Magnetic-Sensitive Behavior of Intelligent Ferrogels for Controlled Release of Drug

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An intelligent magnetic hydrogel (ferrogel) was fabricated by mixing poly(vinyl alcohol) (PVA) hydrogels and Fe_3O_4 magnetic particles through freezing−thawing cycles. Although the external direct current magnetic field was applied to the ferrogel, the drug was accumulated around the ferrogel, but the accumulated drug was spurt to the environment instantly when the magnetic fields instantly switched "off". Furthermore, rapid to slow drug release can be tunable while the magnetic field was switched from "off" to "on" mode. The drug release behavior from the ferrogel is strongly dominated by the particle size of Fe_3O_4 under a given magnetic field. The best "magnetic-sensitive effects" are observed for the ferrogels with larger Fe_3O_4 particles due to its stronger saturation magnetization and smaller coercive force. Furthermore, the amount of drug release can be controlled by fine-tuning of the switching duration time (SDT) through an externally controllable on−off operation in a given magnetic field. It was demonstrated that the highest burst drug amounts and best "close" configuration of the ferrogel were observed for the SDT of 10 and 5 min, respectively. By taking these peculiar magnetic-sensitive characteristics of the novel ferrogels currently synthesized, it is highly expected to have a controllable or programmable drug release profile that can be designed for practical clinical needs.

Introduction

Stimuli-response polymers represent one class of actuators that have the unique ability to change swelling behaviors, permeability, and elasticity in a reversible manner. Owing to these useful properties, stimuli-response polymers have numerous applications, particularly in medicine, pharmaceutics, drug-delivery, biosensors, and enzyme and cell immobilization.[1,2] More recently, increasing interest has been devoted to the exploration of dual-responsive polymers, such as pH/thermo,[3] thermal/magnetic,[4−6] pH/ electric field,[7] and pH/magnetic[8] sensitive hydrogels, which exhibit considerable sensitivity to external stimuli and can be used in extended fields.

Many kinds of such gels have been developed and studied with regard to their applications to several biomedical and industrial fields such as controlled drug delivery systems and muscle-like soft linear actuators. Saslawski et al. reported the gelatin microsphere that was cross-linked by polyethylenimine for the pulsed delivery of insulin by an oscillating magnetic field.[9] The release rate of insulin from the alginate sphere with strontium ferrite microparticles (1 μm) dispersed can be much enhanced compared with that in the absence of a magnetic field. Zrínyi et al. reported that the magnetically sensitive hydrogels can undergo quick, controllable changes in shape by introducing magnetic particles into the chemically cross-linked PVA that can be used as a new type of actuator to mimic muscular contraction.[10−12] Furthermore, the magnetic-sensitive gels, or "ferrogels", are typical representatives of smart materials for mechanical actuators and have been the subjects of many studies in recent years.[13,14]

Recently, it was reported that the polyelectrolyte microcapsule embedded with Co/Au nanoparticles could increase its permeability to macromolecules such as FITC-labeled dextran by an alternating current (AC) magnetic switch.[15] However, the iron oxide nanoparticles have received wider attentions in diagnostic clinical practice as magnetic resonance imaging enhancers and currently in clinical phase IV are the most successful application of nanotechnologies in medicine.[16,17] So far, to the best of our knowledge, little investigation has been addressed on controlled delivery of therapeutic drugs under direct current (DC) magnetic field through the controlled deformation of the ferrogel based on iron oxide nanoparticles upon a simple "on" and "off" switch mode.

Furthermore, this magnetic-sensitive polymer is even superior to that traditional stimuli response polymer, such as pH or thermal sensitive polymer, because magnetic stimulation is an action-at-distance force (noncontact force) which is easier to adapt to

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biomedical devices. The PVA hydrogel was used because it displays amphoteric characteristics and can be applied in aqueous environment as well as in organic solvent for the encapsulation of amphoteric drugs.[18] Moreover, PVA can be used as dispersing agents to uniformly disperse the Fe_3O_4 particles. In this study, we reported a magnetic-field-sensitive PVA-based ferrogel that can be used for controlled release of therapeutic drugs by external magnetic stimulation. The responsivity and characteristics of the PVA-based ferrogel are systematically investigated in terms of iron oxide particles and swelling behaviors. Furthermore, a mechanism of drug release via the on−off operation is also proposed.

Materials and Methods

Ferrogel Preparation. The intermolecular interactions such as hydrogen-bond-bridges or polymer microcrystals are responsible for the formation of the three-dimensional network structure. A so-called freezing−thawing technique was used to prepare the ferrogel.[18] First, 5 wt % poly(vinyl alcohol) (PVA, Fluka, M_w = 72 000, degree of hydrolyzation: 97.5−99.5 mol %) was dissolved in 10 mL of dimethyl sulfoxide (DMSO) at 80 °C under stirring for 6 h and then mixed with 17 wt % of magnetic particles at 60 °C under ultrasonication for 6 h to ensure that the magnetic particles can be well dispersed. Three kinds of magnetic particles were used in this study: (1) larger magnetic particles (LM), diameter ca. 150−500 nm, Aldrich; (2) middle magnetic particles (MM), diameter ca. 40−60 nm, Alfa Aesar; (3) smaller magnetic particles (SM), diameter ca. 5−10 nm, fabricated by an in situ coprecipitation process.[19] The resulting solution was then poured into a plastic dish and kept frozen at −20 °C for 16 h. Subsequently, the gels were thawed at 25 °C for 5 h. This cyclic process including freezing and thawing was repeated 5 times. Finally, prior to the release test, the ferrogels were washed five times and then immersed in the water for 24 h to completely remove DMSO.

The physical gels prepared by this method were stored at 4 °C until they were measured. The swelling ratio (SR) of the ferrogel[20] is defined as

$$\mathrm{SR} = \frac{W_t - W_{dry}}{W_{dry}} \quad (1)$$

where W_{dry} and W_t are the weight of the dry ferrogel and the ferrogel at time t under magnetic-field (MF, 400 Oe) switching, respectively. The free liquid on the surface of the swollen ferrogel was padded dry with filter papers before weighing.

Drug Diffusion Characterizations.[20] The diffusion coefficients of the solutes were measured under switching MF (400 Oe) in a diffusion diaphragm cell (side-by-side cell). The solution in the donor side is 80 mL of isotonic phosphate buffer (PBS) (pH7.4) containing 200 ppm of the model drug (vitamin B_{12}). The receptor compartment, separated by the ferrogel, was filled with 80 mL of PBS solution. The concentration of each compound in the receptor compartment was determined at λ = 361 nm using a UV spectrophotometer. The diffusion coefficient was calculated according to the following equation for the diaphragm cell:

$$\ln\left(\frac{C_{d0}}{C_d - C_r}\right) = \frac{2PAt}{\delta V} \quad (2)$$

where C_{d0} is the initial concentration of the permeant in the donor compartment; C_d and C_r are indicative of the concentrations in the donor side and receptor side, respectively; P is the permeability coefficient (cm²/min); A is the effective area of the ferrogel; δ is the thickness of the ferrogel; V are respectively the volumes of solution in the donor and receptor compartment (both are 80 mL). By plotting $\ln[C_{d0}/(C_d - C_r)]$ versus time (t), the permeability coefficient (P) can be calculated from the slope of the line by eq 2. Each data point was obtained by averaging of at least three measurements.

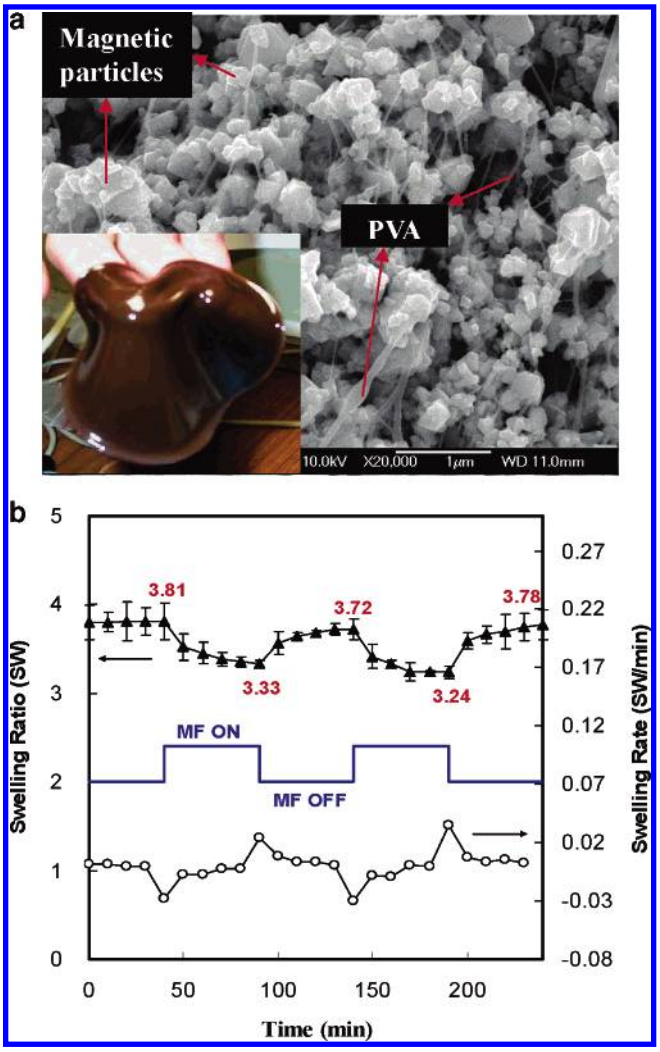

Figure 1. (a) Cross-sectional SEM image of magnetic particles disperse in PVA hydrogels and OM photos of PVA5-LM17 ferrogels; (b) Swelling ratio and swelling rate of PVA5-LM17 ferrogel in the magnetic fields switching "on−off" mode.

Results and Discussion

Characterization of Magnetic-Sensitive Ferrogels. Figure 1a illustrates the photographs of magnetic-sensitive PVA-based (PVA5-LM17) ferrogels, where PVA5-LM17 represents the synthesis of the ferrogels with PVA concentration of 5 wt % and larger-sized magnetic particles (LM) of 17 wt % in this work. Moreover, it is observed that the magnetic-sensitive hydrogel exhibits excellent flexibility and elasticity. Furthermore, it was observed that the Fe_3O_4 nanoparticles were uniformly distributed in the PVA ferrogels as shown in the cross-sectional SEM image as no magnetic field was applied. However, as the magnetic field (MF) was developed, a volume change in response to the on−off magnetization was observed for the PVA ferrogel. This phenomenon seems to reveal that the magnetic Fe_3O_4 nanoparticles are attracted between adjacent neighbors under a magnetic field. Consequently, it implies that the reduced distance between the magnetic Fe_3O_4 nanoparticles as a result of attraction force induced by a given MF can be used to develop a close configuration of the ferrogel for controlled drug release.

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Table 1. Permeability Coefficient of the Ferrogels in "on" or "off" Mode of a Given Magnetic Field

ferrogel	SDT[a]	MF ON[b] drug amount/ min (P)[c]	MF OFF[d] drug amount/ min (P)[c]	magnetic-sensitive behaviors[e]	max. drug bursting[f]
PVA5-LM17	20	1.42 ± 0.05 (109)	3.53 ± 0.08 (303)	2.11 (194)	8.39 ± 0.23
	10	0.97 ± 0.03 (83)	5.24 ± 0.15 (449)	4.27 (366)	18.56 ± 0.56
	5	**0.46 ± 2 (40)**	**6.71 ± 0.31 (586)**	**6.25 (546)**	**11.95 ± 0.43**
PVA5-MM17	5	0.92 ± 0.05 (77)	3.10 ± 0.34 (261)	2.18 (184)	3.81 ± 0.13
PVA5-SM17	5	0.86 ± 0.03 (74)	4.73 ± 0.25 (406)	3.86 (332)	5.08 ± 0.18
pure PVA5	5	1.09 ± 0.03 (107)	1.08 ± 0.08 (105)	−0.01 (−2)	

[a] SDT means switching duration time of the magnetic field. [b] Average drug permeation amount (μg/min) and permeability coefficient (10^{-6} cm^2/min) at magnetic fields (MF) switching "on" ($n = 3$). [c] Permeability coefficient (P) calculated by eq 2 ($n = 3$). [d] Average drug permeation amount (μg/min) and permeability coefficient (10^{-6} cm^2/min)at MF switching "off" ($n = 3$). [e] Average drug permeation amount (μg/min) and permeability coefficient (10^{-6} cm^2/min) at MF ON. ($n = 3$). [f] Average maximum drug bursting amounts (μg/min) of the drug bursting at the moment of switching MF from "on" to "off" mode. ($n = 3$).

The swelling ratio of the ferrogel is decreased (from 3.81 to 3.33) while MF is switching "on" which is due to its contracting pores, but it is increased (from 3.33 to 3.72) while MF was turned off as shown in Figure 1b. Hence, the decreased swelling ratio of the ferrogel in an MF switching "on" mode may be used to explain the slow diffusion of the drug. Furthermore, the calculated swelling rate is also shown in Figure 1b. A transition of the swelling rate was clearly observed in response to the on−off magnetization. During MF switching from "off" to "on" mode, the swelling rate decreased, and in the opposite case, it increased. The magnetically sensitive swelling behaviors indicated that the ferrogel prepared in this investigation has an excellent magnetic-sensitive property.

The magnetic-sensitive behaviors in the ferrogels can be further expressed by the difference in the permeated drug amount between the MF "off" mode and "on" mode, as shown in Table 1. In addition, the calculated permeability coefficient and maximum amount of drug busting were also included. It was observed that the permeability coefficient of the pure PVA5 hydrogel was determined to be 105×10^{-6} cm^2/min, which is lower than that of the PVA5-LM17 ferrogel, i.e., 586×10^{-6} cm^2/min while the MF is "off". However, when MF switching to the "on" mode, the permeability coefficient of the ferrogel decreased sharply (40×10^{-6} cm^2/min), but that of the pure PVA hydrogels remains almost unchanged (107×10^{-6} cm^2/min). This is essentially due to smaller pore size as a result of agglomeration of the nano-magnetic-particles in the ferrogel. Furthermore, in Table 1, it is further indicated that the magnetic-sensitive behavior of the ferrogel (546×10^{-6} cm^2/min) is much superior to that of the pure PVA gel (-2×10^{-6} cm^2/min). Therefore, with an applied magnetic field, considerable differences in magnetic-sensitive permeability coefficient were detected in the ferrogels, as compared to that in pure PVA hydrogel.

Effects of Switching Duration Time (SDT). In Figure 2a, it was found that the quantity and the release profile of the model drug from the ferrogels are strongly affected by the time duration between each on-to-off stage, and here we defined it as the switching duration time (SDT) of the magnetic field. For a 5-min period of SDT, the drug release profiles demonstrate that the best "close" configuration is where the drug was effectively locked in the ferrogel and no sign of drug release can be detected for the SDT of 5 min.

However, increasing SDT to 10 and 20 min, the "close" configuration of the ferrogel becomes less pronounced as time elapsed, wherein a sign of drug release can be clearly detected, as illustrated in Figure 2a and Table 1. In the case of 20 min of SDT, an effective "close" configuration of the ferrogel that can effectively stop drug release can be kept up for 8−10 min; however, the drug was released, although at a relatively slow rate, from the ferrogel after the "effective" time period. Such an effective SDT can be repetitively observed without considerable chang for a number of repetitive on−off operations. Furthermore, irrespective of the SDT, a normal diffusion release profile can be detected right after the given MF switching from "on" to "off".

Since the "close" configuration of the ferrogel is an indication of particle agglomeration of the magnetic particles within the PVA matrix, on this basis, a considerable reduction of the pore size and an increased tortuosity of the pore channels across the ferrogel membrane can be expected. Both factors will effectively hinder or block the diffusion of the drug solution from the other side (i.e., drug-containing donor side) of the ferrogel. The effective SDT of the ferrogels prepared in this study suggests the existence of an effective "closure" configuration of the ferrogel which seems to compromise with the diffusion potential of the drug solution from one compartment to the other. It is believed that such an effective "close" configuration may be explained as a result of "fatigue" of the agglomerated magnetic particles under a given MF. The fatigue behavior can be possibly due to the relaxation of the polymer gel to relieve the stress that is induced by strain in the gel network when the magnetic particles move in response to the magnetic field. This process may be faster in the presence of smaller particles, which provides an explanation on the rapid increase of permeability compared to the ferrogels with larger particles.

Effects of Fe_3O_4 Particle Size. The influence of Fe_3O_4 particle size on the effective "close" configuration is illustrated in Figure 2b and Table 1, where larger particles (LM) show effectively longer SDT. The results show that the average permeability coefficient (40×10^{-6} cm^2/min) of PVA5-LM17 ferrogel at MF switching "on" for 5 min of SDT is much lower than that (77×10^{-6} and 74×10^{-6} cm^2/min) of PVA5-MM17 and PVA5-SM17 ferrogels. Moreover, the magnetic-sensitive behavior and average maximum drug bursting amount of the PVA5-LM17 ferrogel are much better than those of the PVA5-MM17 and PVA5-SM17 ferrogels.

In another comparative investigation, the effect of particle size on the magnetization using a vibrating sample magnetometer

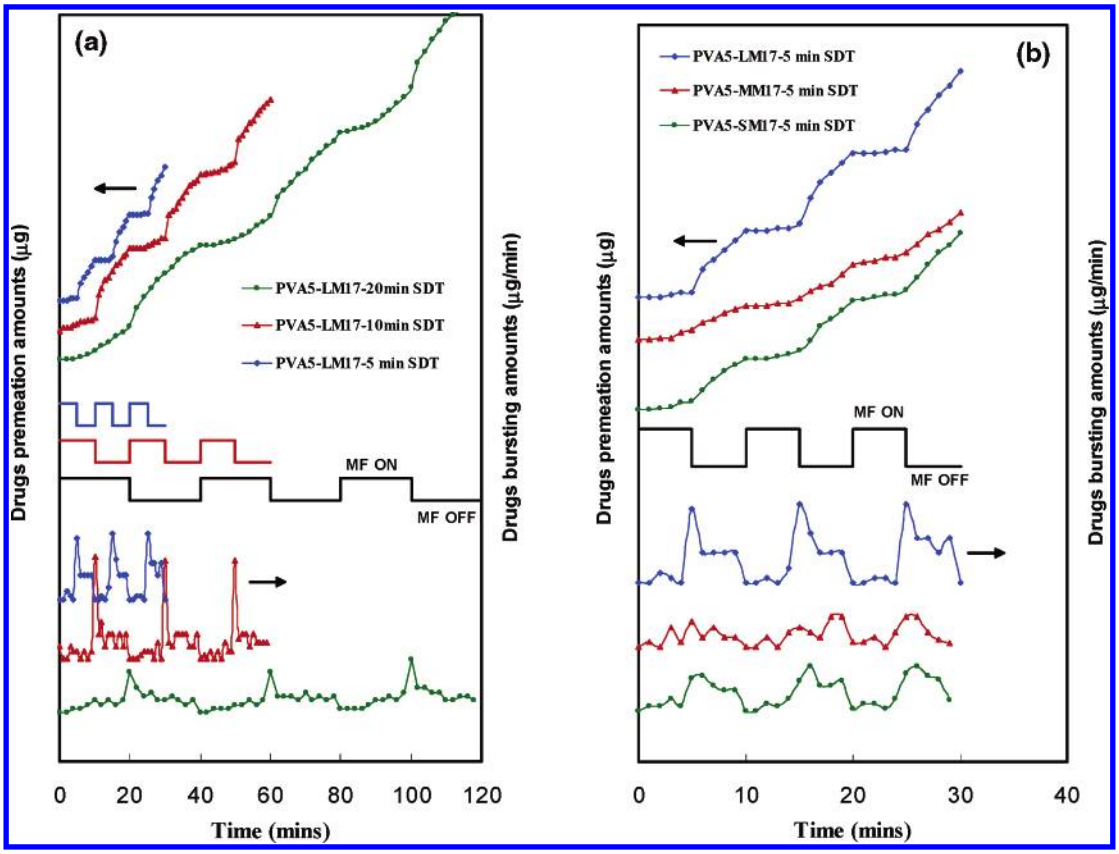

Figure 2. Rapid permeation properties and "close" configuration of the ferrogels dependent on (a) different switching duration time (SDT) and (b) various particle size of Fe_3O_4 of the ferrogels in the continuous switching "on−off" mode for a given magnetic fields; the drug permeation amount on switching "on−off" mode, and corresponding differential curve are shown in each figure in order to show the maximum drug bursting.

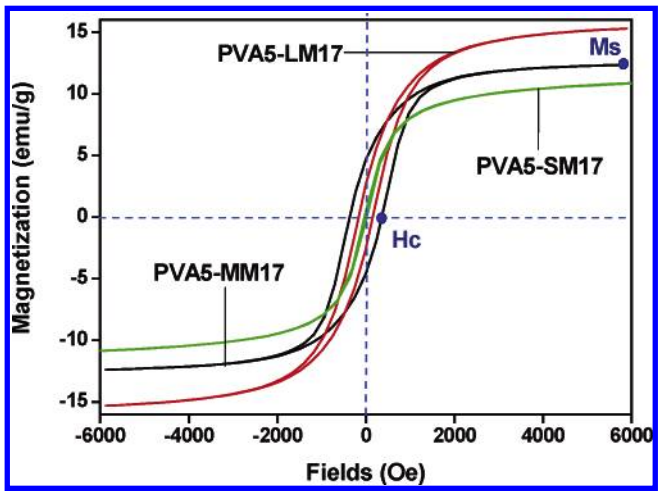

Figure 3. Hysteresis loop analysis of the ferrogels incorporated with various particle sizes of Fe_3O_4.

(VSM, Toei VSM-5, USA) is demonstrated in Figure 3. Ferrogels with larger Fe_3O_4 particle (PVA5-LM17) encapsulated ferrogel display a hysteresis loop with a larger saturation magnetization (Ms) of 15.28 emu/g, compared to those ferrogels with middle and smaller Fe_3O_4 nanoparticles (12.39 emu/g for PVA5-MM17 and 10.84 emu/g for PVA5-SM17), indicating that a strong magnetic field can be induced in the ferrogel. However, the PVA5-MM17 ferrogel presents a broader hysteresis loop and larger coercive force (Hc) than that of PVA5-LM17 (and PVA5-SM17 ferrogels), indicating that it is more difficult to reorient and move the magnetic particles in the ferrogel under magnetic fields. It is known that the hysteresis loss area and Hc are strongly dependent on the particle size and domain characteristics of magnetic particles. The PVA5-MM17 shows larger Hc because its particle size (60 nm) is near the critical size of the single domain which was estimated to be about 100 nm for the Fe_3O_4 particle.[21] Therefore, on this basis, the single-domain MM particles exhibit a greater hysteresis loss area and Hc (353.53 Oe) than the multidomain LM particles (Hc: 159.63 Oe) in a given magnetic field; hence, the magnetic-sensitive behavior and "close" configuration of the PVA5-LM17 ferrogel are superior to those of PVA5-MM17 ferrogel, as shown in Figure 2b and Table 1. On the other hand, although the SM particles display a superparamagnetic behavior with the lowest hysteresis loss area and Hc (17.55 Oe), the Ms of PVA5-SM17 is lower than that of PVA5-LM17, and the fine nanoparticles tend to aggregate together; hence, the observed magnetic-sensitive behavior and "close" configuration of the PVA5-SM17 ferrogel are still less pronounced than that in the PVA5-LM17 ferrogel. The "magnetic-sensitive effects" in those ferrogels are in the order of PVA5-LM17 > PVA5-SM17 > PVA5-MM17 that is dependent on higher Ms and lower Hc, as illustrated in Figure 2b and Table 1. If the above argument is true, then we believe that an "effective SDT" of the ferrogels from a short duration period to a long duration period can be well-designed with different drug release profiles.

Mechanism of Magnetic-Sensitive Drug Release Behavior. The possible mechanism of the drug release profile from the ferrogel is schematically illustrated in Figure 4. In the beginning when there is no magnetic force (MF), the magnetic (fields) moments existing in the ferrogel are randomly oriented. The

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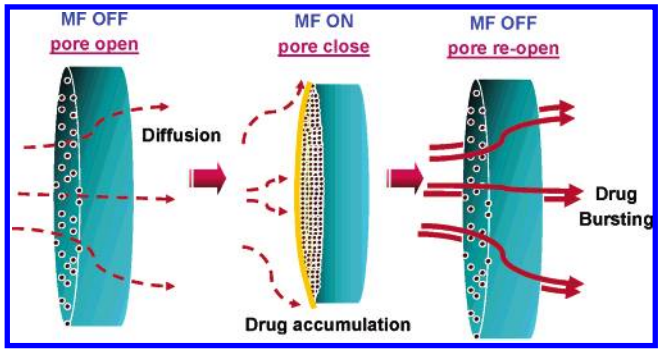

Figure 4. Mechanism of "close" configuration of the ferrogels due to the aggregation of Fe_3O_4 nanoparticles under "on" magnetic fields causes the porosity of the ferrogels to decrease.

ferrogel is subjected to zero magnetization, and the drug release profile displays a normal diffusion mode. While applying MF, the magnetic moments of the particles tend to align with the magnetic fields and produce a bulk magnetic moment. This induces the Fe_3O_4 particles within the ferrogel to aggregate together instantly, leading to a rapid decrease in the porosity of the ferrogel, where the ferrogel was characterized as a "close" configuration. In other words, although the imposed field induces magnetic dipoles, mutual particle interactions occur if the particles are so closely packed that the local field can influence their neighbors. The particles attract with each other when aligned in an end-to-end configuration and thus a "pearl-chain structure" was developed[11] due to the attractive forces that reduced the pore size of the ferrogel. Therefore, the drugs are restrictedly confined in the network of the ferrogel, causing a rapid and significant reduction in the diffusion of the drug through the ferrogel.

When the field is turned off, the pores in the membrane reopen instantly, which correspondingly results in a rapid re-filling of the drug-containing solution into the membrane from the donor side of the membrane, and from the other side of the membrane, the drug solution of both the residual amount and the later refilled amount was released instantly at the moment of pore reopening, resulting in a burst-like profile. However, the release turned back to a normal diffusion profile shortly after the burst. A similar behavior is observed on polyethylenimine cross-linked alginate spheres under oscillating magnetic field.[9] When the three SDTs in the PVA5-LM17 ferrogel are compared, a maximum amount of the drug bursting (18.56 μg/min) from the PVA5-LM17 ferrogel was observed for the SDT of 10 min. That is why the PVA5-LM17 ferrogel after 10 min of SDT displays a more suitable switching duration time and close configuration compared to that after 5 min of SDT and 20-min-SDT, respectively.

In short, the current preliminary investigation suggests a controlled release model together with a predetermined released amount of the drug can be finely tuned through the use of this type of ferrogel, either as a membrane or a bulk structural configuration, via internally or externally magnetically triggered operations. By repeating the "on−off" operation of a given magnetic field, a controllable refilling and a subsequent release of drug from the ferrogel can be programmably designed. A further detailed investigation on the effect of particle size and microstructural variation of the ferrogels on the drug release profile is underway and will be reported shortly.

Concluding Remarks

A PVA ferrogel with magnetic-sensitive properties has been successfully prepared by mixing PVA hydrogels and Fe_3O_4 magnetic particles through freezing−thawing cycles. The best "magnetic-sensitive effects" are observed in PVA5-LM17 ferrogel due to its stronger Ms and smaller Hc. Furthermore, the amount of drug release can be controlled by fine-tuning of the switching duration time (SDT) through an externally controllable on−off operation of the given magnetic field. Moreover, it was found that the amounts of the drug released from the ferrogel can be controlled by changing the duration time between each on−off operation of the magnetic field. This observation suggests that the controlled release of the drug with an adjustable amount can be properly designed for practical needs. This novel ferrogel that displays a magnetic-sensitive behavior can be used as a microdevice with simple and precise control of mechanical movement of the ferrogels for controlled delivery of therapeutic drugs.

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