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Facile One-Pot Synthesis of Iron Oxide Nanoparticles Cross-linked Magnetic Poly(vinyl alcohol) Gel Beads for Drug Delivery

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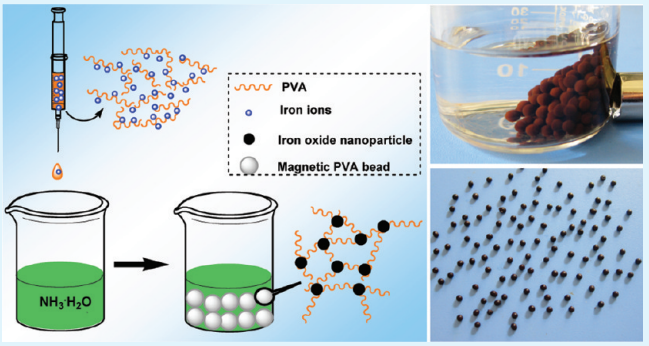
ABSTRACT: In this paper, a facile one-pot strategy for scalable synthesis of robust magnetic poly(vinyl alcohol) (mPVA) gel beads is developed. Through dropwise addition of mixed aqueous solution of iron salts and PVA solution into alkaline (e.g., ammonia, NaOH, and KOH) solution, mPVA gel beads with uniform size and excellent superparamagnetic property can be fabricated based on the simultaneous formation of magnetic iron oxide nanoparticles (MIONs) and cross-link of PVA chains. Moreover, this approach can be extended to prepare dual- or multiresponsive gel beads through simply adding functional fillers into PVA solution (e.g., mPVA-PNIPAM gel beads that possess both magnetic and temperature responsibilities can be readily prepared by adding temperature responsive poly(N-isopropylacrylamide) (PNIPAM) into PVA solution). It is found that that the obtained mPVA gel beads exhibit high drug loading level (e.g., above 70%) after the treatment of freezing-thawing. Drug release experiments reveal that the drug release rate and amount of the mPVA gel beads can be tuned by operating the external magnetic field and adjusting the concentration of iron oxide nanoparticles and temperature (for mPVA-PNIPAM gel beads). The present work is of interest for opening up enormous opportunities to make full use of magnetic gel beads in drug delivery and other applications, because of their facile availability, cost-effective productivity, and tunable drug release performance.



KEYWORDS: *one-pot, magnetic gel bead, poly(vinyl alcohol), responsibility, drug delivery*

1. INTRODUCTION

Controlled drug delivery systems (DDS) for modern drug therapy have attracted increasing attention, because they can display low toxicity, wide therapeutic window, and ideal drug efficacy as compared with conventional DDS.[1−3] Polymeric material, specifically based on polymer hydrogel, is being used as one of the most attractive matrices for construction of DDS in the past decade.[4−7] In particular, controlled DDS based on responsive hydrogels that can sustain release drugs in response to environmental stimuli such as temperature, pH, ionic strength, and magnetic field comes currently to the forefront of drug delivery research.[8−12] Among various responsive hydrogels, magnetic hydrogel (MH, also called ferrogel) is especially attractive for controlled DDS because its release behavior can be actuated controllably using an external magnetic field through noncontact stimuli.[13−15]

Magnetic iron oxide nanoparticles (MIONs) have been developed as promising materials for biological applications such as magnetic resonance imaging (MRI),[16] magnetically targeted hyperthermia,[17] drug delivery,[18] and immobilization of proteins,[19] taking advantages of their intrinsic magnetic property and favorable biocompatibility.[20] To facilitate their bioapplications, it is essential to tailor the surface of MIONs with functional molecules (e.g, anticancer agents, fluorescence labels, and biocompatible molecules) or incorporate the MIONs into cross-linked polymer matrices such as poly(vinyl alcohol) (PVA), gelatin, and poly(N-isopropylacrylamide) (PNIPAM) to afford MHs.[21,22] To date, two main strategies have been adopted to prepare MHs: "hydrogel first" and "MIONs first". The "hydrogel first" involves first synthesizing hydrogels, and then immersing the presynthesized hydrogels into aqueous solution of iron salts to adsorb iron ions, and finally immersing the adsorbed hydrogels into alkaline solution to in situ generate MIONs.[23−26] This approach allows for facile control over the structure and component of the hydrogels. However, it requires multiple steps, and more unfortunately, the MIONs in MHs are not stable and may leach from the polymer matrix without strong anchoring. The "MIONs first" method is to first blend presynthesized MIONs with polymer in solution and then cross-link the polymer.[27−30] This protocol is facile to conduct, but the presynthesized MIONs in polymer matrix easily aggregate, causing reverse influence for drug delivery application. Therefore, it is worthwhile to explore a

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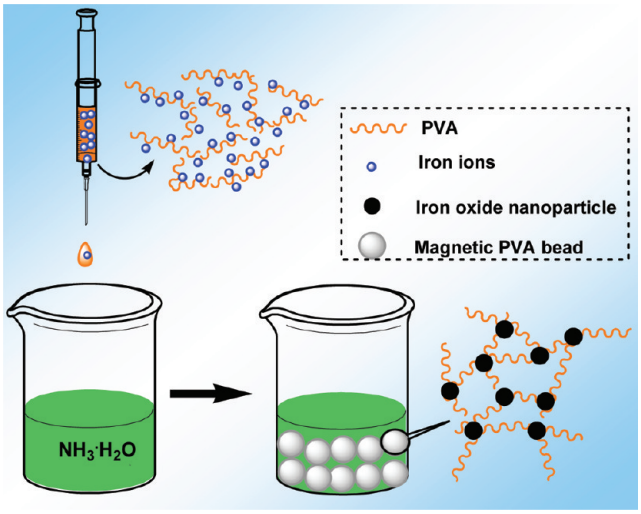
novel method for the fabrication of MHs, which is supposed to be featured as facile and effective.

Among various polymer matrices, increasing attention was paid on PVA, a biodegradable, biocompatible, water-soluble, and inexpensive polymer.[31−33] Previous PVA-based MHs were synthesized based on the "MIONs first" strategy by either chemical cross-link method using irradiation,[34] chemical cross-linking agents such as glutaraldehyde[35] or physical cross-link of PVA chains by freezing-thawing treatment.[36−40] However, the MIONs in the previously reported PVA-based MHs only acted as a functional filler to impart magnetic responsibility to the hydrogels, and thus they may be easily exuded from the MHs. On the other hand, gel bead as a unique shape of hydrogels has been widely studied for drug delivery because of its uniform shape and small size as compared with the conventional hydrogels.[41−43] However, the application of magnetic gel beads for drug delivery was rarely reported.

In this contribution, a novel one-pot strategy for scalable fabrication of magnetic PVA (mPVA) gel beads under room temperature is reported, employing a facile dropwise addition of mixed aqueous solution of iron salts and PVA into alkaline solution (see Scheme 1). The mPVA gel beads were formed immediately based on the simultaneous in situ formation of MIONs and three-dimensional cross-linked PVA networks. The MIONs here not only provide magnetic responsibility but also act as cross-linker for PVA chains. Our synthesis protocol possesses the following merits: (1) the formation of MIONs and gels was achieved in the same reactor by one step, which makes the synthetic process facile and fast; (2) simultaneous in situ formation of MIONs and cross-link of PVA chains not only leads to the uniform dispersion of MIONs but also makes the MIONs stable in PVA matrix;[44,45] (3) PVA is a biodegradable and biocompatible polymer with low cost, thereby the mPVA gel beads are promising in practical applications;[31−33] and moreover, (4) it is very convenient to add other functional fillers into PVA solution to afford dual- or multiresponsive gel beads. In addition, the drug loading and release properties of the mPVA gel beads were investigated in details. Meanwhile, mPVA-PNIPAM gel beads that simultaneously possess temperature and magnetic responsibilities were prepared and their drug delivery behaviors at different temperatures were also investigated.

Scheme 1. Schematic Illustration of Preparing Magnetic PVA (mPVA) Gel Beads by One-Pot Strategy



2. EXPERIMENTAL SECTION

Materials. Poly(vinyl alcohol) (M_w 89 000), iron(III) chloride ($FeCl_3$) powder, iron(II) chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$), tetramethylenediamine (TEMED), ammonia solution (25 wt %), potassium persulfate ($K_2S_2O_8$), and congo red (CR) were purchased from Aladdin Chemistry Co. Ltd. (Shanghai, China) and used as received. Poly(N-isopropylacrylamide) (PNIPAM) was prepared in our lab according to the literature.[46]

Preparation of mPVA Gel Beads. To well-study the influence of reaction conditions on the properties of mPVA gel beads, a series of mPVA gel beads were prepared by adjusting the feed amounts of PVA, iron salts and PNIPAM (see Table 1). In a typical procedure, appropriate amount of $FeCl_3$ and $FeCl_2{\cdot}4H_2O$ (the molar ratio of $FeCl_3/FeCl_2{\cdot}4H_2O$ was kept as constant at 2:1) were added into the aqueous solution of PVA (500 mg, 50 or 100 mg/mL) and the mixture was stirred at room temperature for 30 min. Then, the mixture was gradually dropped into15 mL of ammonia solution (or other alkaline solutions such as aqueous solution of NaOH and KOH) and black mPVA gel beads were formed immediately. After repeatedly being washed by deionized water, the resulting magnetic beads were kept in water. The percentage range of the sol fraction (SF) was determined by weighing and analyzing the resulting solid after drying the residue ammonia solution and the washing solution. It was found that the SF of all the samples was below 2.5 wt %. In addition, mPVA-PNIPAM gel beads were prepared in the same condition as above except the addition of PNIPAM into the mixture of PVA and $FeCl_3/FeCl_2{\cdot}4H_2O$ solution. The SF of mPVA-PNIPAM gel beads was 2.8 wt %.

Table 1. Reaction Conditions for Magnetic PVA Gel Beads

sample	C_{PVA} (mg/mL)[a]	C_{MIONs} (mg/mL)[b]	C_{PNIPAM} (mg/mL)
mPVA-1	50	18	0
mPVA-2	100	18	0
mPVA-3	50	9	0
mPVA-4	50	24	0
mPVA-5	50	18	10
mPVA-6	50	18	20

[a]The total weight of the PVA for preparing each sample was 500 mg. [b]The weight of MIONs was calculated from the feed amounts of iron salts.

mPVA Gel Beads by Freezing and Thawing. Typically, mPVA gel beads after removal of their surface water were transferred to a freezer whose temperature is −15 °C and maintained for 12 h. Then the frozen mPVA gel beads were defrozen at 25 °C for 3 h. The above freezing−thawing process was repeated for five times. After that, the mPVA gel beads were stored at 25 °C.

Swelling Measurements. The swelling properties of the mPVA gel beads before and after 5 cycles of freezing−thawing were determined. The swelling ratio was calculated as follows:

$$\text{swelling ratio} = (W_s - W_d)/W_d$$

where W_d and W_s are the weight of dried mPVA gel beads before and after immersing in aqueous solution for 48 h, respectively.

In addition, the stability of the mPVA gel beads was studied. First, the mPVA gel beads were immersed in aqueous solution for 48 h, and then the mPVA gel beads were separated and the residue aqueous solution was evaporated and weighed. It is found that all the mPVA gel beads showed very little (below 3.5 wt %) weight loss.

Loading CR Molecules by mPVA Gel Beads. The CR dye in here was used as a model drug molecule. For loading CR molecules, 100 mg of mPVA gel beads after 5 cycles of freezing−thawing were left to soak in 3 mL of an aqueous solution of CR (0.1 mmol/L) at room temperature for 48 h. The CR loading efficiency was determined by measuring the amount of free CR remained in the supernatant

solution after collection of mPVA gel beads by magnetic separation. For detection of CR, absorption wavelength of 497 nm was recorded by UV−vis spectrophotometer. Loading level (LL %) = (the total amount of CR used − the amount of CR in the supernatant solution)/(the total amount of CR used) × 100%.

Loading Kinetics Studies. To investigate the loading kinetics of the mPVA gel beads for CR, typically, we left 45 mg of mPVA gel beads after 5 cycles of freezing−thawing to soak in 3.5 mL of an aqueous solution of CR (0.085 mmol/L) at room temperature. After predetermined intervals time, the mPVA gel beads were collected by a magnet and the liquid were taken to be analyzed by UV−vis absorption spectroscopy by monitoring the absorbance changes at a wavelength of maximum absorbance. The amount of CR loaded by the gel beads was calculated from the following mass balance equation[47]

$$Q_t = \frac{(C_0 - C_t)V}{m}$$

where Q_t (mmo/g) is the amount adsorbed per gram of mPVA gel beads at time t, C_0 is the initial concentration of CR in the solution (mmol/L), C_t is the concentration of CR at time t (mmol/L), V is the volume of the solution (L), and m is the mass of the gel beads used (g).

Drug Release from mPVA Gel Beads. A magnetic field, which was provided by an immobilized magnet (5000 Gs), was applied to control the drug release profiles from the magnetic gel beads. For the drug release experiment, the release of CR was also determined with a UV−vis spectrophotometer at λ_{max} = 497 nm at a function of time. The typical procedure used as follows: the above CR-loaded mPVA gel beads were kept immersed in 3 mL water of pH 7.0 at room temperature (or at 40 °C). At specific intervals, the supernatant solution was collected for analysis by UV spectrophotometer. Each experiment was carried out in triplicate. Release % = (the amount of CR released from mPVA gel beads)/(the total amount of CR loaded by mPVA gel beads) × 100%.

Characterization. X-ray powder diffraction (XRD) spectra were taken on a Holland PANalytical X-Pert PRO X-ray diffractometer with Cu−Kα radiation. Absorption spectra were recorded on a UV-3600 UV−vis-NIR spectrophotometer (Shimadzu). The magnetic moment was recorded at 300 K on a MPMS XL-7 vibrating-sample magnetometer (VSM). Thermogravimetric analysis (TGA) was carried on a NETZSCH STA 449C analyzer with a heating rate of 20 °C min^{-1} in nitrogen flow. Scanning electron microscopy (SEM) images were recorded using JSM-6380 LV microscope.

3. RESULTS AND DISCUSSION

Synthesis and Characterization of mPVA Gel Beads. The one-pot approach to large scale synthesis of mPVA gel beads is schematically illustrated in Scheme 1. First, PVA solution and an appropriate amount of iron salts solution were mixed, and subsequently the mixture was added dropwise into ammonia solution (or other alkaline solutions such as aqueous solution of NaOH and KOH). As soon as the mixture contacted the ammonia solution, mPVA gel beads were generated. Obviously, the size of the mPVA gel beads strongly depended on the diameter of the dropper. The obtained mPVA gel beads with spherical shape were dark brown because of the presence of MIONs as shown in Figure 1. In addition, the mPVA gel beads can be easily collected from aqueous solution by a magnet, confirmed their excellent magnetic responsibility (Figure 1b). Compared with the previously reported MHs, these mPVA gel beads have unique advantages for drug delivery due to their small (about 2 mm) and uniform size and spherical shape. Moreover, owing to the facile and fast synthetic process, scalable synthesis of mPVA gel beads in one batch can be readily achieved, which is considerably attractive for practical applications.

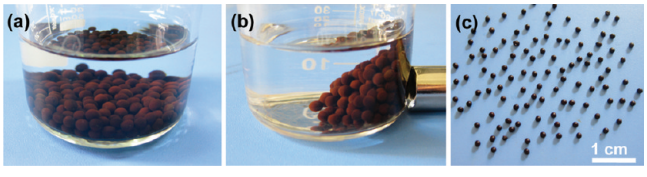


Figure 1. Photographs of the mPVA gel beads.

Our approach to synthesis of mPVA gel beads was perfectly designed based on the consideration of synergetic combination of complexation, coprecipitation, and hydrogening bonding. First, PVA chains can strongly complex iron ions by their numerous hydroxyl groups in aqueous solution. As soon as the mixed aqueous solution of PVA and iron salts contacted alkaline solution, MIONs were in situ formed. The PVA in here acted as stabilizer to inhibit aggregation or further growth of the in situ formed MIONs.[24] At the same time, the MIONs can act as cross-linkers to gelate PVA due to the presence of strong hydrogening bonding interaction between MIONs and hydroxyl groups of PVA chains. This is evidenced by the transition of light yellow PVA-iron salts solution into dark brown mPVA gel beads. To well-investigate the effect of reaction conditions on the properties of the mPVA gel beads, a series of mPVA gel beads were prepared through adjusting the concentration of PVA and iron salts (Table 1). In addition, dual-responsive mPVA-PNIPAM gel beads that simultaneously possess magnetic and temperature responsibilities were also synthesized by adding PNIPAM, whose lower critical solution temperature (LCST) is about 32 °C, into the PVA solution.[46] It should be pointed that almost all the PVA, MIONs, and PNIPAM were incorporated into the mPVA gel beads during the synthetic process based on the determination of the residue weight after evaporating water. In addition, the obtained mPVA gel beads were very stable and very little (below 3.5%) weight loss was detected even the mPVA gel beads were soaked in aqueous solution for 48 h.

To further investigate the stability of the mPVA gel beads, thermo gravimetric analysis (TGA) measurement was performed as shown in Figure 2a. For neat PVA and PNIPAM, they were almost completely decomposed as the temperature approached 500 °C, and their residue weights were 7.0 and 4.8 wt %, respectively. For mPVA-1 and mPVA-5, however, the organic components were completely decomposed until the temperature approached 680 °C, and their residue weights were 35.8 and 31.9 wt %, respectively, suggesting that the mPVA gel beads possess much higher thermal stability than the corresponding polymers. The enhancement of thermal stability is mainly due to the presence of cross-link structure and MIONs components. In addition, the theoretical contents of MIONs according to Table1 for mPVA-1 and mPVA-5 are 26.5 and 23.1 wt %, respectively. The difference of residue weight between mPVA-1 and mPVA-5 from TGA results is 3.9 wt %, which is comparable to the theoretical difference value 3.4 wt %, again indicated that almost all the PVA, MIONs, and PNIPAM were incorporated into the gel beads.

The crystalline structure of mPVA gel beads was determined by XRD measurement as shown in Figure 2b. It can be clearly seen that the peaks at 2θ = 30.1, 35.5, 43.3, 57.3, and 62.7° were assigned to the characteristic peaks of Fe_3O_4, demonstrated that Fe_3O_4 particles were successfully formed in the PVA matrix.[48] The wide peak at 2θ = 19.6° is assigned to the characteristic peak of PVA, confirmed the semicrystalline

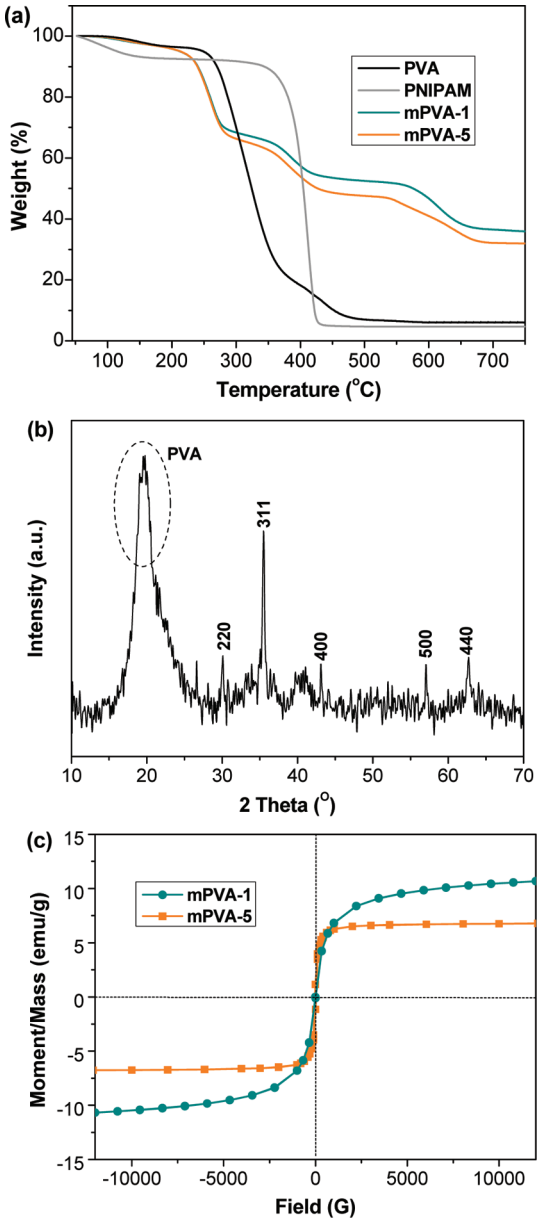


Figure 2. (a) TGA curves of neat PVA and PNIPAM, mPVA-1 and mPVA-5 gel beads. (b) Powder X-ray diffraction (XRD) pattern of the mPVA gel beads. (c) Magnetic hysteresis loops of the mPVA-1 and mPVA-5 gel beads at 300 K.

properties of PVA. Meanwhile, the magnetic properties of mPVA gel beads were measured by VSM at 300 K (Figure 2c). The magnetization curves showed that both mPVA-1 and mPVA-5 gel beads were superparamagnetic with no coercivity at room temperature. The saturation magnetization values for mPVA-1 and mPVA-5 were 10.7 and 6.9 emu/g, respectively, suggesting that magnetic intensity of the mPVA gel beads can be readily tuned by altering the weight ratio of MIONs. This is very important for practical applications because the drug release performance of the mPVA gel beads may be seriously affected by their magnetic intensity when under a certain magnetic field.

Loading Drugs by mPVA Gel Beads. For drug delivery application, the loading level (LL) of the drug carriers is a key parameter in practical application. Here, we chose congo red (CR) as a model drug to investigate the loading and release properties of the mPVA gel beads. The loading process was carried out by immersing dried mPVA gel beads into CR solution for 48 h. It was found that the LL of the as-prepared mPVA gel beads was low (below 50%) (Figure 3b). Such low

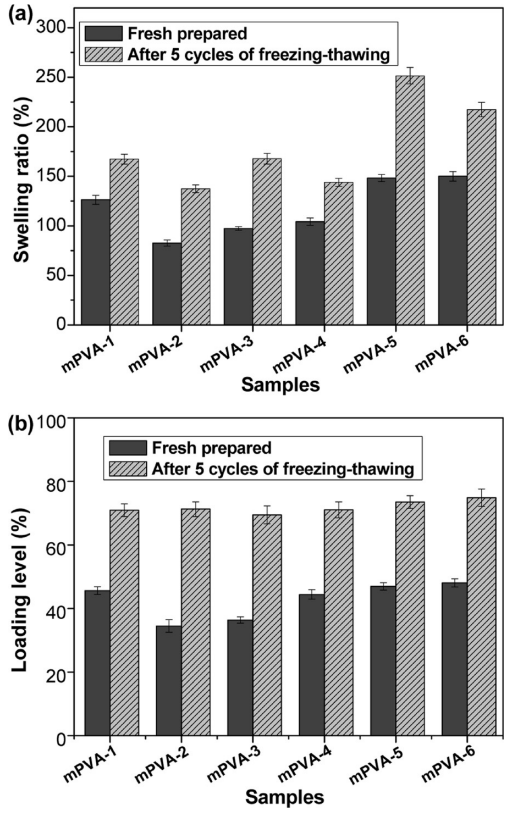


Figure 3. (a) Swelling ratio and (b) loading level of mPVA gel beads of fresh prepared and after 5 cycles of freezing−thawing.

LL is mainly due to the absence of enough cross-linking density in PVA matrix. To enhance the LL of the mPVA gel beads, freezing and thawing treatment was conducted. It was reported that the treatment of freezing and thawing could greatly increase the cross-linking density of PVA hydrogels.[40,49] At low temperature (e.g., −15 °C), the size of ice increases and the motion of PVA chains became very slow as compared with at room temperature, so hydroxyl groups had more contact time to participate in hydrogen bonding. The cycle of freezing−thawing was performed by 5 times and the weight of mPVA gel beads was measured in each time. It was found that the weight of mPVA gel beads decreased significantly as the increase of cycles, indicating the formation of cross-link points and the losing of free water in the interior of mPVA gel beads.

In addition, the swelling properties of the mPVA gel beads before and after 5 cycles of freezing−thawing were studied as shown in Figure 3a. It is well-known that suitable increase of the cross-linking density before excess cross-link can improve the swelling ratio of the gels. Tan and co-worker reported that increase of the cross-linking density of poly(aspartic acid) superabsorbent hydrogels through freezing-thawing treatment can significantly enhance their swelling ratio.[50] As expected, all the samples showed an increase of swelling ratio after 5 cycles of freezing−thawing. To further study the influence of freezing−thawing treatment on the structural variation of mPVA gel beads, their morphology before and after 5 cycles of freezing-thawing was observed by scanning electron microscopy

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(SEM) as shown in Figure 4. It can be clearly seen that the fresh prepared mPVA gel beads showed very smooth surface.

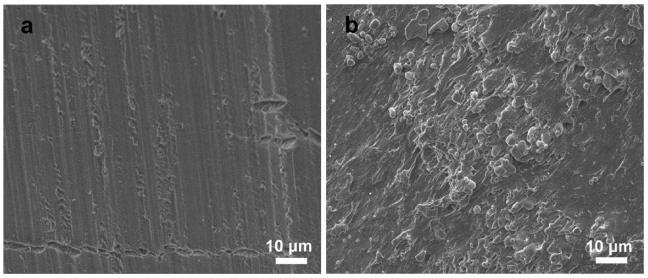

Figure 4. SEM images of mPVA-1 gel beads of (a) fresh prepared and (b) after 5 cycles of freezing−thawing.

After the treatment of freezing-thawing, the surface became coarse with many small pores (Figure 4b), confirming the increase of cross-linking density and the losing of free water. Therefore, it is expected that the treatment of freezing−thawing can enhance the drug loading level of the mPVA gel beads. To our delight, drug loading results indicated that the LL of mPVA gel beads were significantly increased after freezing-thawing (e.g., the LL of mPVA-1 increased from 45.64 to 70.92%), posing a good platform for the following drug release application (Figure 3a). Generally, the mPVA gel beads exhibited a high LL (above 70%).

To well-probe the drug loading process, loading kinetics of the mPVA gel beads was studied. The effect of contact time on the loading of CR by mPVA-1 and mPVA-5 is presented in Figure 5. The initial concentration of CR is 0.085 mmol/L. As can be seen, 50% of CR was loaded within 4 h, and the loading process reached equilibrium in about 10 h for both two samples (Figure 5a). Correspondingly, the loading amounts of CR for mPVA-1 and mPVA-5 are 2.26 and 2.35 mg/g at 4 h, 3.04 and 3.21 mg/g at 10 h, respectively (Figure 5b). We think that the fast loading rate in the first 4 h is mainly resulted from the adsorption of CR by the outmost layer of the mPVA gel beads. After the outmost layer reached loading equilibrium, the interior of the mPVA gel beads began to slow adsorption of CR. In addition, the mPVA gel beads after loading drugs still showed excellent magnetic property as shown in the inset of Figure 5a. Combination of high LL and magnetic property makes the mPVA gel beads promising for bioseparation besides for drug delivery application.

Drug Release Studies. Because the mPVA gel beads can load a large amount of drugs, it is convenient to investigate their drug release properties in vitro. Considering their unique magnetic responsibility, we first investigated the effect of external magnetic field on the release behaviors of the mPVA gel beads. Two typical samples including mPVA-1 and mPVA-5 were chosen and their drug release profiles over time were presented in Figure 6a. As can be clearly observed, the drug release rate and amount of the two samples were both decreased obviously after applying an external magnetic field. This phenomenon was similar to the results reported by Hu et al. on drug delivery application of gelatin-based MH.[44] They ascribed this phenomenon to the formation of magnetic sensitive walls that can decrease the permeability of MH and then retard the drug release under magnetic field as schematically illustrated in Scheme 2. It is worth to note that the prolongation of release time is pursued in actual drug therapy because it can greatly enhance the drug efficacy.[51] In

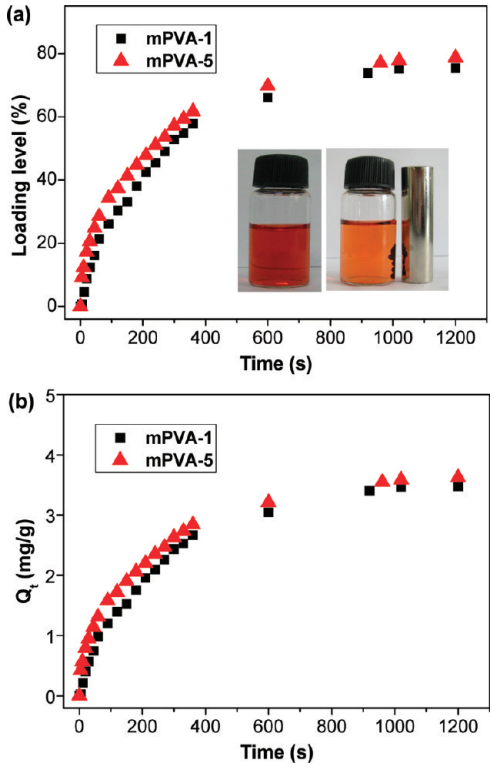

Figure 5. Effect of contact time on the (a) loading level and (b) loading amount of CR (0.085 mmol/L, 3 mL) by mPVA-1 and mPVA-5 gel beads (45 mg) at pH 7.0 and room temperature. The insets of (a) are the photographs of aqueous solution of CR before (left) and after (right) adsorption by mPVA-1 gel beads.

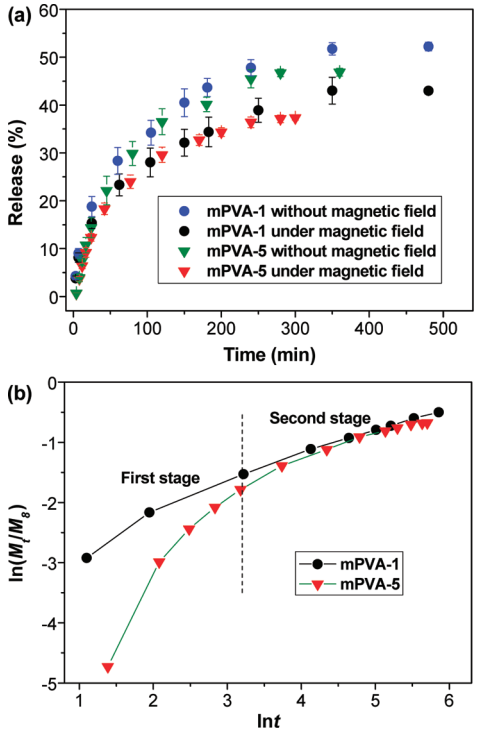

Figure 6. (a) Drug release profiles of mPVA-1 and mPVA-5 gel beads under and without applying magnetic field. (b) The values of $\ln(M_t/M_\infty)$ against $\ln t$ based on the release equation.

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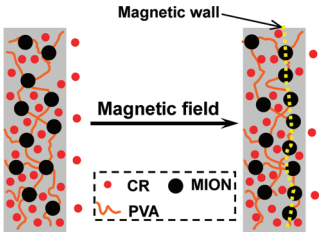
Scheme 2. Schematic Representation of Release of Drugs by mPVA Gel Beads under and without Applying Magnetic Field



addition, it was found that the release rates in the first 60 min were very fast and then presented a relative gently release. This initial burst release is possibly attributed to the quick diffusion of adsorbed drugs from the outermost layer of the mPVA gel beads.

To well-study the release behaviors of the mPVA gel beads under magnetic field, we studied release kinetics by using the classic Korsmeyer–Peppas equation[52,53]

$$\ln\left(\frac{M_t}{M_\infty}\right) = n\ln t + \ln k \quad (1)$$

where M_t/M_∞ is the fraction of drug released after time t relative to the amount of drug released at infinite time, n is a characteristic exponent related to the mode of transport of drug, and k is a constant. This equation can be utilized to describe the release of drug from a diffusion-controlled system. According to the equation, the plots of ln (M_t/M_∞) versus ln t should give a straight line with the slope of n. However, two obvious stages of the plots were emerged in Figure 6b. At first stage, ln (M_t/M_∞) versus ln t was not linear possibly due to the initial diffusion of drugs was mainly happened in the outermost layer of the mPVA gel beads.[44] Nevertheless, at second stage, plots of ln (M_t/M_∞) versus ln t presented a straight line, suggested that the drug release process is well in accordance with the diffusion-controlled mechanism.

To further probe the release properties of the mPVA gel beads, drug release experiments based on a series of mPVA gel beads that prepared by using different concentrations of PVA (C_{PVA}) and MIONs (C_{MIONs}) were investigated. The effect of C_{PVA} on the release of CR is shown in Figure 7a. It was found that the mPVA gel beads prepared with the C_{PVA} 50 mg/mL and 100 mg/mL exhibited similar release behaviors, suggested that the C_{PVA} has no obvious influence on the release of CR. In contrast, the C_{MIONs} presented an obvious influence on the release properties of mPVA gel beads (Figure 7b). On one hand, the release rate and amount of the mPVA gel beads decreased with the increase of the C_{MIONs} to some extent in the absence of magnetic field (e.g, the samples with the C_{MIONs} 9 and 24 mg/mL presented a total released amount of CR 52.1 and 40.2%, respectively). This result is possibly caused by the presence of strong attractive interaction between MIONs and CR. On the other hand, the release rate and released amount of CR were dramatically decreased for the sample with high C_{MIONs} after applying magnetic field. For example, the samples with the C_{MIONs} 9 and 24 mg/mL presented a total released amount of CR 44.3% and 12.7% under magnetic field, respectively. This magnetic responsive release behavior can be explained by the fact that high C_{MIONs} is apt to form magnetic sensitive walls to retard the diffusion of CR from the mPVA gel

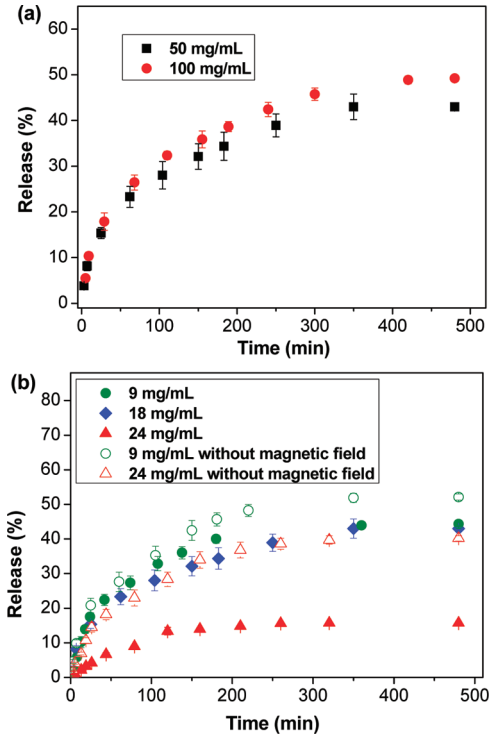


Figure 7. Drug release profiles of mPVA gel beads prepared by using different concentrations of (a) PVA and (b) MIONs.

beads under magnetic field. Therefore, it is also possible to tune the release property of the mPVA gel beads by adjusting the C_{MIONs}.

Recently, dual-responsive DDS has attracted considerable attention because it is more suitable for practical drug delivery application.[54−58] Because of the robustness of our one-pot synthetic approach, dual-responsive mPVA-PNIPAM gel beads that simultaneously possess magnetic and temperature responsibilities were also synthesized by adding PNIPAM into PVA solution during the preparation of mPVA gel beads. The effect of magnetic field on the drug release behavior of mPVA-PNIPAM gel beads is similar to mPVA gel beads as shown in Figure 6a. In addition, the influence of external temperature on the drug release performance of the mPVA-PNIPAM gel beads was studied. The drug release profiles of mPVA-PNIPAM gel beads with PNIPAM concentrations (C_{PNIPAM}) of 10 mg/mL (mPVA-5) and 20 mg/mL (mPVA-6) at 25 and 40 °C, respectiveyl, are shown in Figure 8. Interestingly, as the temperature increased from 25 to 40 °C, the release rate and released amount of CR by mPVA-PNIPAM gel beads were greatly increased. This phenomenon may be explained as follows: first, when the temperature below the LCST of PNIPAM (at about 32 °C), the hydrophilic PNIPAM chains can adsorb CR molecules through strong interactions, such as van der Waals interaction and hydrogen bonding between the polar group of amide in the side chains of PNIPAM and sulfonic group or amino group of the CR molecules.[59,60] The adsorbed CR molecules can disperse in the pores of the mPVA-PNIPAM gel beads. As the temperature increased to 40 °C, the PNIPAM chains changed from hydrophilic to hydrophobic character, and thus the CR molecules especially adsorbed by PNIPAM were squeezed out from the mPVA-PNIPAM gel beads as schematically illustrated in Scheme 3. In addition, the mPVA-5 and mPVA-6

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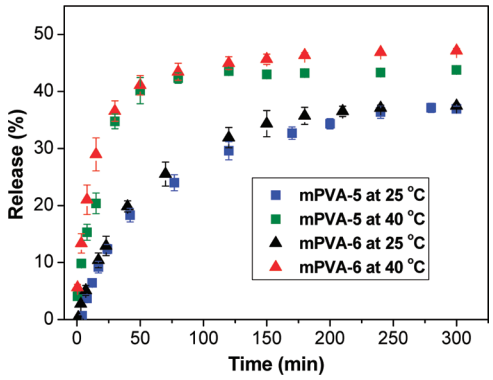
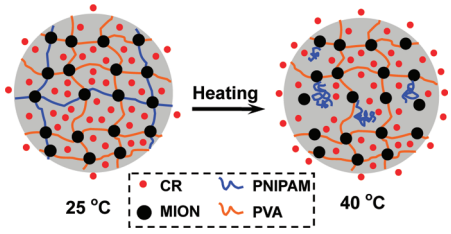


Figure 8. Drug release profiles of mPVA-PNIPAM gel beads at 25 and 40 °C.

Scheme 3. Schematic representation of release of drugs by mPVA-PNIPAM gel beads at 25 and 40 °C



showed similar release performance, suggested that the C_{PNIPAM} 10 mg/mL is enough to prepare a temperature responsive gel beads. Therefore, the drug release properties of the mPVA-PNIPAM gel beads can also be adjusted by altering the external temperature besides the magnetic field.

4. CONCLUSIONS

In conclusion, we successfully demonstrated a simple and effective approach to scalable synthesis of magnetic PVA (mPVA) gel beads. mPVA gel beads with uniform size and excellent superparamagnetic property were prepared via the dropwise addition of mixed aqueous solution of PVA and iron salts into alkaline solution. The PVA acted as stabilizer to inhibit aggregation or further growth of the in situ formed magnetic iron oxide nanoparticles (MIONs), and meanwhile the MIONs acted as cross-linker to gelate PVA. The mPVA gel beads after treating by 5 cycles of freezing-thawing possess high drug loading level. Drug release experiments demonstrated that the drug release rate and amounts of the mPVA gel beads can be tuned by operating magnetic field or adjusting the concentration of MIONs. Dual-responsive mPVA-PNIPAM gel beads that simultaneously possess magnetic and temperature sensitivities were also prepared through simple addition of PNIPAM into PVA solution. Drug release results revealed that their drug release properties were strongly affected by the environmental temperature besides external magnetic field and the concentration of MIONs.

The finding shown in this work clearly highlight the simultaneous formation of MIONs and polymer gels, consequently offering a new strategy for facile and effective synthesis of magnetic gel beads. Moreover, this approach can be extended to prepare dual- or multifunctional gel beads through simply adding functional fillers into PVA solution. It is believed that this work will attract intensive attention from both fundamental research and technological application not only because of the facile and adjustable synthetic strategy but also because of the excellent drug delivery performance of the product.

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