the hydrogel at different pHs is similar, although a rapid drug releasing rate is shown at pH 7.4, indicating a pH sensitive hydrogel, which will affect the drug releasing to some degree.

CONCLUSIONS

PVA/gelatin hydrogel with rich pores was prepared by freezing-thawing. The swelling rate and equilibrium swelling degree increase with increasing the gelatin content. At the same temperature, the swelling rate and equilibrium swelling degree at pH 7.4 are higher than those at pH 1.0. At the same pH, the swelling rate and equilibrium swelling degree at pH 7.4 are higher than those at pH 1.0. At the gelatin content less than 5%, the water diffusion in the hydrogel behaves Fick diffusion. The PVA/Gel hydrogel is sensitive to temperature and pH.

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