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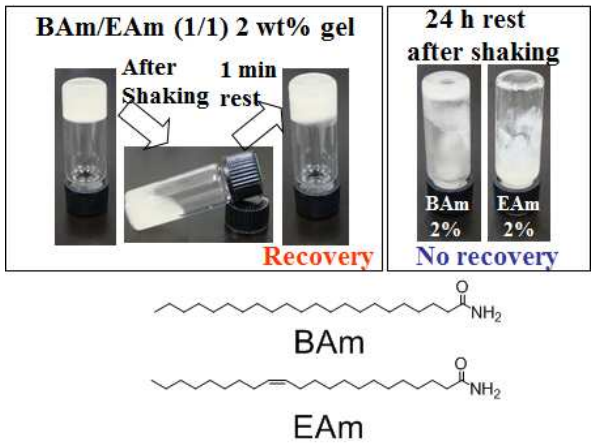
Yutaka Ohsedo,* Makiko Taniguchi, Masashi Oono, Kowichiro Saruhashi and Hisayuki Watanabe

Graphical Abstract:



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ARTICLE

Long-Chain Alkylamide-Derived Oil Gels: Mixing Induced Onset of Thixotropy and Application in Sustained Drug Release

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We showed that the gelation ability of commercially available long-chain alkylamides, behenamide (BAm) and erucamide (EAm) in various solvents for the first time. Furthermore, oil gels derived from mixtures of BAm and EAm, exhibited thixotropic properties although the same property was absent in the oil gels prepared separately using each alkylamide. The thixotropic behaviour of two-component mixed gel was evaluated using a rheometer quantitatively. We also found that the obtained two-component oil gel can be formulated for use as a vehicle for sustained drug release. The drug, antyprine, in BAm/EAm (1/1, w/w) olive oil gel formulation was gradually released into water following Fickian diffusion kinetics.

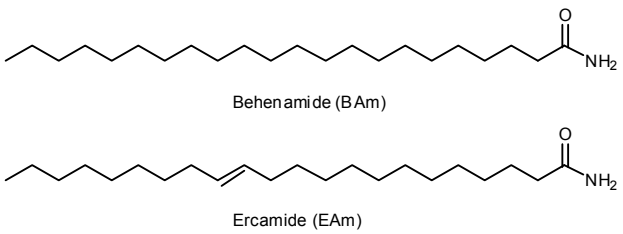
Introduction

Thixotropy, described as shear thinning in polymers and colloids or as a mechanical sol–gel transition in molecular gels, is a desirable property in paints and other spreadable materials.[1] Thixotropic molecular gels, composed of a fibrous network of low-molecular-weight gelators (LMWGs) and solvents, have attracted significant attention because of their potential in drug delivery.[2-5] These agents are being evaluated for their ability to be used as a vehicle, i.e. as a cream or ointment, for the delivery of active medicinal compounds.[6] To widen the thixotropic scope of gels used in medicinal formulations, efforts are primarily focused on the design and synthesis of novel LMWGs.

The development of novel and simple methods that involve the strategic use of established LMWGs can effectively compliment the efforts directed towards the design and synthesis of functional gelators. Several synthetic efforts have led to the successful creation of functionally enhanced molecular gels; however, rather complex organic synthesis may be necessary to generate these gelators, sometimes even tedious peptide synthesis. A method that allows for a simple and easy access to molecular gels with similar functionalities can facilitate the evaluation of their potential in academic and/or industrial applications. The strategic use of commercially available LMWGs can provide efficient methods for the generation of functional molecular gels, e.g. stimuli-responsive molecular gels.[7]

Since the early 1990s, the 'mixing' of LMWGs has been used as a strategy for the generation of gels with enhanced properties.[8,9] Recently, we reported that alkylhydrazides are gelators for organic solvents (organogelators).[10a] Furthermore, we showed that the mechanical properties of organogels from a mixture of alkylhydrazides (varying in alkyl chain length) were superior to those of the organogels prepared separately using either of the individual components, i.e. one-component gels. Intriguingly, the one-component organogels did not exhibit thixotropic behaviour.[10b] Furthermore, we also found similar mixing-induced thixotropy in alkylamide-[10c,f] and alkylurea-derived[10d] organogels and other hydrogel systems.[10g,h] These mixed organogelators are attracting attention due to their potential as new materials for drug delivery.

In this study, we describe the creation of new thixotropic molecular oil gels by simply mixing long-chain alkylamides and the evaluation of their potential in medicinal applications for the candidate of the base material of cream and ointment. In previous studies, we demonstrated that thixotropy in oil gels



Scheme 1 Chemical structures of alkylamides.

was induced by combining a long-chain alkyl derivative with a short-chain alkyl compound, e.g. *n*-octaneamide, which can cause eye and skin irritation (MSDS).[11] In this study, for safe to the human body, we use only long-chain alkylamides (n > 10), behenamide (docosanamide, BAm) and erucamide (13-*cis*-docosenamide, EAm) as LMWGs to create new non-volatile oil gels with thixotropy for drug release application (Scheme 1). These commercially available alkylamides, used for the first time as LMWGs in this study, are widely used as additives that increase the slippage of polyolefin.[12] We also evaluate the potential of the obtained molecular oil gels for drug delivery via diffusion. In a research related to this study, the organogelation ability of long-chain alkylamides that contain stearyl groups was reported by the Weiss group.[13]

Experimental Section

Materials. Behenamide (BAm, 75%) and Erucamide (EAm, 85%) were purchased from Tokyo Chemical Industry Co., Ltd. and used without further purification. All solvents were purchased from Wako Pure Chemical Industries, Ltd. and used without further purification.

Methods. The gelation tests were performed using the vial inversion method. A crystal of alkylamide was placed in a vial with a solvent at a set concentration (wt%) and capped. The vial was heated in a dry bath of 100 °C until the crystal of alkylamide was dissolved. Alkylamide solution was left for 1 h at room temperature, and gelation was checked with naked eyes by inverting the vial.

Thixotropic behaviour was evaluated using the vial inversion method. The alkylamide organogel in the vial was shaken and collapsed using a vortex genie (Scientific Industries, Inc). The obtained sol was then left for a set time at room temperature, and the recovery of the gel state from the sol state was determined by visual observation after inversion of the vial. The oil gel was examined using a Leica DM2500 (Leica Microsystems) polarized optical microscope under crossed nicols.

Thermal analysis was performed with an EXSTAR6000 differential scanning calorimeter DSC (Seiko Instruments Inc.) using an Ag-made closable sample pan. $T_{gel\rightarrow sol}$ and $T_{sol\rightarrow gel}$ of gels were determined as extrapolated onset temperatures from the DSC curves.

Rheological measurements of frequency sweep were performed with an MCR-301 rheometer (Anton Paar Japan K.K.) with a parallel plate (8 mm diameter) at a gap of 0.50 mm and γ of 0.01 % (measurement temperature: 25 °C). Rheological measurements of strain sweep were performed with an MCR-301 rheometer with a parallel plate (8 mm diameter) at a gap of 0.50 mm and constant angular frequency 1 rad s^{-1} (measurement temperature: 25 °C). For rheological measurements, the organogel sample was applied onto the parallel plate and sample stage (the overflow gel was swept). The organogel sample for rheological measurements was placed on a parallel plate and a sample stage (the overflow gel was swept), then the sample was left for 10 min to attain an equilibrium gel state and temperature. Step-shear measurement was carried out by applying normal strain (strain amplitude 0.01 % and frequency 1 Hz) and large strain (shear rate 3000 s^{-1} for 0.1 s), repeatedly.

SEM images were recorded with an SU-8000 scanning electron microscope (Hitachi High-Technologies Corporation) at 1.0 kV; the SEM sample (xerogel made from toluene gel) was vacuum-dried and placed on a conductive tape on the SEM sample stage. Pt, as an electric conductive material, was used as a coating on the sample with a JFC-1600 auto fine coater (JEOL Ltd.**,** Pt coating is 10-nm thick, distance between Pt source and sample: 5.0 cm, 30mA, 40s).

X-ray diffraction data were recorded on a D8 Discover X-ray diffractometer (Bruker AXS K.K.) with CuKα at 26 °C (the sample was filled in a quartz glass capillary tube of 1 mm diameter). Infrared spectroscopy was performed with an FT/IR-620 (JASCO Corporation) using the ATR method (ZnSe prism).

Evaluation of drug release from oil gel. To evaluate antipyrine release from the multicomponent alkyl amide–oil gel, *in vitro* permeation experiment was performed using a modified Franz cell. The diffusion cell consisted of a vertical glass PERMCELL (8 mL, Veadlex. Co. Ltd.) with a membrane area of *ca*. 1.8 cm^2 fitted with a 15 mm diameter permeation part and a stirrer tip (length: 8 mm, diameter: 1.5 mm, 100 rpm). Fisherbrand™ regenerated cellulose dialysis tubing (molecular weight cut off: 3500 Da, Fisher Scientific) was used as a permeation membrane between gel and water in the receiving partition of the diffusion cell. The temperature of the receiver was maintained at 37 ± 0.5 °C using a "Thermo-Elite" BH201/301 thermostat bath equipped with a CR5 program controller (Yamato Scientific Co., Ltd. Tokyo, Japan).

First, the multicomponent alkyl amide–olive oil gel (2 wt%, 0.5 g) loaded with antipyrine (0.5 wt%) was placed on the permeation membrane, and at predetermined time intervals aqueous solution, containing diffused drug (5.0 mL), was extracted from the receiver while fresh water (5.0 mL) was added to the receiver. The antipyrine concentration in this aliquot was determined by UV-vis spectroscopy measurements. The molecular absorption efficiency of antipyrine measured at λ_{max} = 250 nm in aqueous solution (ε = 9380) was used to estimate this concentration, and, thus, the amount of antipyrine in the receiver.

Measurements of absorbance of antipyrine aqueous solution in a quartz crystal cell with a light path length of 10 mm were performed with a measurement system consisting of spectrometer HR4000 (Ocean Optics, Inc.), UV-VIS-NIR light source DH-200-BAL (Mikropack GmbH), and variable attenuator FVA-UV (Ocean Optics, Inc.) controlled by PC software OPwave (Ocean Photonics). The measurement system was constructed by Ocean Photonics.

Results and discussion

Initially, we evaluated the gel-forming ability of the alkylamides, both independently and as mixtures, in the organic solvents and non-volatile, oils, olive oil and squalene (Table 1,

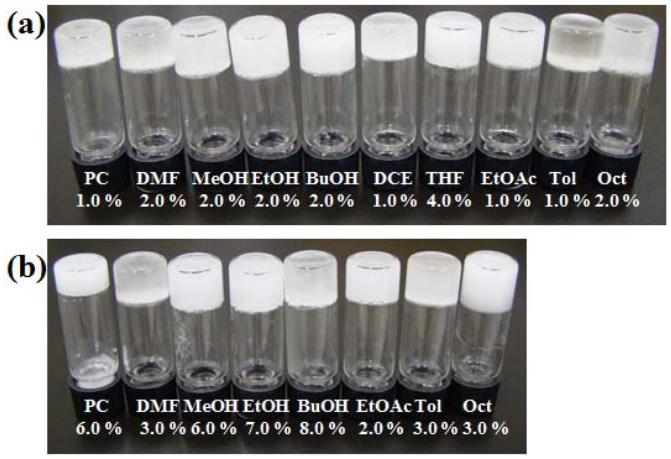


Fig. 1 Photographs of organogels in various organic solvents: (a) BAm organogels and (b) EAm organogels. **Key**: PC: propylene carbonate, DMF: *N,N*-Dimethylformamide, MeOH: methanol, EtOH: ethanol, BuOH: 1-butanol, DCE: 1,2-dichloroethane, THF: tetrahydrofuran, EtOAc: ethyl acetate, Tol: toluene, Oct: *n*-octane.

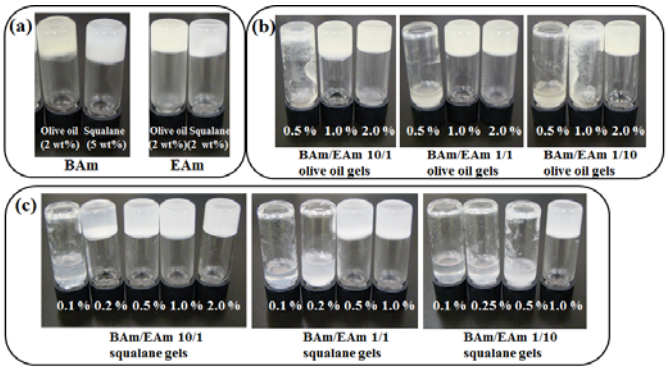


Fig. 2 Photographs of oil gels: (a) one-component oil gels, (b) two-component olive oil gels, and (c) two-component olive oil gels.

Table 1 Critical gelation concentrations (CGC) of alkylamides-derivatives in organic solvents.

Solvent	Bam	EAm	ε [a]
Propylene carbonate	1.0[a]	6.0[a]	66.14
N,N-Dimethylformamide	2.0[a]	3.0[a]	47.24
Methanol	2.0	6.0	33.0
Ethanol	2.0	7.0	25.3
1-Butanol	2.0	8.0	17.84
1,2-Dichloroethane	1.0	K	10.42
Tetrahydrofuran	4.0	S	7.52
Ethyl acetate	1.0	2.0	6.814
Toluene	1.0	3.0	2.379
n-Octane	2.0	3.0	1.948

1) C. Wohlfarth, CRC Handbook of Chemistry and Physics 85th ed., ed. by D.R. Lide , CRC Press 2004, 6-155~6-177. **Key**: S: solution at 10 wt%, TG: turbid gel, OG: opaque gel, CG: clear gel.

Table 2, Fig. 1, Fig. 2 and Fig. 3). It was found that the long-chain alkylamides, BAm and EAm, formed opaque organogels

Table 2 CGC of alkylamides-derived oil gels.

Sample	BAm/ EAm (10/1)	BAm/ EAm (1/1)	BAm/ EAm (1/10)	Bam	EAm
Olive oil	1.0[a]	1.0[a]	2.0[a]	2.0[b]	2.0[b]
Squalane	0.2[a]	1.0[a]	1.0[a]	2.0[b]	1.0[a]

The CGC values are expressed as wt%. [a]translucent gel; [b]opaque gel.

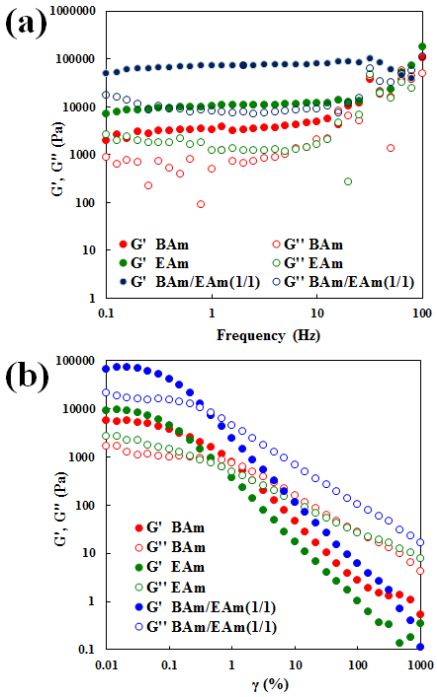


Fig. 3 Dynamic rheological properties of one- and two-component alkylamide-derived oil gels (one-component squalane gels, BAm 2 wt% and EAm 2wt%; two-component BAm/EAm 1/1 (w/w) 2 wt% squalane gels): (a) frequency sweep; and (b) strain sweep.

from various organic solvents with dielectric constants ranging from 2 (octane) to 64 (propylene carbonate). Although these organogels were brittle, they could retain their solidity even after the vials were subjected to a sudden subtle mechanical shock. These organogels did not exhibit further crystallisation and were stable within 3 months. From these results, it was found that BAm and EAm function as new alkylamide organogelators, which might be safe for the human body due to their long alkyl chain length.

Focusing on the creation of thixotropic gels with non-volatile oils for drug delivery application, we applied our mixing method to the long-chain alkylamide/non-volatile oil system. It is evident from the results in Table 2 that two-component alkylamide-based oil gels had lower CGC than one-component oil gels. Furthermore, the CGC of two- component oil gel decreased with increasing amount of BAm in the mixture. These two-component oil gels maintained their state for over 3 months without gel and oil separation.

The states of 'gel' in the oil gels was verified by evaluating

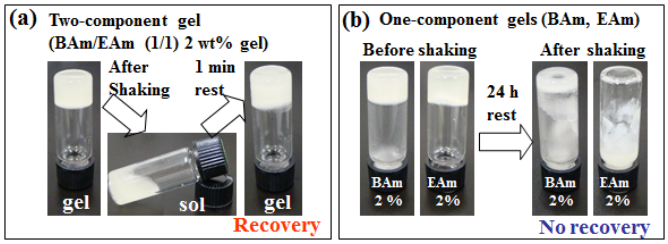


Fig. 4 Photographs of oil gels before, during and after thixotropic tests. (a) BAm/EAm 1/1 (w/w) 2 wt% olive oil gel; and (b) one-component olive oil gels, BAm 2 wt% and EAm 2 wt%.

Table 3 Recovery time of two-component oil gels after shaking.

Sample	BAm/EAm (10/1)	BAm/EAm (1/1)	BAm/EAm (1/10)
Olive oil 0.5 wt%	No gelation	No gelation	No gelation
Olive oil 1.0 wt%	30 min	–[a]	
Olive oil 2.0 wt%	1 min	1 min	–[a]
Squalane 0.5 wt%	–[a]	–[a]	No gelation
Squalane 1.0 wt%	30 min	30 min	–[a]
Squalane 2.0 wt%	1 min	1 min	–[a]

[a]no recovery of gelation in 24 h after shaking.

the dynamic rheological properties using a rheometer. Fig. 3a shows profiles of G′ and G″ versus the frequency of the oil gels. These results confirmed the existence of gel state (G′ > G″) in the one- and two-component oil gels,[14] and also indicated that the two-component oil gel possessed a higher G value (harder material) compared to the one-component oil gels of the same concentration. The strain sweeps of the oil gels in Fig. 3b indicated that the oil gels underwent gel (G′ > G″) to sol (G′ < G″) change by applying larger deformation. These results show mixing-induced enhancement on mechanical property (toughness) of gels as shown in our previous studies.[10]

These two-component olive oil/squalane gels exhibited thixotropic behaviour, a trend similar to that observed with other mixed organogel systems (Fig. 4 and Table 2).[10b-e] The sol-to-gel and gel-to-sol transformations reversibly occurred with the two- component oil gels, while one-component alkylamide-derived oil gels did not show such behaviour. The recovery of gel networks was more prominent in oil gels with higher concentration and content of BAm (Table 3).

The thixotropic behaviour of two-component mixed gel was measured using a rheometer (Fig. 5). The analysis of the rheology data showed that the two-component oil gels were gel-like, i.e. the magnitude of the recovered storage modulus, G′, was higher than that of the recovered loss modulus, G″, after the application of large deformation shear. The observed reduction in recovered values of G′ and G″ indicated a change in the gel network after shearing; however, this change was not sufficiently large to destroy the gel. By contrast, similar values of G′ and G″ were obtained on shearing one-component gels,

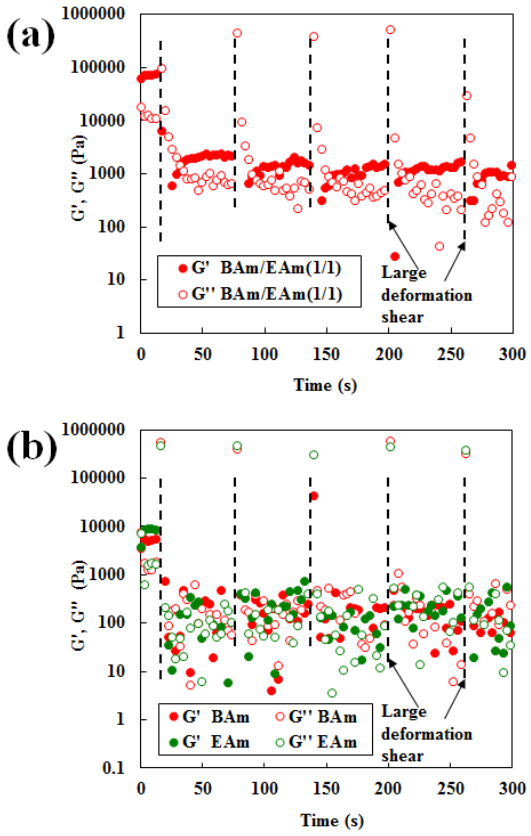


Fig. 5 Periodical step-shear test results for (a) BAm/EAm 1/1 (w/w) 2 wt% squalane gel; and (b) one-component squalane gels, BAm 2 wt% and EAm 2wt%.

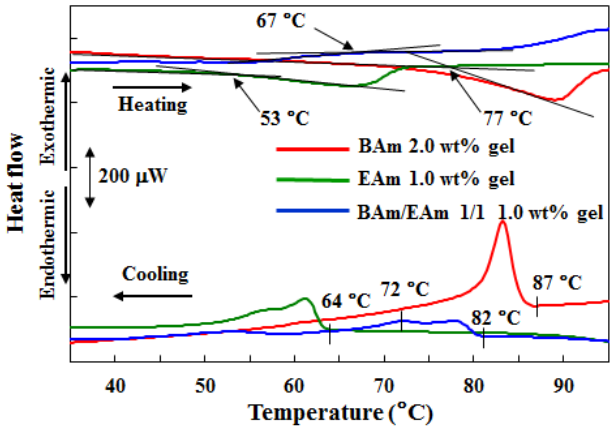


Fig. 6 DSC curves of CnAm organogels in squalane (2 °C/min).

indicating that the gels are destroyed. These results provide evidence for the onset of thixotropic behaviour in gels derived after mixing two long-chain alkylamides, BAm and EAm.

Next, we investigated sol-to-gel and gel-to-sol transitions in the gelator phase diagrams of oil gels by differential scanning calorimetry (DSC). The analysis of the DSC scan (Fig. 6 and Table 4) shows that ΔH values involved in both sol-to-gel and gel-to-sol transformations in all oil gels were similar. The temperatures at which these sol-to-gel/gel-to-sol transitions occur in the two-component mixture were intermediate between

Table 4 Transition temperatures of squalane organogels obtained by differential scanning calorimetry (DSC) measurements (heating and cooling rates were 2 °C/min)

Sample	$T_{gel\rightarrow sol}$ /°C (ΔH/mJ mg^{-1})	$T_{sol\rightarrow gel}$ /°C (ΔH/mJ mg^{-1})
BAm 1 wt% gel	77 (2.7)	87 (2.8)
EAm 1 wt% gel	53 (1.5)	64 (1.5)
BAm/EAm 1/1 1 wt% gel	67 (1.4)	82, 72[a] (1.4)

[a]Peak temperatures

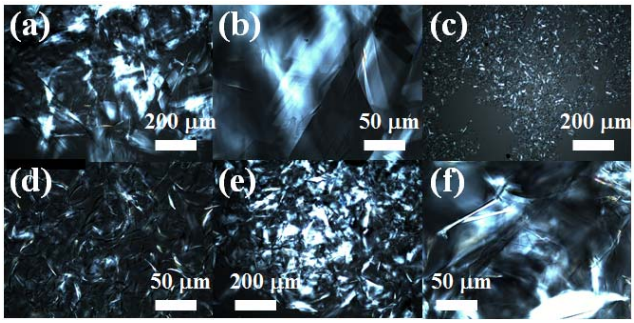


Fig. 7 POM images of squalane gels: (a and b) BAm 1 wt%; (c and d) EAm 1 wt%; and (e and f) BAm/EAm 1/1 (w/w) 1 wt%.

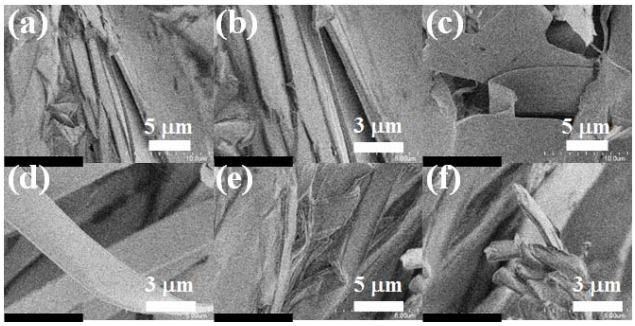


Fig. 8 SEM images of xerogels: (a and b) BAm (1 wt%); (c and d) EAm (3 wt%); and (e and f) BAm/EAm 1/1 (w/w, 1 wt%). The values in parentheses denote the concentration of the toluene gels (CGC) before generation of the xerogels.

the temperatures corresponding to maximum heat flow for similar transitions in BAm- and EAm-derived one-component oil gels. These results suggest that the gel network in the two-component oil gels is different from that in one-component alkylamide-derived gels.

Polarized optical microscopy (POM) was used to observe the one- and two-component oil gels (Fig. 7). Optical micrographs of BAm-derived and two-component oil gels (Fig. 7a and b) showed a network of strand-like crystals (dozen micrometers ~ sub-micrometers width), similar to that observed in alkylamide toluene gels.[10c] The EAm-derived oil gel showed homogeneous fine texture (Fig 7c-f; only broken pieces of gel were observed). In addition, to investigate the microstructures of the mixed gel, scanning electron microscopy (SEM) measurement of the xerogels obtained from the one- and two-component toluene gels which showed mixing enhanced

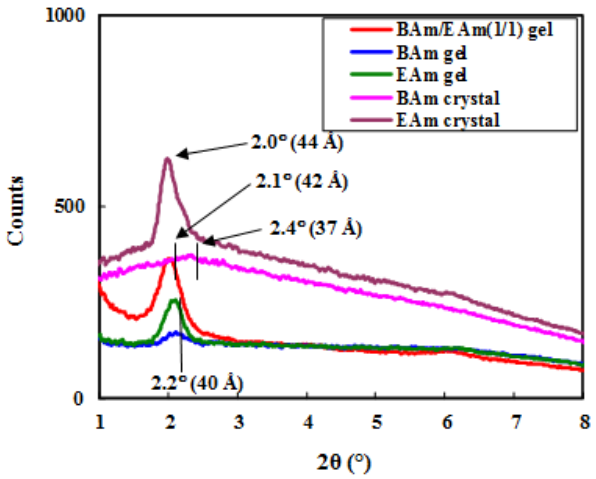


Fig. 9 XRD data of BAm/EAm squalane gels with mixing ratio denoted as w/w and crystals (reagent grade). The values in parenthesis denote the d values.

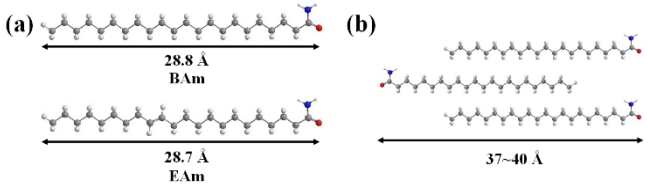


Fig. 10 Theoretical contour lengths of alkylamides. (a) results of MM2 calculations using ChemDraw; (b) schematic illustration of interdigitated lamellar packing in BAm.

gelation were examined (CGC of mixed BAm/EAm 1/1 (w/w) 1 wt% toluene gel was enhanced comparing with those of one components (BAm;1 wt%, EAm; 3 wt%)). In the SEM images (Fig. 8), the one-component xerogels comprised sheet- like crystals with laminar figures that were several dozen micrometres in length and sub-micrometres in thickness. In contrast to the microstructure of the one-component organogels, that of the mixed system gels was finer laminar figures comprising micrometre-sized tape-like crystals that were several dozen micrometres in length and sub-micrometres in thickness. From POM and SEM images, it is concluded that the increased network density of finer tape-like crystals may contribute to the enhancement of the mechanical properties of mixed organogel systems, such as that seen in polymer networks. These results are consistent with those of one- and two-component alkylamide organogel systems with shorter alkyl chain length.[10c]

The X-ray diffraction (XRD) analysis of oil gels might indicate that alkylamides form a bilayered structure (two molecules interacted at the amide moiety through hydrogen bonding to form dimers, and adjacent dimers formed additional hydrogen bonds yielding extended chains) in fibres as reported previously.[15] The peak positions in the XRD patterns of two-component oil gels were largely coincident with those observed for the one-component oil gels (Fig. 9), indicating that the molecular packing arrangements responsible for the gel assembly in both systems are similar. Calculated contour lengths of BAm and EAm are 28.8 and 28.7 Å, respectively

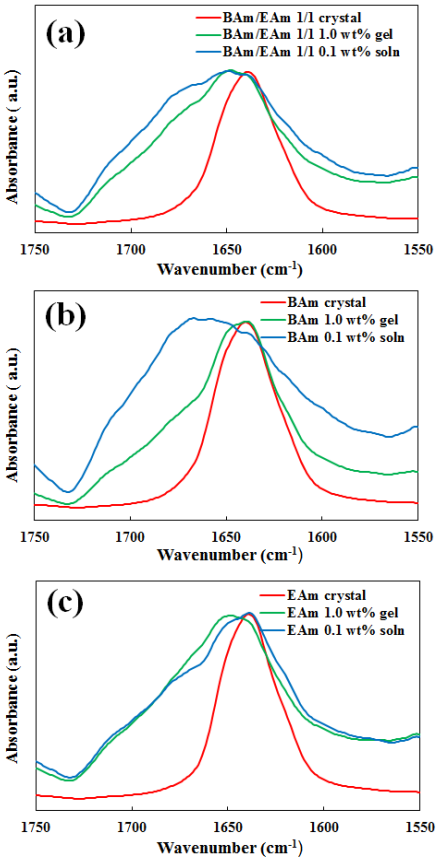


Fig. 11 IR spectra of the BAm/EAm squalane systems in different states (crystal {reagent}, gel and solution) in the region of carbonyl stretching: (a) BAm/EAm 1/1 (w/w); (b) BAm; (c) EAm.

(Fig. 10). The difference in molecular length can be rationalized by the formation of interdigitated lamellar-like structures (e.g. as in alkylamides[10c] and alkylureas[10d]) in the one- and two- component alkylamide-derived oil gels.

To investigate the driving force of fibre formation in alkylamides, the infrared (IR) spectra of BAm/EAm squalane systems in different states in the carbonyl stretching region were measured (Fig. 11). In Fig.11, one of the main absorption peaks of the carbonyl group in the higher wavenumber region increases when the state changes from solution to gel and from gel to crystal. The absorption peak of the higher wavenumber (1660 – 1770 cm^{-1}) could be attributed to the carbonyl stretching of non-interactive, free molecules and that of the lower wavenumber (1637 cm^{-1}) could be attributed to the carbonyl stretching of intermolecular interaction due to hydrogen bonding. This tendency was observed in the two- and one-component systems. These results suggest that the driving force of the self-assembly tendency probably depends on the hydrogen bonding of alkylamides.

Although the mechanism of mixing induced onset and the dependence of BAm/EAm ratio on thixotropic behaviour are under investigation, considering prominent recovery of higher content of BAm in mixed gels, it might be possible that the improved mixed gels are BAm fibres reinforced by EAm fibres.

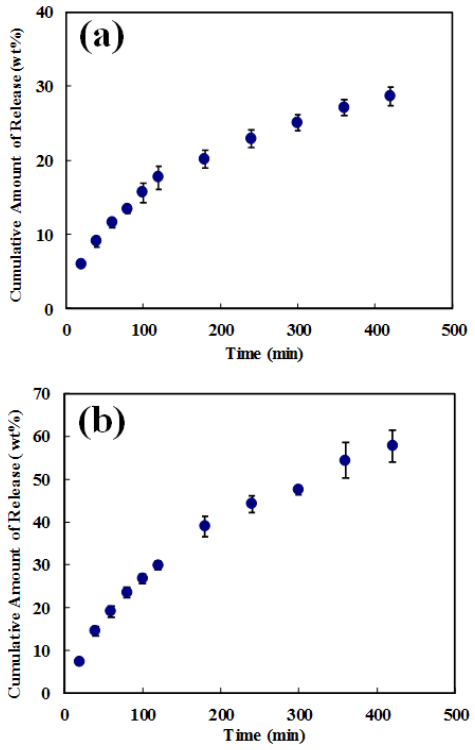


Fig. 12 Cumulative drug release curves. (a) BAm/EAm 1/1 (w/w) 2 wt% olive oil gel formulation of antipyrine (0.5 wt%); (b) olive oil solution containing antipyrine (0.5 wt%). The error bars represent standard deviations from average values.

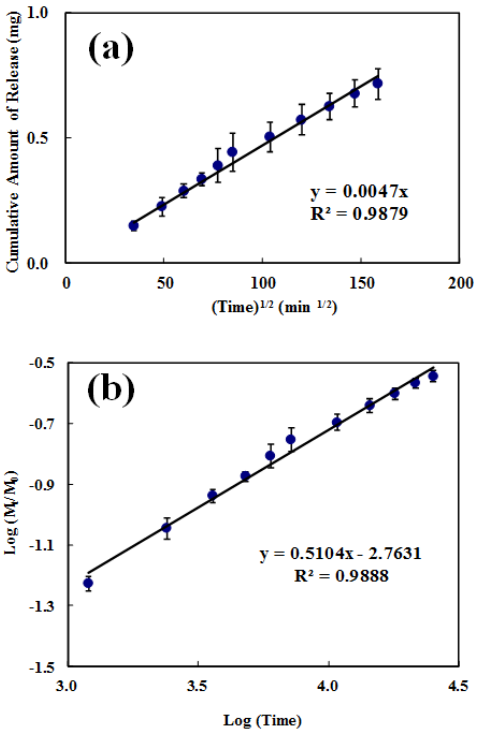


Fig. 13 Kinetic data analysis for the release of drug from BAm/EAm 1/1 (w/w) 2 wt% olive oil gel formulation of antipyrine (0.5 wt%). (a) fitting of data to Higuchi's model; and (b) fitting of data to the Korsmeyer–Peppas model. The error bars represent the standard deviations from average values.

In this model, the BAm fibres and/or network are extended by the addition of EAm fibres, which enables sufficient crosslinking of the fibres and/or network probably due to the assistance of hydrogen bonding of amide groups, resulting in an enhancement of toughness, thixotropic behaviour and a decrease in CGC of the mixed gels compared to that of the one-component gels.

Finally, preliminary investigation into the drug-releasing ability of two-component oil gel was performed. The control sample in these assays is the solution of the drug in olive oil. The non-steroidal anti-inflammatory drug antipyrine—2,3-dimethyl-1-phenyl-5-pyrazolone—selected for this study is soluble only in olive oil (not in squalane). Fig. 12a shows the cumulative antipyrine release curve of drug containing the formulation of BAm/EAm (1/1, w/w) olive oil gel at 37 °C. The amount of antipyrine released into water by the BAm/EAm (1/1, w/w) olive oil gel formulation gradually increased during the initial period (several hours). At the end of 7 h, 30 wt% of the total drug in the formulation was released into water. In the same period, the control olive oil solution released ~60 wt% of the dissolved drug (Fig. 12b). Therefore, this data shows that the release of drug from the two-component oil gel formulation is retarded, thereby allowing for a sustained drug release.

Kinetic models for the drug release data of the formulations favoured both Higuchi-diffusion and Korsmeyer–Peppas models (Fig. 13).[16,17] A good linear fit was obtained for the kinetic data using both models. This suggested that the release of antipyrine from the drug-encapsulating two-component oil gel follows Fickian diffusion kinetics.

Conclusions

In conclusion, we developed a method for the preparation of molecular oil gels by mixing commercially available two long-chain alkylamides, behenamide (BAm) and erucamide (EAm), in the presence of non-volatile oils. The use of long-chain alkylamides minimized the potential risk of eye and skin irritation associated with small-chain alkylamides. The two-component oil gels exhibited thixotropic behaviour, while this behaviour was absent in the corresponding one-component oil gels. Furthermore, we demonstrated that the encapsulation of a drug in the two-component oil gel allowed for its controlled release from the oil gel formulation. Whereas the control olive oil solution released ~60 wt% of the dissolved drug (antipyrine) at the end of 7h, in the same period, 30 wt% of the total drug in BAm/EAm (1/1, w/w) olive oil gel formulation was gradually released into water following Fickian diffusion kinetics. Efforts are underway to further tune the properties of the multi-gelator gels and widen the scope of encapsulated guests.

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