Research Letter

Fast Drug Release Using Rotational Motion of Magnetic Gel Beads

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Accelerated drug release has been achieved by means of the fast rotation of magnetic gel beads. The magnetic gel bead consists of sodium alginate crosslinked by calcium chlorides, which contains barium ferrite of ferrimagnetic particles, and ketoprofen as a drug. The bead underwent rotational motion in response to rotational magnetic fields. In the case of bead without rotation, the amount of drug release into a phosphate buffer solution obeyed non-Fickian diffusion. The spontaneous drug release reached a saturation value of 0.90 mg at 25 minutes, which corresponds to 92% of the perfect release. The drug release was accelerated with increasing the rotation speed. The shortest time achieving the perfect release was approximately 3 minutes, which corresponds to 1/8 of the case without rotation. Simultaneous with the fast release, the bead collapsed probably due to the strong water flow surrounding the bead. The beads with high elasticity were hard to collapse and the fast release was not observed. Hence, the fast release of ketoprofen is triggered by the collapse of beads. Photographs of the collapse of beads, time profiles of the drug release, and a pulsatile release modulated by magnetic fields were presented.

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1. INTRODUCTION

Many systems of drug release have been fabricated using polymer gel. Polymer gel is a material of open system, and is able to transport drug molecules through crosslinked network of the gel. According to this, spontaneous slow (sustained) release can be achieved. The sustained release is caused by the osmotic pressure difference $\pi_{\text{in}} - \pi_{\text{out}}$ at the inside and outside of the gel [1]. Furthermore, a novel drug delivery system (DDS) was developed by means of various stimuli-responsive polymers. Polymer gels synthesized with the stimuli-responsive polymers undergo a volume phase transition in response to stimuli such as temperature, solvent, or pH. When the gel achieved the volume phase transition, additional pressures are generated on the gel. Owing to the additional pressure contributed from the mixing π_{mix} and elastic π_{el} energies [1], the drug release is accelerated. Thus, the accelerated release of drugs is attributed to the volume contraction triggered by the additional pressures.

Various stimuli-responsive gels responding to temperature, pH, electric field, chemicals, and UV light have been

employed to fabricate the novel drug delivery system. Poly(N-isopropylacrylamide) (PNIPAA) gel is well known for a temperature-sensitive gel which exhibits a volume phase transition originating from the lower critical solution temperature. PNIPAA gel copolymerized with alkyl methacrylates demonstrates complete on-off release of indometacin in response to stepwise temperature changes between 20 and 30°C [2, 3]. The regulated drug release is explained by the squeezing mechanism [4]. A pulsatile release of ketoprofen occurs when the gel was cycled in buffer solutions between pH 3.0 and pH 6.5 [5]. It has been shown that protein lysozyme is released from the carboxy methyl dextran hydrogel membranes in the pH range of 6.5–9.0 [6]. Electrically stimulated drug release of pilocarpine hydrochloride, glucose, and insulin has been fabricated using chemomechanical shrinking and swelling of polyelectrolyte gels under electric fields [7]. A sharp pulsatile release of glucose from a microcapsule of plant lectin has also been demonstrated based on the concept of competitive binding [8]. An on-off modulation for protein permeation by UV irradiation has been constructed by an azoaromatic polymer membrane [9].

In the present study, we attempted to construct the new system of drug delivery using magnetic gels responding to magnetic fields.

It has been reported that the magnetic gel undergoes a variety of motion under magnetic fields. For example, the magnetic gel consisting of magnetic fluids shows elongation by means of the gradient of magnetic field [10, 11], and it has been applied for a fluid valve [12]. Carrageenan magnetic gel containing magnetic particles presents an isotropic deformation under uniform magnetic fields [13]. Recently, we found that the magnetic gel consisting of sodium alginate and barium ferrite particles demonstrates a rotational motion in response to rotational magnetic fields [14, 15]. Using the rotational motion of the magnetic gel, we have succeeded in the fast and controllable release of ketoprofen from the magnetic bead. The release behavior is briefly reported and the mechanism of the fast release is discussed.

2. EXPERIMENTAL PROCEDURES

2.1. Synthesis of magnetic beads

The bead of magnetic gels consists of Sodium alginate (Wako Chemicals, Osaka, Japan) as gel matrices, barium ferrite ($\text{BaFe}_{12}\text{O}_{19}$) (Sigma-Aldrich Co., Mo, USA) as magnetic particles, and (2RS)-2-(3-Benzoylphenyl)propanoic acid (ketoprofen) (Saitama Daiichi Pharmaceutical Co., LTD., Saitama, Japan) as drugs. The chemical structure of ketoprofen is shown in the inset of Figure 2. A pre-gel solution consisting of sodium alginate (0.3 wt.%), barium ferrite (3.0 wt.%), and ketoprofen (9.0 wt.%) was prepared. The ketoprofen was dissolved in methanol before mixing these chemicals. The magnetic gel beads were obtained by dropping the pre-gel solution in a methanol/water mixed solvent containing CaCl_2 (3.0 wt.%). The concentration of methanol in the mixed solvent was 30 vol.%. The obtained beads were stocked in a beaker filled with pure water. The mean diameter of a magnetic particle was determined as $15\ \mu\text{m}$ by using a Particle size analyzer (Mastersizer 2000, Malvern Instruments, Malvern, UK). The bead was irradiated by a 1 T magnetic field for 1 minute in order to give the bead a remanent magnetization.

2.2. UV measurements

The absorbance at 280 nm was measured using a UV spectrometer (Shimadzu UVmini-1240). The measurement was carried out using a flow cell at room temperature. The total volume of the sample space of the flow cell including a flow tube was 34.9 mL. The flow rate was constant to be 46 mL/min. We evaluated the amount of drug released from the gel by the absorbance at 280 nm. The absorbance (Abs) showed linear relationship with the concentration of ketoprofen c_{KP} ; $\text{Abs} = 284.06 \times c_{\text{KP}}$. The data presented in this paper is the drug release in a phosphate buffer solution. The buffer solution was prepared by dissolving potassium hydrogen phosphate (0.8 wt.%, Wako Chemicals) and sodium dihydrogenphosphate (1.5 wt.%, Wako Chemicals) in pure water.

FIGURE 1: Schematic illustration of the geometry of magnetic gel bead and permanent magnet. Photographs representing the collapse of magnetic gel beads by rotational motion with 5000 rpm: (a) 0 minute, (b) 0.5 minute, (c) 1.0 minute, (d) 1.5 minutes.

2.3. Microscope observations

Microscope observations were carried out using a microscope (Digital microscope VHX-900, VH-Z00R, Keyence Co., Osaka, Japan).

3. RESULTS AND DISCUSSION

Figure 1 shows the time course of the shape of magnetic gel beads showing rotational motion. As seen in Figure 1(a), the bead was turbid and it had a shape of sphere with rough surface. Sodium alginate was soluble in water; however ketoprofen was insoluble in water, but soluble in methanol. Immediately after mixing the sodium alginate aqueous solution and ketoprofen/methanol one, the mixed solution was clouded. The solution was stable in emulsion and it did not show any precipitation. It is considered that the emulsion directly gelled by an addition of calcium chloride. The diameter of the bead decreased with an elapse of the rotation time (Figures 1(b)–1(d)). The bead was collapsed and disappeared 3 minutes after starting rotation. This strongly suggests that the bead is easy to collapse by the strong water flow induced by the rotation. Only magnetic particles tied each other and remained in the buffer solution. Magnetic particles embedded in the bead did not disperse in the solution and made a string because each particle has magnetic poles.

Figure 2 shows the effect of rotation on the time profile of the ketoprofen release from the beads. The bead was not rotated till 5 minutes and was rotated at the time indicated by the arrow. Ketoprofen was soluble in not only methanol but

FIGURE 2: Time profile of the ketoprofen release for a magnetic gel bead (sodium alginate: 0.3 wt%, ketoprofen: 5 wt%, barium ferrite: 3 wt%). The bead rotated (5000 rpm) at the time indicated by the arrow.

also phosphate buffer solution (pH~6). Below the time of 5 minutes, the gradual increase in the ketoprofen release was due to spontaneous release from the bead. The bead maintained its spherical shape and the size was not changed. At 5 minutes, it was observed that the ketoprofen release dramatically increased simultaneously with the rotation. Furthermore, the bead was observed to be collapsed remarkably by rotation as shown in the photographs in Figure 1. Therefore, the increase in the ketoprofen release is not attributed to the squeezing effect of drug molecules by volume changes, which has been employed in the drug delivery of polymer gels. Probably the bead was collapsed by strong water flow at the interface between the bead and water generated by the rotation; as a result, the ketoprofen was rapidly released from the bead. Beads were rich in elastic modulus when the concentration of sodium alginate increased. The beads with high elasticity were hard to collapse, and the amount of ketoprofen release has not reached high value seen in Figure 2. The rapid release of ketoprofen was not seen in a magnetized bead without rotation. This means the rapid release was not caused by the collapse due to the magnetic attractive force between magnetic particles. For example, when the concentration of sodium alginate was 2 wt.%, the amount of ketoprofen released from the gel was 0.16 mg at 5 minutes, which equals entirely the value without rotation. These results strongly suggest that the fast release of ketoprofen is triggered by the collapse of beads.

Figure 3 shows the time profiles of the amount of ketoprofen released from the beads with various rotation rates. Generally, drug release from swellable polymer M_t can be described by the following empirical equation [16]:

$$\frac{M_t}{M_\infty} = kt^n, \quad (1)$$

where M is the drug release at equilibrium state. Also, k , t , and n are the rate constant, time, and the order of drug re-

FIGURE 3: Time profiles of the ketoprofen release for the beads with various rotation rates; ($\circ$): 0 rpm, ($\square$): 2500 rpm, ($\diamond$): 5000 rpm (sodium alginate: 0.3 wt%, ketoprofen: 9 wt%, barium ferrite: 3 wt%).

lease, respectively. In the case of Fickian diffusion, the diffusion obeys Fick's second law and the order n in (1) is equal to 0.5. In the case of bead without rotation, the drug release was explained by the above empirical equation. The order n was estimated to be 0.6, indicating anomalous (non-Fickian) diffusion. The saturation value of the ketoprofen released from the bead was approximately 0.90 mg, which was seen at 25 minutes after starting rotation. When the rotation speed was 2500 rpm, the drug release increased and reached the saturation value at 12 minutes. At 5000 rpm of the maximum rotation speed, the drug release was further accelerated and achieved the saturation at only 3 minutes. All beads collapsed before the ketoprofen release reaches to the saturation value. A bead was ground by a mortar and dissolved in the buffer solution in order to estimate the maximum value (perfect release) of ketoprofen in the bead; the estimated value was 0.97 ± 0.03 mg. This value was in good agreement with the saturation values seen in Figure 3. This means that the most of ketoprofen embedded in the bead (>90%) was released into the buffer solution by the fast rotation.

Figure 4 shows the pulsatile release of ketoprofen from the beads upon changes of on/off rotation. Increase in the ketoprofen release during the first 2 minutes is clearly caused by the spontaneous release. It is considered that the release rate due to the spontaneous release corresponds to 4.0×10^{-2} g/g/min. After 2 minutes, a pulsatile drug release synchronized with the rotation of beads was observed. The drug delivery system undergoing pulsatile release has been mainly constructed by using temperature responsive gels. In the temperature responsive drug delivery, the temperature of the environment surrounding the gel has to be changed by heating. Accordingly, it must take a considerable time to modulate the drug release. The drug release controlling by electric stimulus can be modulated within several minutes, however the system needs electrical wires to supply electric power to the gel. The drug delivery system presented here

FIGURE 4: Release of ketoprofen from the beads in response to step-wise rotation speeds between 0 and 5000 rpm (sodium alginate: 0.3 wt%, ketoprofen: 9 wt%, barium ferrite: 3 wt%).

showed drug release without lag time because the magnetic force directly acts on the gel. Although it is needless to say that the collapse of beads by water flow also plays an important role of the first release. Thus the pulsatile release by using magnetic field was demonstrated by the present study.

4. CONCLUSION

Drug delivery system controlled by magnetic fields has been constructed by means of the fast rotation of magnetic gel beads. The magnetic gel bead consists of sodium alginate crosslinked by calcium chlorides, which contains barium ferrite of ferrimagnetic particles, and ketoprofen as a drug. The bead underwent rotational motion in response to rotational magnetic fields. In the case of bead without rotation, the amount of drug release showed non-Fickian diffusion. When the bead was rotated, the drug release rapidly increased and reached the perfect release shortly. The drug release was accelerated with increasing the rotation speed. The shortest time achieving perfect release was approximately 3 minutes, which corresponds to 1/8 of the time without rotation. Simultaneous with the fast release, the bead was collapsed probably due to the strong water flow surrounding the bead. The beads with high elasticity were hard to collapse and the fast release was not observed. Hence, the fast release of ketoprofen is triggered by the collapse of beads, not by the squeezing effect of drug that has been employed in the drug delivery of polymer gels in the past. We also succeeded in pulse release of the drug controlled by the magnetic field. The drug delivery system presented here has an advantage of the drug release without ragtime because the magnetic force directly acts on the gel. In addition, no electric wires for modulating the drug release are needed for this system. If the magnetic bead can be delivered to the target such as cancer tissues, intensive drug release only around the target will be possible. Magnetic beads presented here would have

a great potential as a new capsule of drugs without harmful side effects.

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