

Cellulose/Guar Gum Hydrogel Microspheres as a Magnetic Anticancer Drug Carrier

Yanli Li,^{a,b} Yucheng Feng,^{a,b} Jun Jing,^a and Fei Yang^{*,a,b}

A novel magnetic anticancer drug carrier based on cellulose, guar gum, and Fe₃O₄ hydrogel microspheres was synthesized by chemical crosslinking. These microspheres were crosslinked with epoxy chloropropane and loaded with 5-fluorouracil (5-fu). The effect of the ratio of cellulose to guar gum on bead size, drug loading, and *in vitro* release behaviors were investigated. The influence of the magnetic content on drug loading and *in vitro* release behaviors were also evaluated. The magnetic hydrogel microspheres were characterized via an optical microscope, Fourier transform infrared spectroscopy, swelling behavior analysis, vibrating sample magnetometer, and ultraviolet absorption spectroscopy. The results showed that as the ratio of cellulose to guar gum increased from 3:1 to 5:1, the particle size increased from 395 to 459 μm. Moreover, the drug loading capacity, encapsulation efficiency, and *in vitro* release behavior were influenced by the ratio of cellulose/guar gum and Fe₃O₄ content. Finally, the Fe₃O₄ particle had an adsorption effect on the drug, thereby reducing the maximum cumulative release.

Keywords: Cellulose; Guar gum; Fe₃O₄ nanoparticle; Hydrogel microsphere; Drug controlled release

Contact information: a: State Key Laboratory of Pulp and Paper Engineering, South China University of Technology, Guangzhou 510640, China; b: United Lab of Plant Resources Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China;

* Corresponding author: yangfei@scut.edu.cn

INTRODUCTION

Currently, cancer is one of the most life-threatening diseases worldwide, especially in China where cancer incidence and mortality has continued to increase and has become a major public health problem (Chen *et al.* 2016). The treatment for cancer includes surgery, radiation, and chemotherapy. Chemotherapy is one of the most useful treatments for cancer. However, the improvement in quality of life and increasing safe awareness assure that high quality and safe drug therapies are a priority for policymakers and multidisciplinary scientists. Controlled drug delivery technology has had a more dominant role in recent years due to its advantages compared to the conventional medicine system, including improved efficiency and reduced dosage (Uhrich *et al.* 1999; Babu *et al.* 2007). Drug carriers have an important role in the drug release system and are a main factor in affecting drug efficacy (Uekama and Otagiri 1987). Polymeric hydrogels are cross-linked hydrophilic materials that have a three-dimensional network structure and can absorb large quantities of water without dissolving (O'Connor and Gehrke 2015; Liu *et al.* 2009). In recent years, much attention has been focused on hydrogel microspheres for the delivery of water-solution drugs due to their outstanding characteristics such as excellent water-absorption, water-retention, and slow-release (Korsmeyer *et al.* 1983; Liu *et al.* 2006a; Karaaslan *et al.* 2010).

Biopolymeric resources are promising feedstocks to produce sustainable products (Nurunnabi *et al.* 2015; Aravamudhan *et al.* 2016; Shaghaleh *et al.* 2018).

Cellulose is the most abundant natural polymer on Earth (Bledzki and Gassan 1999; Fan *et al.* 2017). Because cellulose has an abundant number of hydroxyl groups, it can be used to prepare hydrogels easily with fascinating structures and properties (Chang and Zhang 2011; Xu *et al.* 2018). For example, previous work exploited carboxymethyl cellulose (CMC) beads *via* a liquid curing method in the presence of trivalent ferric ions, and epichlorohydrin was covalently bonded to the CMC beads (Yakup 2015). Cellulose (or its derivatives) blended with other polymers is an extremely attractive, inexpensive, and advantageous method to obtain new structural materials (Bajpai *et al.* 2008), such as chitosan (Nan and Bai 2005), starch (Faroongsarn and Sukonrat 2008), and polyvinyl alcohol (Salmawi 2007; Chang *et al.* 2010). Guar gum is one of the most abundant natural polysaccharides in the world, consisting of a 1,4- β -D-mannose backbone and 1,6- α -D-galactose side chain, with a ratio of galactose/mannose of 1:2 (Sinha and Kumria 2001; Li *et al.* 2008). It has been suggested as a vehicle for oral controlled release purposes and for colon targeting due to its biodegradability and biocompatibility (Huang *et al.* 2007). However, to the authors' knowledge, there have been few reports on the investigation of cellulose blended with guar gum microspheres.

Recently, magnetic nanoparticles have gained attention because of their unique features (Rani *et al.* 2010; Fan *et al.* 2011). They can be used in medical applications, such as drug targeting for drug control release and targeted release, especially for cancer therapy (Liu *et al.* 2006b). This innovative strategy for targeted drug delivery consists of coupling the drug to magnetic nanoparticles that can be guided to the target by means of external magnetic fields (Barbucci *et al.* 2012). In the present paper, the objective is to prepare a magnetic hydrogel microsphere, consisting of cellulose, guar gum, and Fe₃O₄, while the microspheres were located with 5-fluorouracil (5-fu). The effect of the ratio of cellulose to guar gum on bead size and drug loading as well as the *in vitro* release behaviors were investigated. The influence of magnetic content on drug loading and *in vitro* release behaviors were also studied. The magnetic hydrogel microspheres were characterized using an optical microscope, Fourier transform infrared spectroscopy (FTIR), and swelling behavior, vibrating sample magnetometer (VSM) to investigate the shape synthesis. Additionally, ultraviolet (UV) absorption spectroscopy was performed to evaluate the drug loading and release.

EXPERIMENTAL

Materials

Jute pulp was supplied by China Tobacco Mauduit (Guangdong, China). Guar gum was bought from Wuhan Shengruiyuan Biotechnology Co., Ltd. (Wuhan, China), Liquid paraffin, epoxy chloropropane, sodium hydroxide, and urea were supplied by Guangzhou Congyuan Instrument Corporation (Guangzhou, China). Iron vitriol and anhydrous ferric chloride were bought from Tianjin Damao Chemical Reagent Factory (Guangzhou, China) and 5-fluorouracil (5-fu) was supplied by Aladdin Reagent Co., Ltd. (Shanghai, China). All of the chemical reagents were of analytical grade without further purification.

Methods

Preparation of cellulose/guar gum hydrogel microspheres

Jute pulp was dissolved in a NaOH/urea aqueous solution at a low temperature to form a cellulose solution with a concentration of 2 wt% as previously described (Qin *et al.* 2013). Guar gum was dissolved in water by stirring overnight to form a guar gum solution with a concentration of 1 wt%. The gel beads were produced in a 250-mL round-bottom flask equipped with a stirrer. Liquid paraffin (100 mL) in a continuous phase was added to provide a reaction environment and Tween 80 was added as a 0.1 mL/mL mixed solution as dispersants. Then, the mixture of cellulose and guar gum was poured into the continuous phase while it was being stirred at a speed of 800 r/min. When the mixed solution was dispersed into droplets in liquid paraffin, epoxy chloropropane was added as a 0.1 mL/mL mixed solution. The solution was kept at 30 °C for 30 min and then heated to 60 °C. Five hours later, the reaction was stopped, and the gel beads were obtained. The microspheres were then frozen and freeze-dried in a lyophilizer (FD5-2.5; Gold SIM, Los Angeles, USA) (-58°C, 0.22 mbar) for 48 h before further analysis.

Preparation of cellulose/guar gum/Fe₃O₄ hydrogel microspheres

The Fe₃O₄ magnetic fluid was prepared *via* chemical coprecipitation of iron vitriol and anhydrous ferric chloride solution (0.25 mol/L) with ammonia as the precipitant (Deng *et al.* 2003). To the resultant suspension, the Fe₃O₄ magnetic fluid was washed by deionized water until pH = 7 and was then stored in 50 mL of alcohol. The obtained magnetic nanoparticles were added to a cellulose/guar gum mixture during the process of the polymerization reaction. The magnetic hydrogel microspheres were treated with Fe₃O₄ magnetic fluid with different volumes of 0.2 mL, 0.4 mL, and 0.6 mL and were coded as M1, M2, and M3, respectively. The samples that were loaded with Fe₃O₄ were calcined at 600 °C for 5 h to obtain iron oxide. Then, the content of Fe₃O₄ loaded into the hydrogel was calculated from the Fe₂O₃.

Morphology of hydrogel microspheres

An optical microscope (SZX12; Olympus, Tokyo, Japan) was used to observe the size of the gel beads. The bead size was the average size determined by measuring 200 samples of beads (O'Connor and Gehrke 2015).

Fourier transform infrared spectroscopy

The FTIR spectral measurements were performed using a Nicolet FTIR spectrometer (Nicolet Nexus 670; Nicolet Instrument Technologies, Inc., Madison, WI, USA) to confirm the presence of cross-linking in the cellulose-guar gum gel beads. The blended particles were finely ground with KBr to prepare the pellets, and the spectra were scanned between 600 and 3700 cm^{-1} .

Swelling behavior analysis

Swelling experiments were conducted in distilled water at 25 °C. The weighed mass of dry microspheres were dipped in the distilled water. After preset time intervals, the sample was blotted with filter paper to remove excess water from the hydrogel surface and the sample was weighed. The swelling ratio (S) was calculated according to,

$$S = \frac{W_t - W_d}{W_d} \quad (1)$$

where W_t (g) and W_d (g) are the weights of microsphere at any time (min) and the initial weight of the dry gels, respectively.

Magnetic properties analysis

The magnetic properties of the microspheres were measured with a vibrating sample magnetometer (VSM, Lake Shore, Columbus, OH, USA) at 25 °C, and the hysteresis loop was obtained in a magnetic field that was varied from 1.0 to +1.0 T.

Drug loaded into hydrogel microspheres

A sample of 20 mg of 5-fu was dissolved into the mixture of cellulose and guar gum (mixture of cellulose, guar gum, and Fe_3O_4 magnetic fluid) during the heat-initiated free radical polymerization process. The syntheses of composite microsphere and drug loaded process were presented in Fig. 1. After polymerization, drug-loaded hydrogels were frozen and then freeze-dried in a lyophilizer (-58 °C, 0.22 mbar) for 48 h. The drug-loading content (Q) and encapsulation efficiency (EE) were determined using a UV-spectrophotometer (UV-2600, Shimadzu, Suzhou, China) at 265 nm.

$$EE (\%) = \left(\frac{W_d}{W_t} \right) \times 100 \quad (2)$$

$$Q (\%) = \left(\frac{W_d}{W} \right) \times 100 \quad (3)$$

where W_t is the total amount (g) of 5-fu employed and W_d is W_t minus the amount (g) of unloaded 5-fu and W is the weight (g) of microsphere.

In vitro release

A sample of 20 mg of drug-loaded cellulose/guar gum (cellulose/guar gum/ Fe_3O_4) hydrogel microspheres were dispersed in 20 mL of artificial simulation intestinal fluid, and then was stirred at 100 rpm at 37 °C. The drug release behavior from the microspheres was studied in the intestinal fluid. At regular intervals of time, 2 mL of release media was removed and replaced by fresh release media. The

concentration of 5-fu released was determined using a UV-spectrophotometer (UV-2600; Shimadzu, Suzhou, China) at 265 nm.

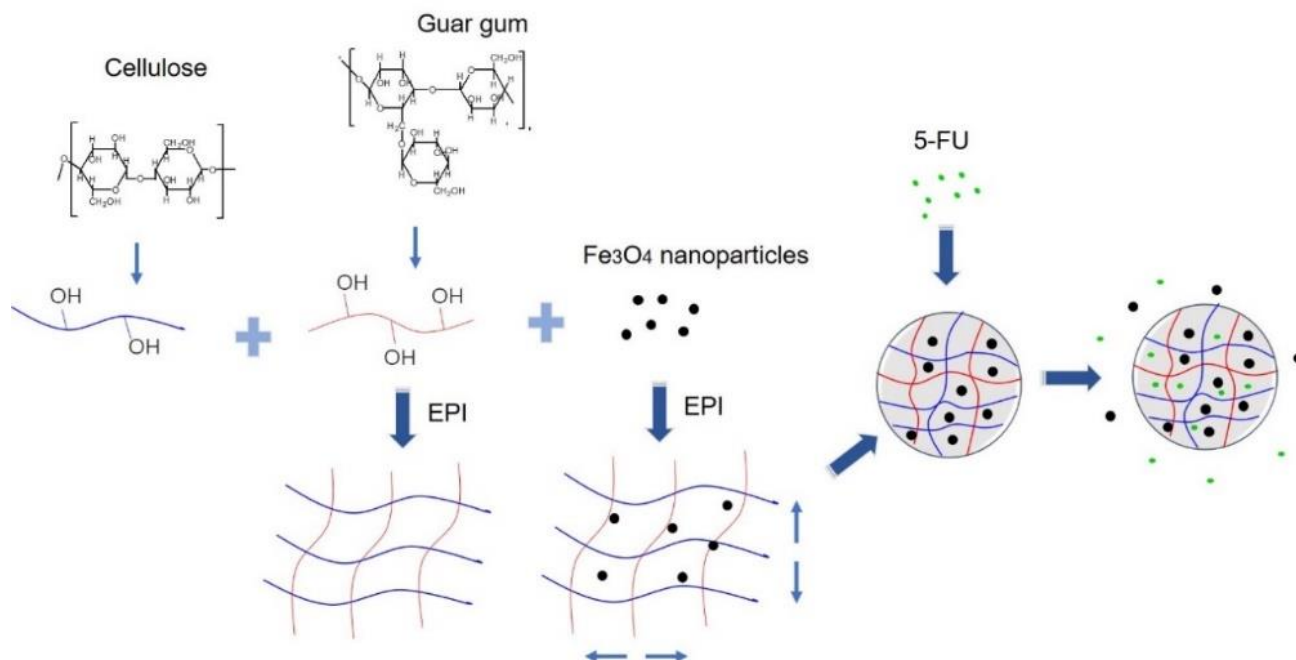


Fig. 1. Preparation of the drug-loaded cellulose/guar gum/Fe₃O₄ hydrogel nanosphere

RESULTS AND DISCUSSION

Microscopic Study

The microspheres prepared by different methods had different particle sizes, as shown in Table 1 and Fig. 2.

Table 1. Results of Particle Size of Different Ratios of Cellulose to Guar Gum

Samples	Ratio of Oil to Mixture	Ratio of Cellulose to Guar Gum	Particle Size (um)	Drug Loading (%)	Encapsulation Efficiency (%)
C-1	8:1	-	523	1.27	23.8
CG-1	8:1	5:1	459	5.3	89.1
CG-2	8:1	4:1	425	3.5	68.8
CG-3	8:1	3:1	395	1.5	28.9

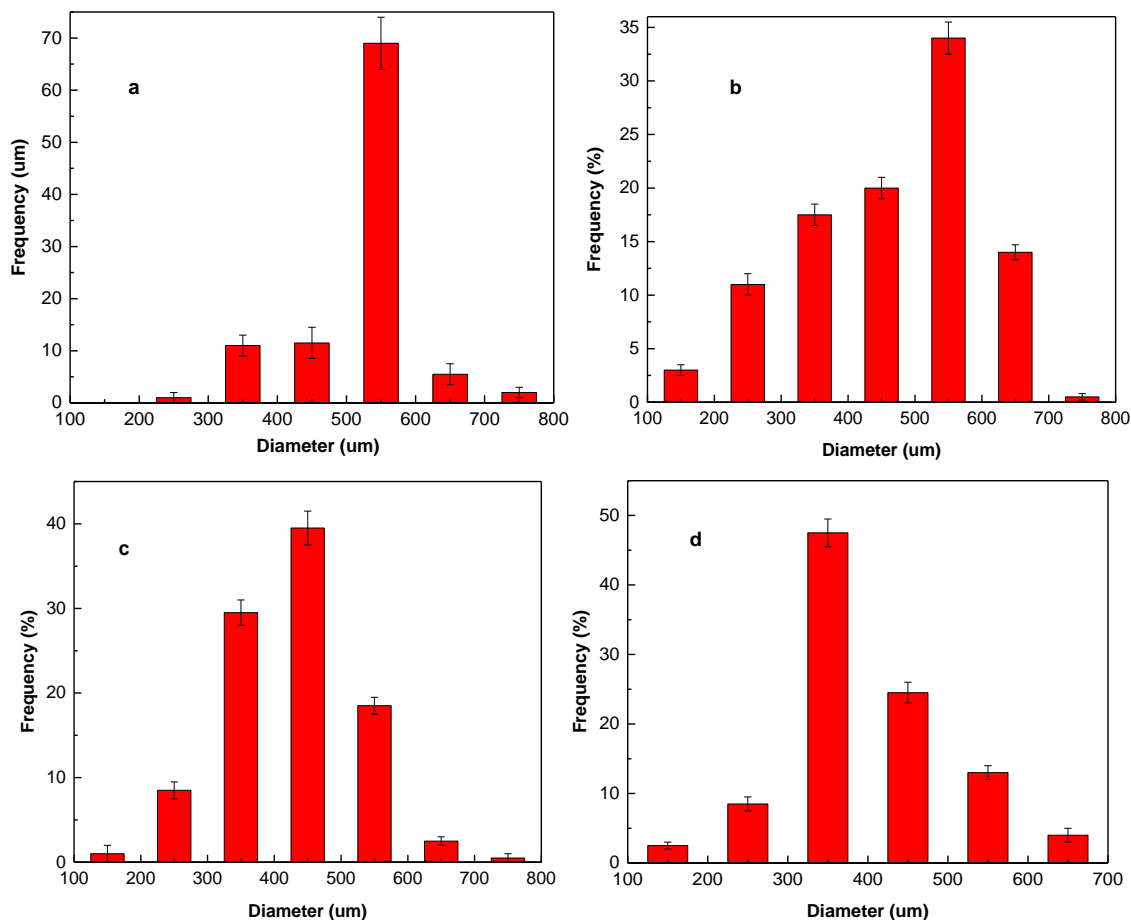


Fig. 2. The size distribution of gel beads. (a) C-1, (b) CG-1, (c) CG-2, (d) CG-3

Results indicated that gel bead diameter was influenced by the guar gum content of the microsphere. It is known that the particle size of the pristine cellulose was higher than those of the cellulose/guar gum composite microspheres. Table 1 also shows that as the ratio of cellulose to guar gum increased from 3:1 to 5:1, the average size increased from 359 to 459 μm ; this change can be seen by size distribution of gel beads (Fig. 2). The size distributions generally could be fitted to the Gaussian distribution. With an increase of guar gum content, the size of beads moves toward to lower size. As the amount of guar gum in the microsphere increased, the interfacial viscosity of the polymer droplets in the emulsion also increased. Because the number of free sites available for cross-linking was more with the increasing amount of guar gum, the size of the microspheres also decreased. The optical microscope micrographs of C-1 are shown in Fig. 3.



Fig. 3. Optical microscope micrographs of C-1

FTIR Spectroscopy Analysis

IR spectra of composite hydrogel are depicted in Fig. 4.

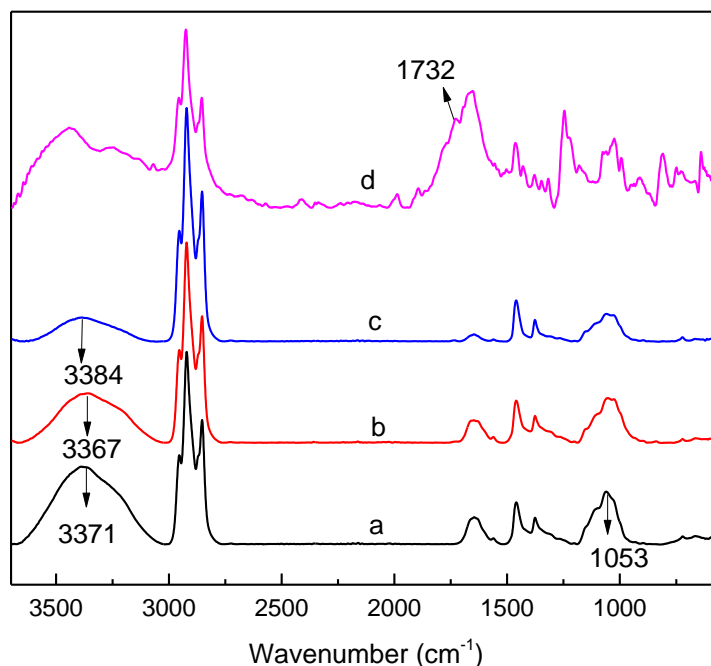


Fig. 4. FTIR spectra of gel beads: (a): CG-1 (Cellulose/guar gum = 5:1), (b): CG-3 (Cellulose/guar gum = 3:1), (c): C-1 (pure cellulose) and (d) DC-1 (Drug loaded C-1)

There were strong absorption peaks at about 3384 to 3367 cm^{-1} in Fig. 4 (a, b and c), attributed to the stretching of -O-H from gel beads. In addition, the peak at 1053 cm^{-1} was assigned to the C-O-C, which suggests the cross-linking reaction of cellulose or guar gum with epoxy chloropropane. As Fig. 4 shows, the vibration peak of -O-H was stronger and exhibited a shift towards a slightly lower wavenumber direction with increased guar gum content relative to cellulose. This suggested that cellulose/guar gum was well mixed and led to noticeable changes in the interaction between the molecules. In Fig. 4 (d), a significant new peak appears at 1732 cm^{-1} (C=O stretching) of carbonyl group of 5-Fu; this result indicated that the 5-fu were loaded with C-1.

Swelling Behavior Analysis

The swelling kinetics curves of samples in distilled water at 25 °C were displayed in Fig. 5. As we can see, compared with CG composited hydrogel, pristine cellulose hydrogel has much lower swelling ratio. With an increase of guar gum content, the equilibrium swelling ratios of the hydrogels increases from 14.0 to 20.1 wt%. The more guar gum content, the more available free volume of the expanded polymer matrix and availability of group such as -OH able to form hydrogen bonds with water. As a consequence, compared with the same hydrogels with lower guar gum content, high guar gum content hydrogel showed a higher swelling ratio.

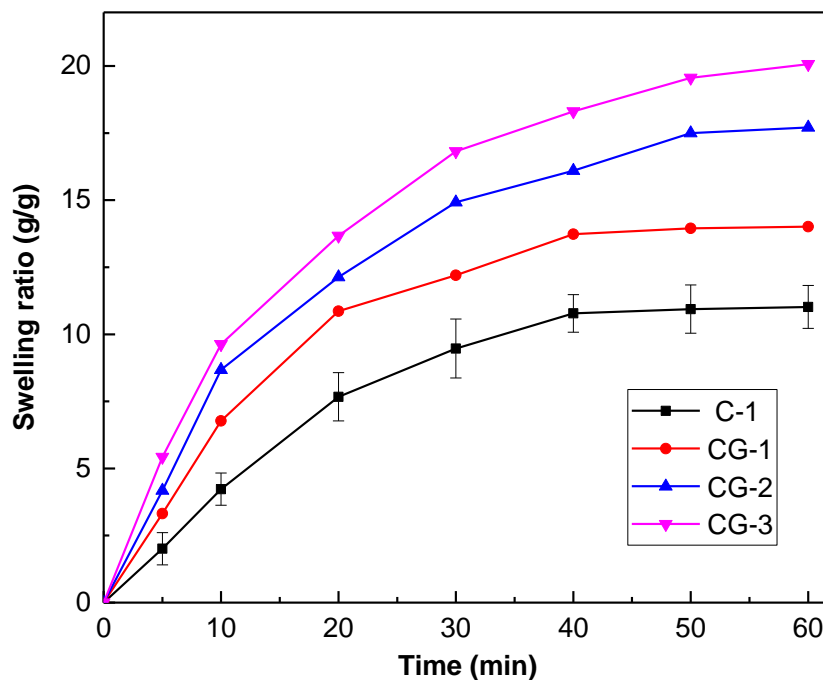


Fig. 5. Swelling kinetics curves of C-1, CG-1, CG-2, and CG-3 in distilled water at 25 °C

Magnetic Properties

Figure 6 shows the images of M1, M2, and M3 in a magnetic field. As can be seen, the samples could align in the magnetic field. Also, the magnetic response of hydrogel microsphere was more sensitive with the increasing of Fe_3O_4 content. This revealed that the magnetic hydrogel microsphere could move directionally by introducing a magnetic field. Therefore, the goal of site-specific drug delivery of the magnetic beads loaded drug can be achieved by using an external magnetic field.

The magnetization of M1, M2, and M3 as a function of the magnetic field at 298 K is shown in Fig. 6. As can be seen, their magnetization increased with an increase of the magnetic field. This clearly shows that they exhibited an extremely small hysteresis loop and low coercivity, which demonstrated the superparamagnetism of the particles. The result indicated that the magnetic composite microspheres possessed good magnetic property and thus, showed promise in biomedical applications.

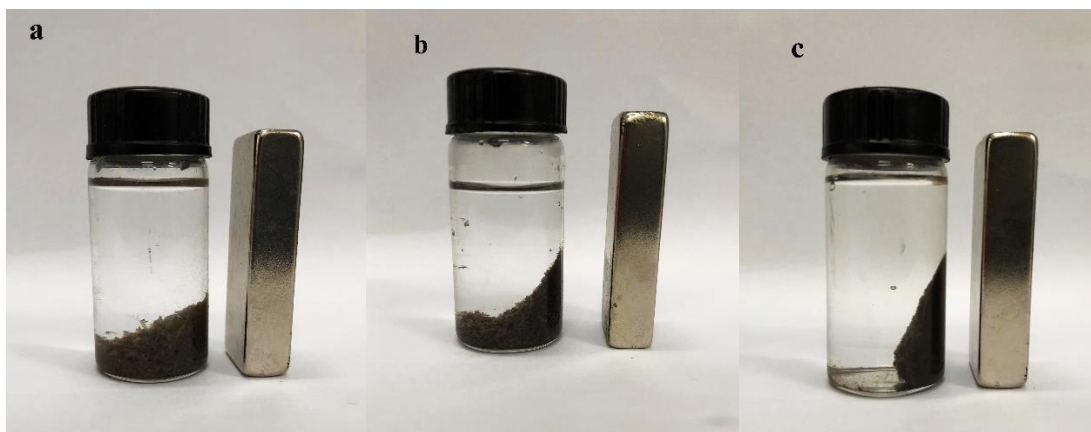


Fig. 6. Photos of M1, M2, and M3 on in a magnetic field. (a) M1, (b) M2, (c) M3

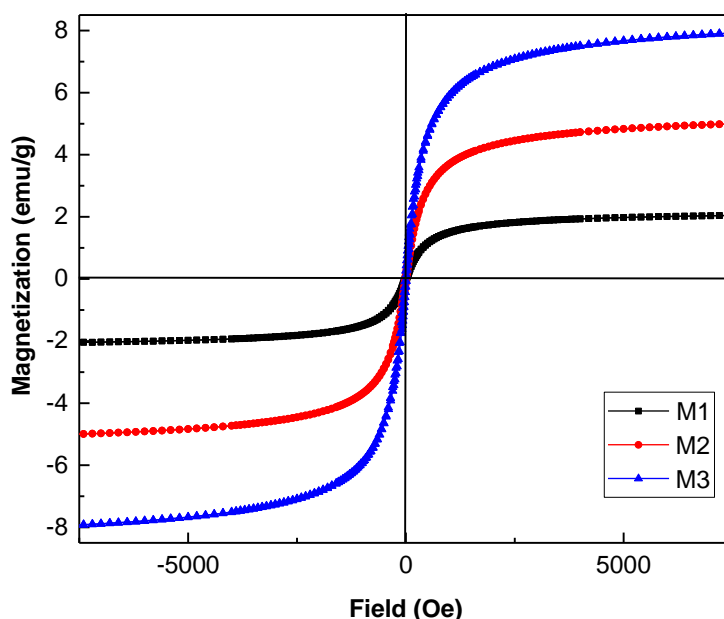


Fig. 7. The magnetic hysteresis loops of the microspheres M1, M2, and M3 at 25 °C

Effect of Ratio of Cellulose to Guar Gum

The effect of the ratio of cellulose to guar gum on 5-fu loading and release behavior was studied. The results of the drug loading and encapsulation efficiency in Table 1 showed an increasing trend with an increasing ratio of cellulose to guar gum. A drug loading of 1.27% and encapsulation efficiency of 23.8% were observed for pristine cellulose microspheres. There was a lesser amount of 5-fu in the cellulose microspheres due to the cellulose hydrogel having less cross-links and a bigger free volume space, thereby causing drug run off.

When the ratio of cellulose/guar gum was 5:1, 4:1, and 3:1, the 5-fu loading was 5.3, 3.5, and 1.5%, and the encapsulation efficiency increased to 89.1, 68.8, and 28.9%, respectively (Table 1). These were higher than the numbers reported in the cellulose hydrogel microspheres. By increasing the guar gum content of hydrogel, the cross-link points and density increased, thereby reducing the drug loading into gel beads runoff. The results can also indicated that guar gum with more -OH group contributed to the 5-fu adsorption through hydrogen bonding. However, the microspheres became rigid and the

free volume space decreased with increased guar gum content. These tendencies resulted in a decrease of the 5-fu loading and encapsulation efficiency.

The release behavior of the gel beads was also examined. Figure 8 shows that the guar gum content of the microspheres strongly affected the drug release behavior. When the guar gum content increased from 0 to 33.3%, the cumulative drug release decreased from 76.2 to 50.2% in a 36-h period. The release rate also was clearly reduced. In general, the drug release behavior from the hydrogel was driven by two forces: diffusion effect and degradation or erosion of the hydrogels (Bromberg and Ron 1998; Wang *et al.* 2010). The performance of this drug release indicated that a higher guar gum content hydrogel had a larger amount of water absorbed and displayed a swelling behavior. This can be confirmed from Fig. 5. As a result, by controlling guar gum content, the drug controlled release can be achieved.

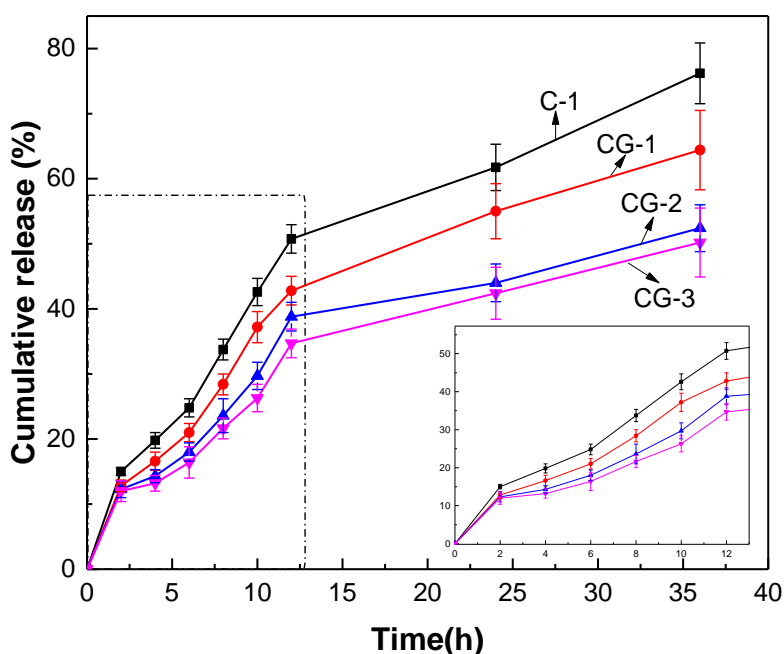


Fig. 8. The effect of guar gum content on drug cumulative release

Effect of Magnetic Content of Hydrogel Microsphere

The loading behavior of 5-fu onto the hydrogel microspheres with different magnetic content was performed, and its loading and encapsulation efficiency profile are displayed in Fig. 9. It was found that the Fe_3O_4 content had a great effect on the loading and encapsulation of 5-fu. When the Fe_3O_4 content increased from 0 to 30%, the drug loading and encapsulation efficiency decreased from 5.3 to 2.7% and 89.1 to 50%, respectively.

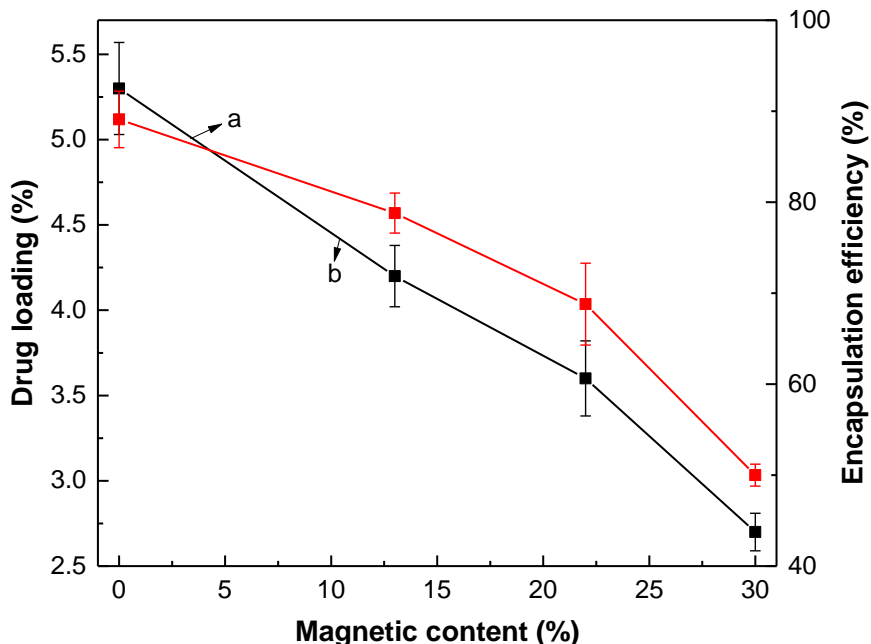


Fig. 9. The effect of magnetic content of hydrogel on drug loading (a) and encapsulation efficiency (b)

The time dependence of 5-fu release from the drug-loading hydrogel microspheres with different magnetic content was investigated. The obtained data was plotted in Fig. 10.

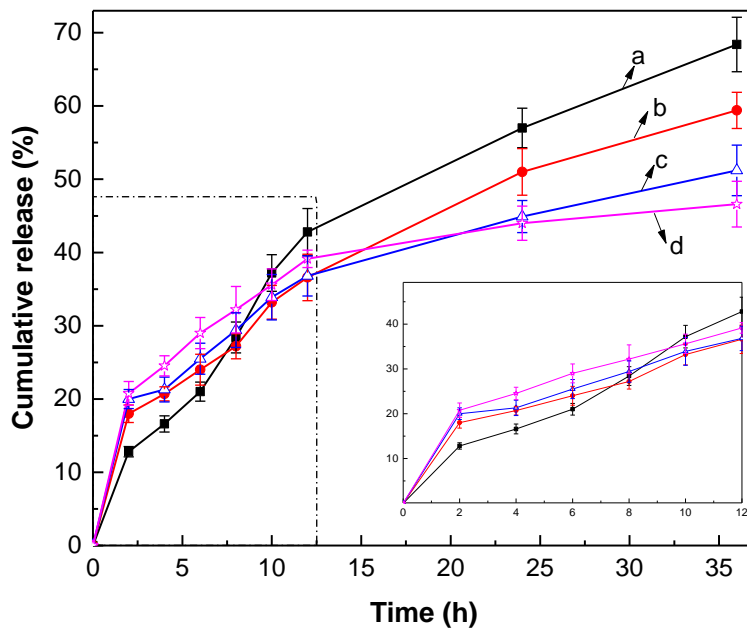


Fig. 10. The effect of magnetic content on drug cumulative release; (a) 0%, (b) 13%, (c) 23%, and (d) 30%

Figure 10 shows that the 5-fu maximum cumulative release and release rate noticeably slowed down when the Fe₃O₄ content increased from 0 to 30% and the cumulative release reached 68.4%, 59.4%, 51.2%, and 46.6% in a 36-h time period when

the Fe₃O₄ content was 0%, 13%, 23%, and 30%, respectively. The results indicated that the Fe₃O₄ content played an important role in reducing the cross-linking concentration such that the microspheres became slack (Gao *et al.* 2014); thereby an increase in the release rate was observed. However, the cumulative release of the drug from gel beads was also prevented by the adsorption of Fe₃O₄ (Wang *et al.* 2017). These tendencies resulted in the decrease of the maximum release in the time of 36 h.

CONCLUSIONS

1. Compared to the cellulose/guar gum hydrogel microspheres, the particle size of the pristine cellulose was higher. As the ratio of cellulose to guar gum increased from 3:1 to 5:1, the particle size increased from 395 to 495 μm .
2. The ratio of cellulose to guar gum had a great influence on the drug loading and release behaviors. When the ratio of cellulose/guar gum were 5:1, 4:1, and 3:1, the 5-fu loading was 5.3, 3.5, and 1.5%, and the encapsulation efficiency increased to 89.1%, 68.8, and 28.9%, respectively. Moreover, when the ratio of cellulose to guar gum increased from 3 to 5:1, the cumulative drug release decreased from 76.2 to 50.2% in a 36-h period.
3. It was indicated that Fe₃O₄ content strongly affected drug loading and release behaviors. When the Fe₃O₄ content increased from 0 to 30%, the drug loading and encapsulation efficiency decreased from 5.3 to 2.7% and 89.1 to 50%, respectively. Additionally, the cumulative release reached 68.4%, 59.4%, 51.2%, and 46.6% in a 36-h time period when the Fe₃O₄ content was 0%, 13%, 23%, and 30%, respectively.

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REFERENCES CITED

- Aravamudhan, A., Ramos, D. M., Jenkins, N. A., Dymont, N. A., Sanders, M. M., Rowe, D. W., and Kumbar, S. G. (2016). "Collagen nanofibril self-assembly on a natural polymeric material for the osteoinduction of stem cells *in vitro* and biocompatibility *in vivo*," *RSC Adv.* 2016(84), 80851-80866. DOI: 10.1039/C6RA15363A
- Babu, V. R., Sairam, M., Hosamani, K. M., and Aminabhavi, T. M. (2007). "Preparation of sodium alginate-methylcellulose blend microspheres for controlled release of nifedivine," *Carbohydr. Polym.* 69(2), 241-250. DOI: 10.1016/j.carbpol.2006.09.027

- Bajpai, A. K., Shukla, S. K., Bhanu, S., and Kankane, S. (2008). "Responsive polymers in controlled drug delivery," *Prog. Polym. Sci.* 33(11), 1088-1118. DOI: 10.1016/j.progpolymsci.2008.07.005
- Barbucci, R., Giani, G., Fedi, S., Bottari, S., and Casolaro, M. (2012). "Biohydrogels with magnetic nanoparticles as crosslinker: Characteristics and potential use for controlled antitumor drug-delivery," *Acta Biomater.* 8(12), 4244-4252. DOI: 10.1016/j.actbio.2012.09.006
- Bledzki, A. K., and Gassan, J. (1999). "Composites reinforced with cellulose based fibres," *Prog. Polym. Sci.* 24(2), 221-274. DOI: 10.1016/S0079-6700(98)00018-5
- Bromberg, L. E., and Ron, E. S. (1998). "Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery," *Adv. Drug Deliver. Rev.* 31(3), 197-221. DOI: 10.1016/S0169-409X(97)00121-X
- Chang, C., Lue, A., and Zhang, L. (2010). "Effects of crosslinking methods on structure and properties of cellulose/PVA hydrogels," *Macromol. Chem. Phys.* 209(12), 1266-1273. DOI: 10.1002/macp.200800161
- Chang, C., and Zhang, L. (2011). "Cellulose-based hydrogels: Present status and application prospects," *Carbohydr. Polym.* 84(1), 40-53. DOI: 10.1016/j.carbpol.2010.12.023
- Chen, W., Zheng, R., Baade, P. D., Zhang, S., Zeng, H., Bray, F., Jemal, A., Yu, X. Q., and He, J. (2016). "Cancer statistics in China, 2015," *CA- Cancer J. Clin.* 66(2), 115-132. DOI: 10.3322/caac.21338
- Fan, J., Li, T., Ren, Y., Qian, X., Wang, Q., Shen, J., and Ni, Y. (2017). "Interaction between two oppositely charged starches in an aqueous medium containing suspended mineral particles as a basis for the generation of cellulose-compatible composites," *Ind. Crop. Prod.* 97, 417-424. DOI: 10.1016/j.indcrop.2016.12.048
- Fan, T., Li, M., Wu, X., Li, M., and Wu, Y. (2011). "Preparation of thermoresponsive and pH-sensitivity polymer magnetic hydrogel nanospheres as anticancer drug carriers," *Colloid. Surface. B* 88(2), 593-600. DOI: 10.1016/j.colsurfb.2011.07.048
- Farooqsarng, D., and Sukonrat, P. (2008). "Thermal behavior of water in the selected starch- and cellulose-based polymeric hydrogels," *Int. J. Pharm.* 352(1), 152-158. DOI: 10.1016/j.ijpharm.2007.10.022
- Gao, Y., Wei, Z., Li, F., Yang, Z. M., Chen, Y. M., Zrinyi, M., and Osada, Y. (2014). "Synthesis of a morphology controllable Fe₃O₄ nanoparticle/hydrogel magnetic nanocomposite inspired by magnetotactic bacteria and its application in H₂O₂ detection," *Green Chem.* 16(3), 1255-1256. DOI: 10.1039/C3GC41535J
- Huang, Y., Yu, H., and Xiao, C. (2007). "pH-sensitive cationic guar gum/poly (acrylic acid) polyelectrolyte hydrogels: Swelling and *in vitro* drug release," *Carbohydr. Polym.* 69(4), 774-783. DOI: 10.1016/j.carbpol.2007.02.016
- Karaaslan, A. M., Tshabalala, M. A., and Buschlediller, G. (2010). "Wood hemicellulose/chitosan-based semi-interpenetrating network hydrogels: Mechanical, swelling and controlled drug release properties," *BioResources* 5(2), 1036-1054. DOI: 10.15376/biores.5.2.1036-1054
- Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., and Peppas, N. A. (1983). "Mechanisms of solute release from porous hydrophilic polymers," *Int. J. Pharm.* 15(1), 25-35. DOI: 10.1016/0378-5173(83)90064-9

- Li, X., Wu, W., and Liu, W. (2008). "Synthesis and properties of thermo-responsive guar gum/poly(n-isopropylacrylamide) interpenetrating polymer network hydrogels," *Carbohydr. Polym.* 71(3), 394-402. DOI: 10.1016/j.carbpol.2007.06.005
- Liu, C., Wei, N., Wang, S., and Xu, Y. (2009). "Preparation and characterization superporous hydroxypropyl methylcellulose gel beads," *Carbohydr. Polym.* 78(1), 1-4. DOI: 10.1016/j.carbpol.2009.02.024
- Liu, T. Y., Chen, S. Y., Lin, Y. L., and Liu, D. M. (2006a). "Synthesis and characterization of amphiphatic carboxymethyl-hexanoyl chitosan hydrogel: Water-retention ability and drug encapsulation," *Langmuir* 22(23), 9740-9745. DOI: 10.1021/la061471n
- Liu, T. Y., Hu, S. H., Liu, K. H., Liu, D. M., and Chen, S. Y. (2006b). "Preparation and characterization of smart magnetic hydrogels and its use for drug release," *J. Magn. Magn. Mater.* 304(1), e397-e399. DOI: 10.1016/j.jmmm.2006.01.203
- Nan, L., and Bai, R. (2005). "Copper adsorption on chitosan-cellulose hydrogel beads: Behaviors and mechanisms," *Sep. Purif. Technol.* 42(3), 237-247. DOI: 10.1016/j.seppur.2004.08.002
- Nurunnabi, M., Parvez, K., Nafiujjaman, M., Revuri, V., Khan, H. A., Feng, X., and Lee, Y. (2015). "Bioapplication of graphene oxide derivatives: Drug/gene delivery, imaging, polymeric modification, toxicology, therapeutics and challenges," *RSC Adv.* 5(52), 42141-42161. DOI: 10.1039/c5ra04756k
- O'Connor, S. M., and Gehrke, S. H. (2015). "Synthesis and characterization of thermally - responsive hydroxypropyl methylcellulose gel beads," *Journal of Applied Polymer Science*, 66(7), 1279-1290. DOI:10.1002/(SICI)1097-4628(19971114)66:73.0.CO;2-D
- Qin, X., Lu, A., Cai, J., and Zhang, L. (2013). "Stability of inclusion complex formed by cellulose in naoh/urea aqueous solution at low temperature," *Carbohydr. Polym.* 92(2), 1315-1320. DOI: 10.1016/j.carbpol.2012.10.004
- Rani, M., Agarwal, A., and Negi, Y. S. (2010). "Review: Chitosan based hydrogel polymeric beads - As drug delivery system," *BioResources* 5(4), 2765-2807. DOI: 10.15376/biores.5.4.2765-2807
- Salmawi, K. E. (2007). "Application of polyvinyl alcohol (PVA)/carboxymethyl cellulose (CMC) hydrogel produced by conventional crosslinking or by freezing and thawing," *J. Macromol. Sci. A* 44(6), 619-624. DOI: 10.1080/10601320701285045
- Shaghaleh, H., Xu, X., and Wang, S. (2018). "Current progress in production of biopolymeric materials based on cellulose, cellulose nanofibers, and cellulose derivatives," *RSC Adv.* 8(2), 825-842. DOI: 10.1039/C7RA11157F
- Sinha, V. R., and Kumria, R. (2001). "Polysaccharides in colon-specific drug delivery," *Int. J. Pharm.* 224(1), 19-38. DOI: 10.1016/S0378-5173(01)00720-7
- Uekama, K., and Otagiri, M. (1987). "Cyclodextrins in drug carrier systems," *Crit. Rev. Ther. Drug* 3(1), 1-40. DOI: 10.1097/00002826-198710000-00013
- Uhrich, K. E., Cannizzaro, S. M., Langer, R. S., and Shakesheff, K. M. (1999). "Polymeric systems for controlled drug release," *Chem. Rev.* 99(11), 3181-3198. DOI: 10.1021/cr940351u
- Wang, K., Xu, X., Wang, Y., Yan, X., Guo, G., Huang, M., Luo, F., Zhao, X., Wei, Y., and Qian, Z. (2010). "Synthesis and characterization of poly(methoxyl

ethylene glycol-caprolactone-co-methacrylic acid-co-poly(ethylene glycol) methyl ether methacrylate) pH-sensitive hydrogel for delivery of dexamethasone,” *Int. J. Pharm.* 389(1), 130-138. DOI: 10.1016/j.ijpharm.2010.01.026

Wang, L., Yu, Y., and Yao, W. (2017). “Preparation of nanocrystalline Fe₃O₄ and study on their adsorption performance for congo red,” *Inorg. Chem. Ind.* 49(4), 37-40, 45.

Xu, J. Y., Yuan, T. Q., Xiao, L., and Sun, R. C. (2018). “Effect of ultrasonic time on the structural and physico-chemical properties of hemicelluloses from *Eucalyptus grandis*,” *Carbohyd. Polym.* 195, 114. DOI: 10.1016/j.carbpol.2018.04.067

Yakup Arica, M. (2015). “Immobilization of polyphenol oxidase on carboxymethylcellulose hydrogel beads: Preparation and characterization,” *Polym. Int.* 49(7), 775-781. DOI: 10.1002/1097-0126(200007)49:7<775::AID-PI454>3.0.C

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