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Preparation of thermosensitive polymeric organogels and their drug release behaviors

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ABSTRACT

Stimuli-sensitive drug delivery systems—in particular, stimuli-sensitive polymeric hydrogels swollen with water—have attracted considerable attention in medical and pharmaceutical fields. This study concerns with the synthesis of thermosensitive polymeric organogels for controlled drug release; a copolymerization of stearyl acrylate (SA) with a cross-linker and the loading of indomethacin as a model lipophilic drug were accomplished in oleyl alcohol. The pulsatile (on–off) drug release was successfully conducted: release was halted at 36 °C and release occurred at over ca. 40 °C. This drug release pattern is suitable for thermochemotherapy combined with hyperthermia. The differential scanning calorimetric measurement suggests the following mechanism: the ordered crystalline structure, i.e., the alignment of hydrophobic alkyl side chains, works to prevent indomethacin diffusion from the organogel below the crystallization temperature, while the disordered amorphous structure above the melting temperature allows indomethacin to diffuse.

1. Introduction

Stimuli-sensitive polymeric gels change their physical properties and network structures abruptly in response to external stimuli. The gels have attracted considerable attention in the field of drug delivery systems (DDSs). Stimuli-sensitive DDSs have been discussed in several reports; the external stimuli studied include temperature [1–3], pH [1–3], electric fields [1,2,4], and biomolecules such as glucose and protein [2,5]. The majority of the literature related to the development of stimuli-sensitive DDSs deals with polymeric hydrogels swollen with water. Moreover, organogels swollen with organic solvents have also been developed [6]. An advantage of using organogels for DDSs is that they have the capacity to load a large amount lipophilic drug. Organogels are divided into polymeric and low molecular weight organogelators. Low molecular weight organogels formed by hydrophobic interaction release drugs in response to a temperature change as a result of the destruction of the gel network. Polymeric organogels can achieve a pulsatile (on–off) drug release in response to stimuli. Thus far, there are few reports of stimuli-sensitive polymeric organogels.

Thermosensitive polymeric organogels for controlled drug release are proposed in this study; it is critical to determine suitable polymer and organic solvent. We focused on polymers with long alkyl side-chains, e.g., stearyl acrylate (SA). Osada and co-workers reported that poly(SA–acrylic acid) gel undergoes a reversible order–disorder transition associated with the interactions between the alkyl side chains because of changes in temperature. The gel shows a dramatic change in its Young's modulus, and shape memory functions [7–9]. It is reported that the transition temperature of poly(SA) is approximately 45 °C [10]. SA hydrogels copolymerized with a hydrophilic monomer have been developed, while there are few reports of SA organogels. The properties of organic solvent required for the preparation of thermosensitive SA organogels are as follows; ability to dissolve poly(SA), but the

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solvent does not prevent poly(SA) from forming the ordered crystalline structure; ability to dissolve a drug, but the drug is distributed to an aqueous solution; low toxicity.

A schematic diagram of controlled drug release from thermosensitive SA organogels swollen with oil is given in Fig. 1, and explained as follows. SA organogels loading a lipophilic drug can be prepared by the polymerization of gels in a type of oil that can dissolve the drug, or by immersing the dry gels in the oil. Below the crystallization temperature, the hydrophobic alkyl groups are aligned side-by-side and an ordered structure is formed [7]. The crystalline lamellar structure prevents drug diffusion from the organogel. When the organogel is heated to temperatures above the melting temperature, the side chains' packing becomes amorphous [7], and the drug can be released. SA organogels can achieve a pulsatile (on–off) drug release in response to a step-wise temperature change (release occurring at higher temperatures and stopping at lower temperatures). SA organogels that release the drug above 42 °C can potentially provide thermochemotherapy for tumors; this therapy involves parenteral administration, followed by local heating, which is also used for hyperthermia treatment.

The purpose of this study is to develop thermosensitive SA organogels and to characterize their temperature-dependent controlled drug release. Oleyl alcohol (plant-derived oil) was used as an organic solvent, as concluded from the preliminary experiment. SA organogels loaded with indomethacin, which was used as a model lipophilic drug; the gel polymerization and drug loading were accomplished simultaneously. The feasibility of the pulsatile drug release from the SA organogels when subjected to a change in temperature was examined. The transition temperature of the SA organogels was investigated by differential scanning calorimetric (DSC) measurements.

2. Experimental

2.1. Preparation of SA organogels

The SA organogel was synthesized in oleyl alcohol by a free radical polymerization. First, two types of solutions were prepared; the pre-gel solution was 4 cm^3 oleyl alcohol containing SA (primary monomer; 1500 or 2000 mol/m^3), ethylene glycol dimethacrylate (EGDM; cross-linker; 15–200 mol/m^3), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (accelerator; 30 mol/m^3), and indomethacin (0.00313 g/cm^3); the initiator solution was 0.4 cm^3 oleyl alcohol containing 2,2′-azobis(2,4-dimetylvaleronitrile) (initiator; 40 mol/m^3), where the material concentrations were represented for the overall volume 4.4 cm^3. Nitrogen gas was bubbled through the solutions at room temperature for 1 h. Thereafter, the initiator solution was injected into the pre-gel solution in a polytetrafluoroethylene tube (inner diameter: 6 mm) using a syringe. Polymerization was conducted at 45 °C for 1 day under a nitrogen atmosphere. The resulting organogel was used for drug release experiments and DSC measurements.

2.2. DSC measurement

Thermal properties were examined using a differential scanning calorimeter (DSC-60, Shimadzu Co.). SA organogels in both dried and swollen states were used as samples. The dry gel was prepared by washing the organogel with toluene, followed by drying in an oven at 60 °C. An aluminum cell with a ground sample of 4 mg was heated and then cooled between 25 and 55 °C at a constant heating/cooling rate of 2 °C/min. The melting and crystallization temperatures were determined as the intersection point of two asymptotic lines at any two points surrounding the inflection point of the DSC curve; this measurement was obtained by using a computer combined with the calorimeter.

2.3. Indomethacin release experiment

Indomethacin release experiments were carried out using the batch method. A cylinder-shaped organogel (0.1 g, approximately ϕ 6 × 3.5 mm) loading indomethacin and an aqueous solution (3 cm^3) of 0.01 kmol/m^3 phosphate buffered saline (PBS) were mixed in a quartz cell. The cell was immediately placed in a temperature-controlled holder attached to an ultraviolet spectrophotome-

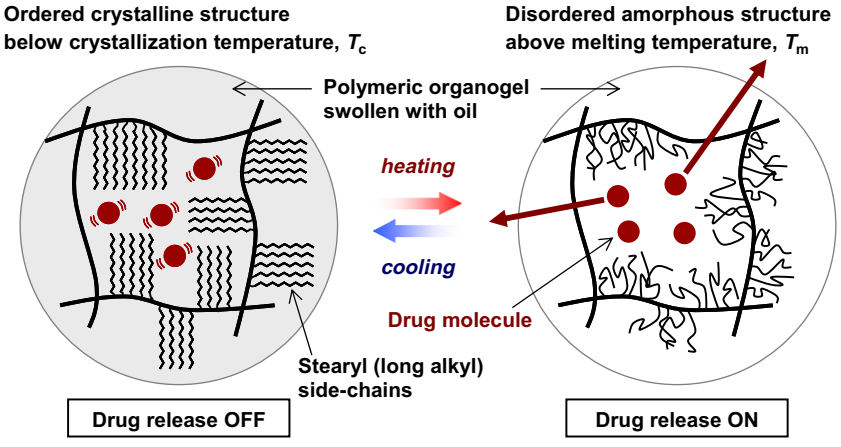


Fig. 1. Schematic diagram of the pulsatile drug release from a thermosensitive SA organogel subjected to a temperature change.

ter. The solution was stirred during the experiment. The organogel was held in a certain position and prevented from emerging from the water. Using a temperature controller, a constant temperature was maintained in the range of 33–46 °C, or the temperature was repeatedly varied between 36 °C for 2 h and 44 °C for 1 h. The concentration of indomethacin released in the PBS solution was continuously monitored by measuring the absorbance at 322 nm.

3. Results and discussion

3.1. Thermosensitive properties of SA organogels

The properties of the resulting SA organogels were strongly temperature-dependent. The photographs in Fig. 2 show the appearance of the SA organogel (SA:EGDM = 2000:50 mol/m^3). Below ca. 37 °C, the organogel is opaque in appearance and behaves as a hard plastic. The measured value of the compressive strength was ca. 1.2 MPa at 20 °C; a weight was loaded to the cylinder-shaped organogel in a length direction, and the stress at which the organogel was crushed was measured. However, on increasing the temperature, the appearance changes from opaque to slightly transparent at 38 °C (transparent above 40 °C) and the organogel becomes very soft and flexible. When a weight (see Fig. 2) was loaded onto the organogel at 39 °C, the organogel was crushed. The temperature-dependent change in both the appearance and the mechanical strength is reversible (the hysteresis was observed as described hereafter), and can result from the crystalline-to-amorphous transition of stearyl side chains.

In order to clarify the crystalline-to-amorphous transition, DSC measurements were conducted. Fig. 3 shows DSC curves of the SA organogel (SA:EGDM = 2000:50 mol/m^3) in both dried and swollen states. The melting temperature, T_m, and crystallization temperature, T_c, of the SA dry gel were determined as 44.8 °C and 41.8 °C, respectively, and hysteresis was observed. The DSC thermogram of the SA dry gel observed in this study is approximately the same as that reported in the literature [10]. The stearyl side chains form a crystalline lamellar structure below the T_c, while the packing of the side chains is amorphous above the T_m. The SA organogel also expresses the crystalline-to-amorphous transition; the T_m and T_c are 37.6 °C and 37.2 °C, respectively. The organic solvent (oleyl alcohol containing indomethacin) in the SA organogel can be

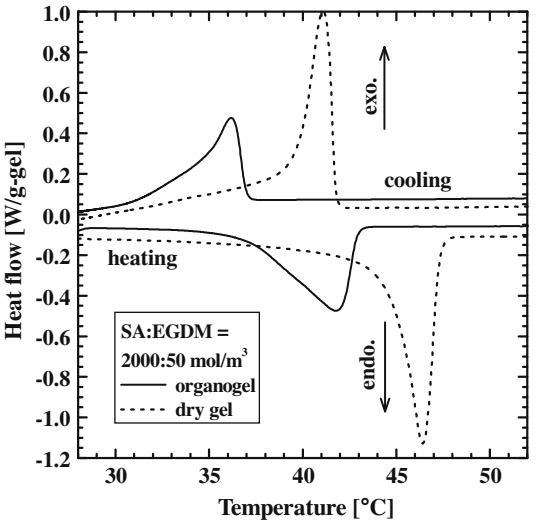


Fig. 3. DSC curves of the SA organogel (SA:EGDM = 2000:50 mol/m^3) in dried and the swollen states. Each sample amount was 4 mg.

adsorbed into an amorphous region outside the tail-to-tail alignment of the stearyl group with a length of 2.57 nm [7]. The transition temperature of the SA organogel is lower than that of the SA dry gel. This indicates that the organic solvent in the organogel reduces the crystalline region. The endothermic and exothermic peaks for the SA dry gel are intense and sharp, while those of the SA organogel are weak. One reason for the difference in the peak area is that the same amount of sample (4 mg) is used regardless of the state, that is, the dry gel contains much amount of stearyl acrylate unit per gram of the sample. The DSC thermograms of the SA organogel with oleyl alcohol shown in Fig. 3 are similar to those of the SA gel swollen with 1-octanol [10].

Fig. 4 shows the effect of SA and EGDM (cross-linker) organogels' monomer composition on the T_m and T_c. In all the tested organogels, the T_m was higher than the T_c for all observed hystereses. An increase in EGDM and/or overall monomer concentrations in the pre-gel solution causes a slight decrease in the transition temperature as well as the degree of crystallization. The degree of crystallization was evaluated by comparing the endothermic and exothermic peak areas in the DSC thermograms (data are omitted). The decrease in the amount of SA and/or the in-

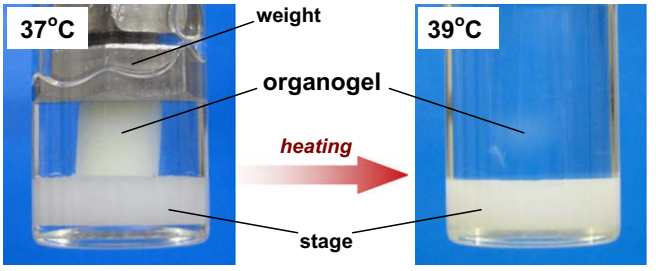


Fig. 2. Photographs of the SA organogel (SA:EGDM = 2000:50 mol/m^3). The size of the cylinder-shaped organogel is ϕ 6 × 6 mm. At 37 °C a weight (50 g) was longitudinally loaded on the organogel while it was held vertically.

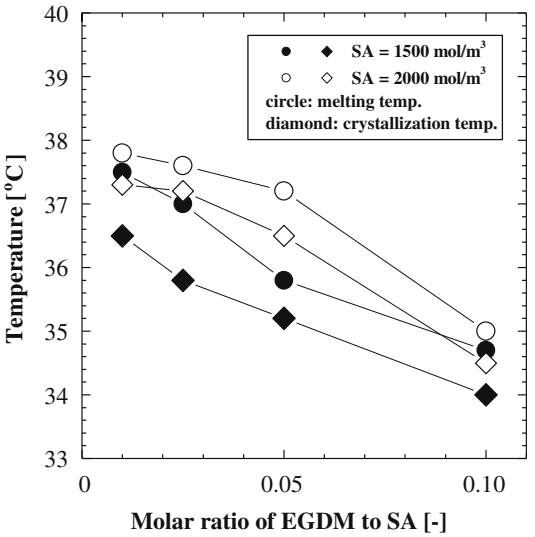


Fig. 4. Melting and crystallization temperatures of the SA organogels differing in EGDM to SA molar ratios.

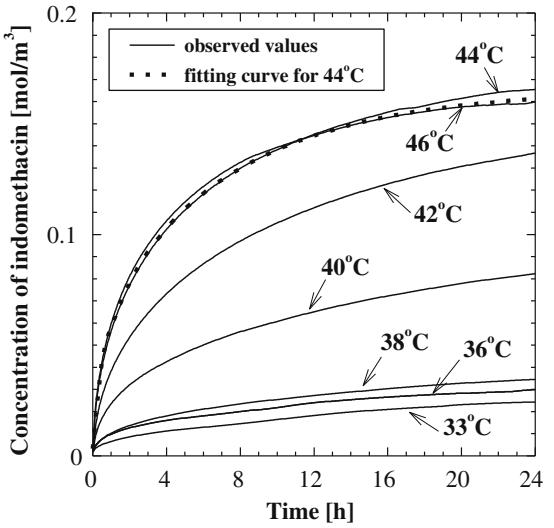


Fig. 5. Indomethacin release profile (concentration of indomethacin vs. time) from the SA organogel (SA:EGDM = 2000:50 mol/m^3) in a 0.01 mol/m^3 PBS solution at given temperatures. The fitting curve was obtained using the Fickian diffusion equation.

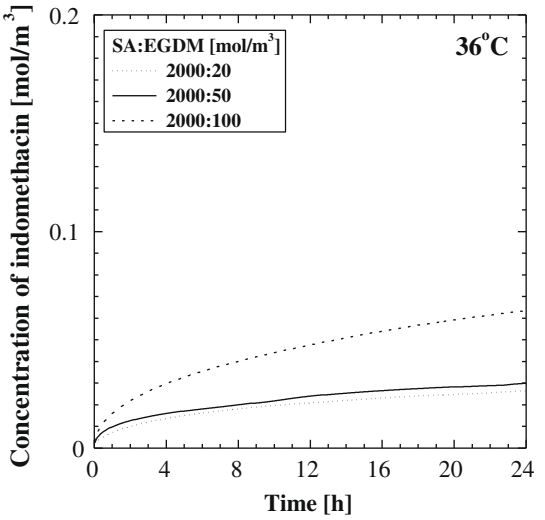
crease in crosslinking points in the polymer network leads to a lower degree of intermolecular aggregation of stearyl side chains, i.e., crystallization. The composition dependence of the transition temperature, as shown in Fig. 4, suggests the feasibility of thermosensitive organogels having suitable transition temperatures for their applications. Furthermore, the transition temperature of organogels could possibly be controlled by using polymers (other than the stearyl chain) with long alkyl side-chains [11]. It could also be accomplished by using copolymers of SA with an alkyl acrylate such as methyl acrylate, ethyl acrylate, and so on [10].

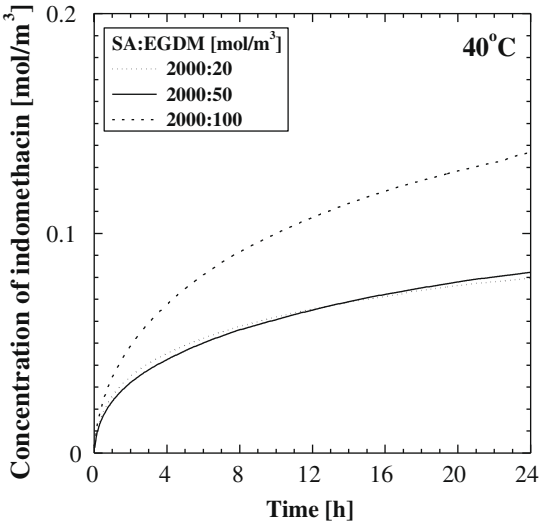
3.2. Drug release from SA organogels

Fig. 5 shows the time course for the concentration of indomethacin released from the SA organogel (SA:EGDM = 2000:50 mol/m^3) at given temperatures. The release rate, i.e., the concentration gradient, at temperatures less than 38 °C is low; the released amount of indomethacin at 38 °C after 24 h was 11% of the initial amount included in the organogel. However, the release rate increases with an increase in the temperature in the range of 36–44 °C. The release rate at temperatures higher than 44 °C is independent of temperature; at 44 °C after 24 h, 53% of the drug was released (the equilibrium was almost attained). The temperature dependence of the indomethacin release rate corresponds to the crystalline-to-amorphous transition revealed by the DSC measurements. As shown in Fig. 1, the ordered crystalline structure below T_c works to prevent diffusion of indomethacin from the organogel, while the disordered amorphous structure above T_m allows for diffusion of indomethacin. In addition to the crystalline-to-amorphous transition of the SA organogel, the indomethacin release should be discussed in terms of the distribution ratio. The indomethacin is transferred from the oil phase initially contained in the organogel to the aqueous phase outside the organogel. In our previous study [12], the distribution ratio of indomethacin (D = [indomethacin]$_{aq.}$/[indomethacin]$_{oil}$) was obtained as 0.09 in a system of 0.01 kmol/m^3 PBS and oleyl alcohol. The release rate tends to decrease with time, as shown in Fig. 5. This is attributed to the decrease in the driving force of the mass transfer, i.e., the concentration difference between the organogel phase and the outer aqueous solution phase.

As shown in Fig. 4, the monomer composition of SA and EGDM affects the T_m and T_c. The influence of the monomer composition on the release of indomethacin was investigated, and the indomethacin release profile from the SA organogels is shown in Fig. 6. The organogels of SA:EGDM = 2000:20 and 2000:50 mol/m^3 exhibit a similar release pattern. The organogel of SA:EGDM = 2000:100 mol/m^3 exhibits the faster release rate at 36 and 40 °C than the other lightly cross-linked organogels. This is due to the decrease in the T_m and degree of crystallization; and to a corresponding increase in EGDM, as mentioned above. The organogel of SA = 1500 mol/m^3 showed a similar release pattern depending on the EGDM concentration, although the data are omitted. The drug release rate is controlled by adjusting the monomer composition, especially cross-linker concentrations. The organogels of SA:EGDM = 2000:20–50 mol/m^3 are the most promising for the on–off drug release from internally-administered SA organogels at 36 °C; the synthesis of the organogels with EGDM concentrations less than 20 mol/m^3 is difficult.

The feasibility of the pulsatile drug release from the SA organogels when subjected to a change in temperature was examined. Fig. 7 shows the time course for the concentration and release rate of indomethacin from the SA organogel (SA:EGDM = 2000:50 mol/m^3) when subjected to a change in temperature from 36 to 44 °C. On–off drug release is successfully realized (release occurring at 44 °C





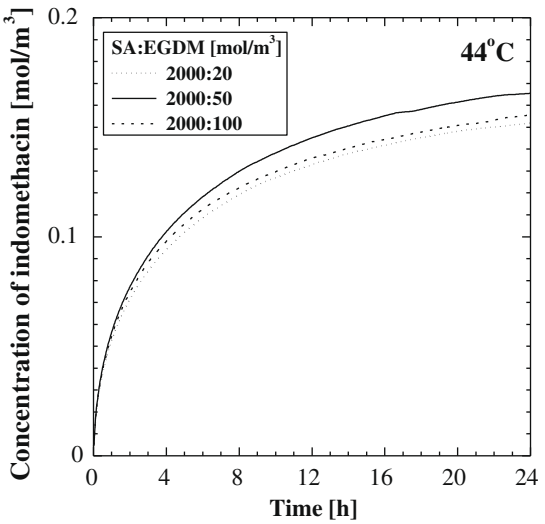


Fig. 6. Indomethacin release profile (concentration of indomethacin vs. time) from the SA organogels synthesized at various cross-linker concentrations in a 0.01 mol/m^3 PBS solution at 36, 40, and 44 °C.

and halting at 36 °C). The concentration of indomethacin after 24 h in Fig. 7 is in excellent agreement with that after 8 h at 44 °C in Fig. 5. This fact also supports release occurring at 44 °C and halting at 36 °C. According to the schematic diagram shown in Fig. 1, the pulsatile on–off drug release is successfully conducted by the reversible crystalline-to-amorphous transition of the SA organogel in response to the step-wise change in temperature. During the first 2 h at 36 °C, indomethacin loaded around the surface can be eluted. The release rate tends to decrease with time based on the batch experiment. Immediately after a change in temperature, the concentration of indomethacin increases or decreases instantaneously. After 6 h, the release rate at 36 °C is slightly negative. The reason for these changes in concentration is still unclear.

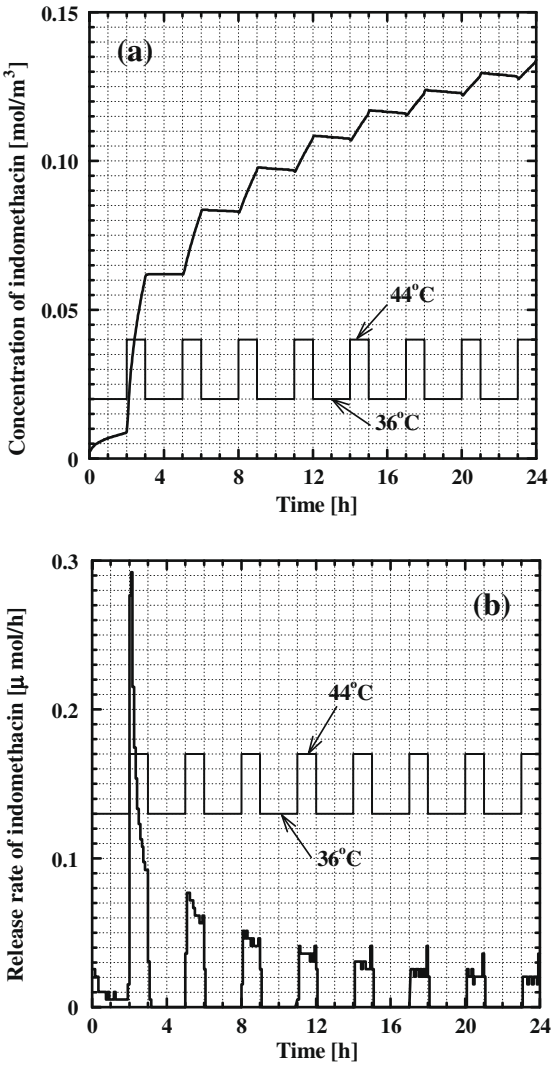


Fig. 7. Indomethacin release profile ((a) concentration and (b) release rate of indomethacin vs. time) from the SA organogel (SA:EGDM = 2000:50 mol/m^3) in a 0.01 kmol/m^3 PBS solution, when subjected to a change in temperature from 36 to 44 °C at fixed intervals. The release rate was determined from the difference equation at 5-min intervals, and the trivial minus rate was treated as 0.

The release rate was analyzed using the Fickian diffusion equation in terms of the diffusivity of indomethacin within the SA organogel. The total amount of diffusing indomethacin leaving the organogel is given by the solution of the diffusion equation within a sphere [13].

$$\frac{M_t}{M_{\inf}} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{D_e n^2 \pi^2 t}{a^2}\right) \quad (1)$$

where D_e is the effective diffusivity of indomethacin within the SA organogel; M_t and $M_{\inf}$, the amount of indomethacin released at time t and at infinite time (at equilibrium), respectively; and a is the radius of the sphere. The release rate was analyzed; $M_t/M_{\inf}$ was treated as $C_t/C_{\inf}$, $C_{\inf}$ was the concentration after 24 h (equilibrium was almost attained), and a was 2.6 mm (the radius of the sphere having a surface area equal to that of the cylinder-shaped gel used). The fitting curve for the release rate at 44 °C is shown in Fig. 5; it is in excellent agreement with the observed values, where D_e is 2.5×10^{-11} m^2/s. The value of D_e obtained in this study has the same order of magnitude as the one obtained in our previous study regarding the system of an emulsion gel (hydrogel containing randomly distributed oil microdroplets) and indomethacin [12].

4. Conclusions

Thermosensitive polymeric organogels for controlled drug release were synthesized; the free radical polymerization of SA and EGDM and the loading of indomethacin as a model lipophilic drug were simultaneously accomplished in oleyl alcohol. The DSC measurement reveals the reversible crystalline-to-amorphous transition of the SA organogel in response to a step-wise change in temperature. The pulsatile (on–off) drug release from the SA organogels to a PBS solution was successfully conducted by a change in temperature from 36 °C (no release) and 44 °C (release). The ordered crystalline structure below T_c works to prevent the diffusion of indomethacin from the organogel, while the disordered amorphous structure above T_m allows the indomethacin to diffuse.

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