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Preparation and characterization of smart magnetic hydrogels and its use for drug release

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Abstract

The magnetic hydrogels were successfully fabricated by chemically cross-linking of gelatin hydrogels and Fe_3O_4 nanoparticles (ca. 40–60 nm) through genipin (GP) as cross-linking agent. The cross-sectional SEM observation demonstrates that the Fe_3O_4 nanoparticles were fairly uniformly distributed in the gelatin matrix. Moreover, in vitro release data reveal that drug release profile of the resulting hydrogels is controllable by switching on or off mode of a given magnetic field. While applying magnetic fields to the magnetic hydrogels, the release rate of vitamin B_{12} of the hydrogels was considerably decreased as compared with those when the field was turned off, suggesting a close configuration of the hydrogels as a result of the aggregation of Fe_3O_4 nanoparticles. Based on this on-&-off mechanism, the smart magnetic hydrogels based on the gelatin-ferrite hybrid composites can be potentially developed for application in novel drug delivery systems.

Keywords: Magnetic hydrogels; Swelling rate; Smart drugs release

1. Introduction

In recent years, stimuli-responsive polymers, which can respond to external stimuli, such as pH, temperature and electric field, have attracted a great deal of interest due to their potential applications in controlled drug delivery [1]. Gelatin is a widely used polymer in pharmaceutical products [2]. Furthermore, it is of special interest in controlled release applications because of their soft tissue biocompatibility, the ease with which the drugs are dispersed in the matrix, and the high degree of control achieved by selecting the physical and chemical properties of the polymer network.

Magnetic materials have been widely used in the field of biotechnology in bio-separation, artificial muscles and drug carriers [3–5]. Some researchers have reported that the drug carriers of magnetic gels could be applied in targeting [6]. However, to our best knowledge, it is barely found to use magnetic fields (MF) for controlled release of drug. Therefore, a combination of gelatin and magnetic particles is a potential approach to prepare a responsive composite that can be applied as a drug delivery system by MF.

2. Experimental

For the preparation of the magnetic hygrogels (or called ferrogel), gelatin (15 wt%) was first dissolved in deionized water at 45 °C to ensure that the gelatin can be fully dissolved. After that, 4 wt% Fe_3O_4 nanoparticles (from Alfa Aesar) including 0.03 wt% drugs (vitamin B_{12}, from Sigma) and genipin (GP, Challenge Bioproducts Co., Ltd., Taiwan) with different weight ratio were added to the above gelatin solution under stirring for 30 min at 40 °C and then incubated at 25 °C for 2 days. The GP-cross-linked ferrogels were designated as Ge0.06, Ge0.03, Ge0.01 and Ge0.003 according to their different cross-link density. For example, Ge0.06 indicates that GP content is 0.06 wt%.

The swelling rate of the ferrogels was measured as described in our previous study [7] and a given MF of about 400 Oe was used during the on-off operation. For drug release test, the ferrogels containing vitamin B_{12} were

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first immersed in 20 ml of phosphate buffer (PBS) (pH7.4) and then UV-visible spectroscopy was used for the characterization of absorbance peaks at 361 nm to determine the release concentration of the vitamin B_{12}.

3. Results and discussion

As the gelatin hydrogels were loaded with vitamin B_{12} (without Fe_3O_4 particles) and cross-linked by GP with various weight ratios, the photographs in Fig. 1(a) present different colors. After the gelatin/GP solution was incubated for 2 days, the color (vitamin B_{12}) of the gels changed from pink to purple (lower cross-linked density) or dark blue (higher cross-linked density). The UV spectra in Fig. 1(b) also demonstrate a color change. The above results may suggest that the gelatin could react with a variety of the GP concentrations to display different color and morphology. In general, the darker the color of the gels, the denser the structure of the gels obtained. Therefore, the porosity or pore size of the gelatin gels would influence the drug release profile. In addition, it was observed that the Fe_3O_4 nanoparticles were fairly uniformly distributed in the gelatin matrix as evidenced from a cross-sectional SEM image illustrated in Fig. 2(a).

The swelling properties of the magnetic hydrogels as a function of switching MF were illustrated in Fig. 2(b). While switching on mode of a given MF, it was found that not only swelling rate decreased sharply but also de-swelling in the differential curve. On the other hand, while switching off, it will restore to original state. The sensitive properties can be attributed to the fact that the porosity or the pore size in the ferrogels possibly change with the switching "on or off' mode. Such a decreased porosity or pore size suggests a "close" configuration of the ferrogels and can be further illustrated in Fig. 3. While the MF was on, the Fe_3O_4 particles tend to aggregate together and this causes the porosity of the ferrogel to decrease. As a result, a swelling rate was reduced and a decreased drugs release rate was induced.

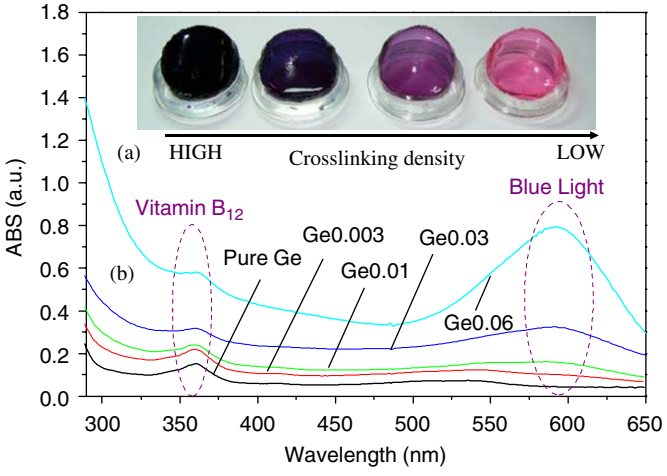

Fig. 1. (a) Photographs of the gelatin gels with different cross-linked densities, and (b) UV spectroscopy analysis of different cross-linked gelatin hygrogels.

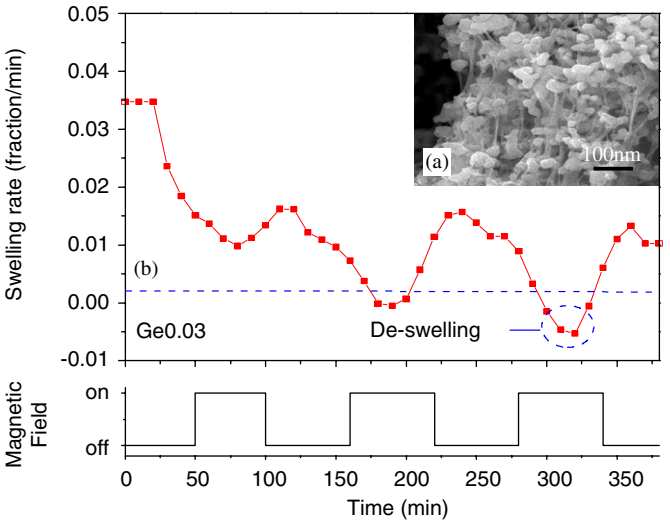

Fig. 2. (a) SEM observation of Fe_3O_4 nanoparticles distributed in gelatin hydrogels, and (b) sensitive swelling rate of the ferrogels dependent on switching MF.

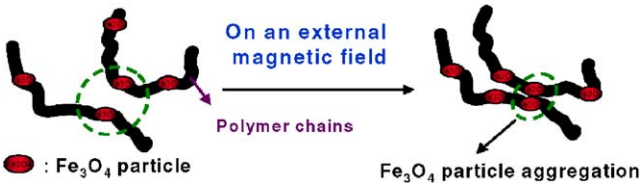

Fig. 3. Mechanism of "close" configuration of the ferrogels due to the aggregation of Fe_3O_4 nanoparticles under "on" MF causes the porosity of the ferrogels to decrease.

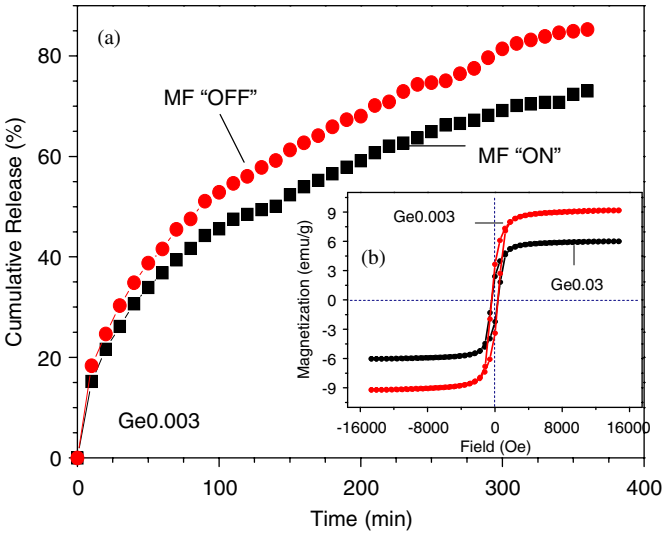

Fig. 4. (a) Drugs release rate profiles of the Ge0.003 ferrogels in MF switching "on" or "off" mode, and (b) hysteresis loop analysis of the magnetic hydrogels using VSM.

Fig. 4(a) exhibits the close configuration of Ge0.003 ferrogel. The drug release rate was decreased upon

Table 1
Cumulative drugs release of the ferrogels in "on" or "off" mode of a given magnetic field for 120 min

Ferrogel	Ge0.003	Ge0.01	Ge0.03	Ge0.06
MF OFF	56.5%	52.2%	49.9%	48.0%
MF ON	47.4%	45.5%	44.4%	44.1%
OFF-ON	9.1%	6.7%	5.5%	3.9%

switching on. Moreover, Table 1 shows the released vitamin B_{12} amount from the hydrogels cross-linked with different GP concentrations under a given on or off mode. It was observed that in the ferrogels, the lower the GP concentration, the stronger the magnetic responsive properties (OFF-ON) (9.1%).

This behavior can be related to structure and characteristics of the ferrogels. It was inferred that the ferrogels with a lower GP concentration display the softer properties and this could cause the porosity to be easily modified through free movement of the chains in the gelatin hydrogels. Furthermore, the Ge0.003 ferrogel show a higher magnetization (Ms) (9.199 emu/g) than Ge0.03 ferrogel (6.023 emu/g) measured using the vibrating sample magnetometer (VSM) in Fig. 4(b). Based on the above two reasons, it could be demonstrated that the ferrogels with a lower cross-linked density display more obvious magnetic sensitive properties. Besides, the magnetic responsive properties of the drugs release could be found in a consecutive switching "on-off" mode for a given MF, as shown in Fig. 5. The differential curve showed that the release rate of the drug in the ferrogels was considerably decreased under switching "on" mode but increased upon switching "off" mode.

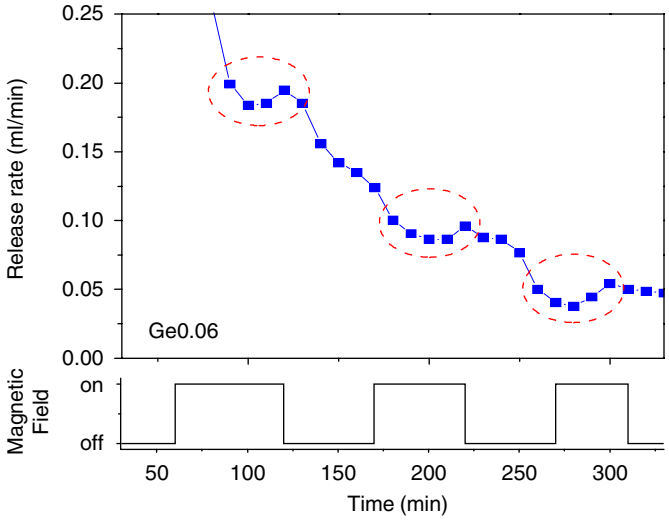

Fig. 5. Sensitive drugs release properties of the ferrogels dependent on switching "on-off" mode for a given MF.

4. Conclusion

Smart magnetic hydrogels based on gelatin-ferrite composites were investigated and can be applied for the development of a new magnetically induced drug delivery system. Furthermore, the drug release profile of the resulting hydrogels is controllable by switching "on" or "off" mode of a given magnetic field.

References

[1] M. Zrínyi, Colloid. Polym. Sci. 278 (2000) 98.
[2] R. Cortesi, C. Nastruzzi, S.S. Davis, Biomaterials 19 (1998) 1641.
[3] T. Neuberger, B. Dchöpf, H. Hofmann, M. Hofmann, B. Rechenberg, J Magn. Magn. Mater. 293 (2005) 483.
[4] Q.A. Pankhurst, J. Connolly, S.K. Jones, J. Dobson, J. Phys. D:Appl. Phys. 36 (2003) 167.
[5] A.J. Rosengart, M.D. Kaminski, H. Chen, P.L. Caviness, A.D. Ebner, J.A. Ritter, J Magn. Magn. Mater. 293 (2005) 633.
[6] O. Rotariu, N.J.C. Strachan, J Magn. Magn. Mater. 293 (2005) 639.
[7] M.C. Yang, T.Y. Liu, J. Membrane Sci. 226 (2003) 119.