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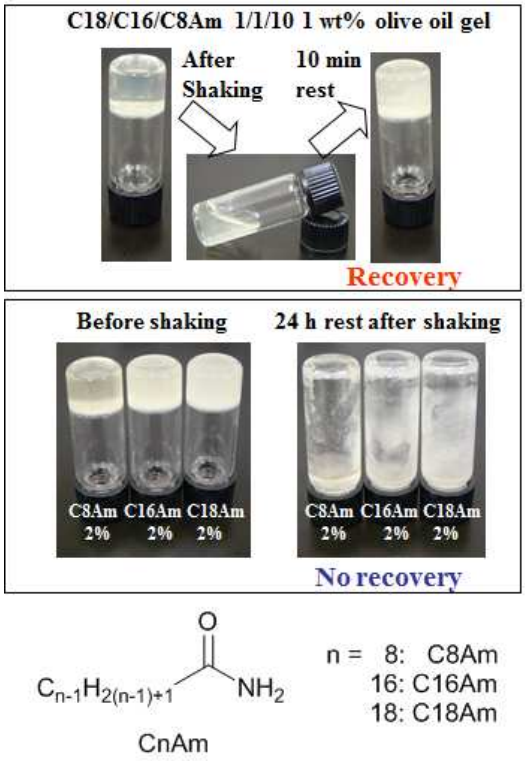
Graphical Abstract:



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ARTICLE TYPE

Creation of Thixotropic Multicomponent Alkylamide Organogels Containing Non-volatile Oil as Potential Drug Release Host Materials

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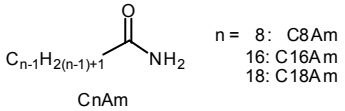
Multicomponent alkylamide organogels containing non-volatile oils were generated as potential thixotropic host materials for medicinal applications such as ointments. In the presence of these non-volatile oils, a three-component alkyl amide system exhibited mixed induced thixotropy. This thixotropic organogel showed drug release abilities following diffusion kinetics and may be a suitable drug release host materials.

Molecular gels composed of low-molecular-weight gelators (LMWG)[1,2] have been extensively studied in this decade. When creating multi-stimuli responsive molecular gels and other functional soft materials, their well-defined molecular structures make their properties relatively more designable and tuneable compared to polymers.[3] Numerous trials have been conducted for the generation of molecular gels, especially molecular hydrogels, that are injectable in their gel state and readily collapse under certain conditions for medicinal applications.[4]

In addition, several molecular organogels containing LMWGs and oil, such as sunflower and olive oil, have been evaluated as host materials for medicinal ointments and patches to effectively disperse and apply medicinal active ingredients by diffusion into an affected area.[5] Because of their easy molecular design, organogels have become important gelling agents of oil, prompting the investigations of their molecular gel properties in ointments. However, these studies have been limited to conventional LMWGs. An increasing need for materials that prevent accidental problems, such as skin rash upon gel contact, requires the design of molecular organogels incorporating newly synthesised LMWGs.

Multi-component LMWG gels have been recently studied to develop a new organogel creation method.[6,7] LMWG components with different alkyl chain lengths, such as alkylhydrazides, alkylamides and alkylureas, were simply mixed to form organogels with enhanced properties. [8] In addition, these organogels exhibited a mechanically induced sol–gel transition.[8] This thixotropic behaviour[9,10] is necessary for organogel-based medicinal ointments and/or patches because it provides them with spreadability and stability. To achieve this, new thixotropic organogels composed of LMWGs and non-volatile oils were generated through the previously reported mixing method.[8b-d] Octadecaneamide,



Scheme 1 Chemical structures of alkylamiide derivatives.

hexadecaneamide and octaneamide (CnAm, Scheme 1) were selected as LMWGs because these are commercially available alkyl amides and show better thixotropy when mixed with organic solvents. Olive oil and squalane, which have been widely investigated for medicinal and skincare purposes, were chosen as non-volatile oils. Related to this study, the organogelation ability of alkylamides that contain stearyl groups was reported by the Weiss group.[11]

First, the gel forming properties of each alkylamide were examined in the presence of the non-volatile oils. Table 1 summarises the gelation test results of alkylamide–oil gels and Figs. S1 and S2 (see ESI†) show the photographs of the obtained alkyl amide organogels. The CnAm compounds formed oil gels at moderate critical gelation concentrations (CGCs). Next, the gel forming properties of alkyl amide mixtures with olive oil and squalane were evaluated (Table 1). The multicomponent gels showed lower CGCs compared with the single component gels, especially in squalane oil. About the difference of CGC between olive oil and squalane, we think that the polarity of solvent play an important role in fibre formation and CGC of alkylamides which has polar amide group. The polarity of olive oil is larger than that of squalane, because olive oil contains unsaturated fatty acid, which has polar carboxylic group and squalane is saturated hydrocarbon, which has no polar group. Considering them, in olive oil, the fibre formation of alkylamides probably driven by hydrogen bonding between amides might be disturbed due

Table 1 Critical gel concentrations, in weight percent, of alkylamide derivatives in non-volatile oils.

Sample	Olive oil	Squalane
C18Am	1.0 (TG)	2.0 (TG)
C16Am	1.0 (TG)	2.0 (TG)
C8Am	2.0 (CG)	1.0 (CG)
C18/C16/C8Am (1/1/1)	2.0 (TG)	0.5 (CG)
C18/C16/C8Am (1/1/10)	1.0 (TG)	0.2 (CG)

TG: turbid gel; CG: clear gel.

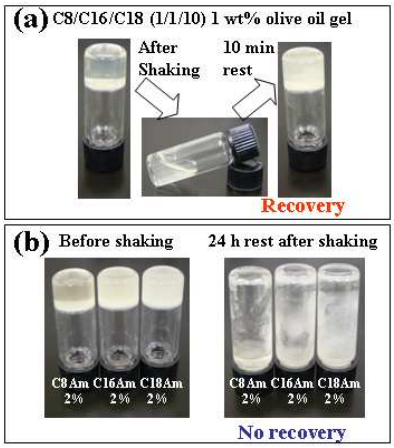


Fig. 1 Photographs of organogels after gelation and thixotropic tests. (a) 1 wt% gel containing 1/1/10 C18Am/C16Am/C8Am mixture (w/w/w) in olive oil, (b) C18Am (2 wt%), C16 (2 wt%) and C8Am (2 wt%) single component gels in olive oil.

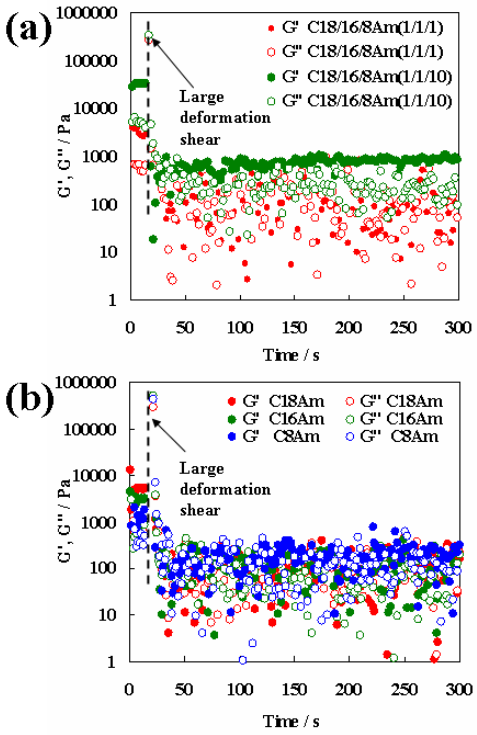


Fig. 2 Periodical step shear tests. (a) 2 wt% gels containing 1/1/1 or 1/1/10 C18Am/C16Am/C8Am mixtures (w/w/w) in squalane, (b) C18Am (2 wt%), C16Am (2 wt%) and C8Am (2 wt%) single component gels in squalane.

to polar moiety of olive oil. On the other hand, in squalane, the fibre formation of alkylamides might be disturbed at the lower extent compared to olive oil and resulted in lower CGC. These organogels formed in moderate concentration ranges and did not display any gel–oil phase separation after at least 6 months.

Differential scanning calorimetry (DSC) measurements were performed to determine the temperature-induced sol-to-gel and gel-to-sol changes of the organogels (see ESI,† Fig S3 and Table S1). Sol-to-gel and corresponding gel-to-sol

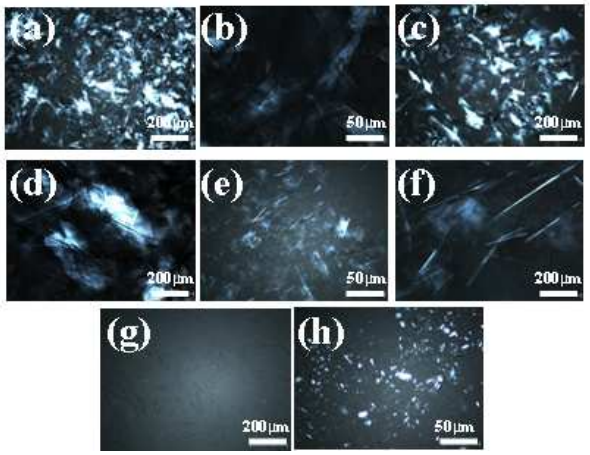


Fig. 3 POM images of CnAm–squalane gels. (a,b) C18Am (2 wt%), (c,d) C16Am (2 wt%), (e,f) C8Am (2 wt%) and (g,h) 1 wt% gel containing 1/1/10 C18Am/C16Am/C8Am mixture (w/w/w).

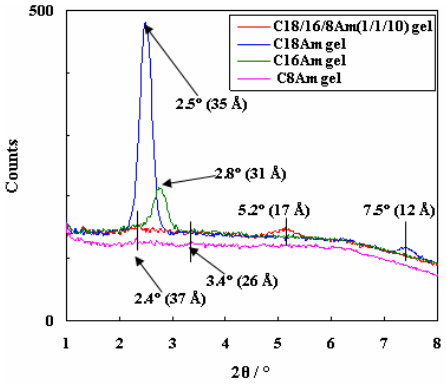


Fig. 4. XRD patterns of CnAm–squalane gels.

transitions shifted to lower enthalpy values and temperatures in multicomponent gels compared to single gels. This lower shift of transition temperatures might suggest the existence of a fine network in multicomponent gels.

The results of thixotropic test indicate that these olive oil and squalane-based gels are thixotropic close to their critical gel concentration (Fig. 1 and see ESI,† Table S2). Upon shaking, multicomponent gels with high C8Am content and gel concentration recovered their initial gel state. In contrast, single component gels and multicomponent gels with low C8Am content did not recover.

Rheometric measurements were conducted to evaluate the thixotropic behaviour of the multicomponent gels (Fig. 2). Multicomponent gels with higher C8Am contents displayed a gel state (storage modulus (G') > loss modulus (G''). under high deformation shear whereas single component and multicomponent gels with smaller C8Am content showed a liquid-like state (G' ~ G"), consistent with the visual tests. Lower G' and G" values were observed after recovery, suggesting that the gel network changed under high deformation shear but this change maintained the gel itself. These measurements provide a quantitative evaluation of thixotropic behaviours of multicomponent oil gels. Additional rheometric data validated the 'gel state' of multicomponent and single component oil gels (see ESI,† Figs. S4 and S5).[8]

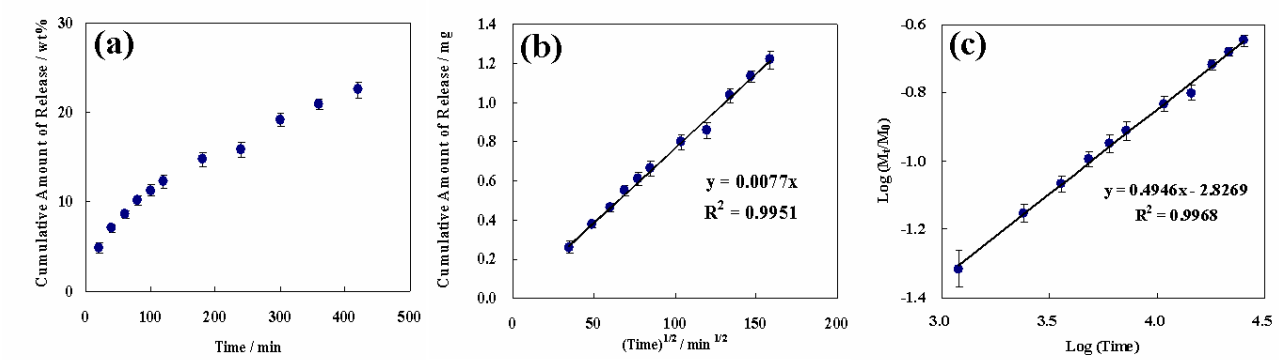


Fig. 5 Cumulative drug release curve and fitting lines of the 1/1/10 C18Am/C16Am/C8Am mixture (w/w/w) in olive oil (2 wt%) loaded with 1.0 wt% antipyrine. (a) Cumulative drug release curve of antipyrine from the multicomponent gel to aqueous media, (b) fitting line using the Higuchi model, (c) fitting line using the Korsemeyer–Peppas model. Error bars correspond to standard deviations from average values.

Polarized optical microscopy (POM) was used to closely examine the organogels. Figure 3 shows POM images of single- and multi-component CnAm–squalane systems at CGC. Single component organogels consisted of a network of 0.1μm wide tape-like crystals similar to alkylamide–toluene gels shown in the literature.[8c] Multicomponent gels showed homogeneous outlooks with broken pieces of gel (Fig. 3h). These results suggest that multicomponent alkylamide–squalane gels may form a network containing much smaller and finer tapes or fibre-like crystals than single component gels, as previously observed for alkylamide–toluene gels. [8c] The xerogels were not examined by scanning electron microscopy because their non-volatile oil gel state hindered sample preparations.

X-ray diffraction (XRD) patterns were acquired to elucidate the fibre structure of the gels. Alkylamides have been reported to adopt a dimer structure, in which two molecules interact through hydrogen bonding of their amide moieties.[12] The multicomponent gel appeared to present a peak at the same position as its main component C8Am (Fig. 4). However, the results of calculated contour length of dimer CnAm (C18Am: 49Å, C16Am: 45Å and C8Am: 25Å) were longer than the results obtained from XRD.[8c] These results may indicate the existence of interdigitated alkyl structures between the dimerized CnAms in fibre, such as an interdigitated (shorted) lamellar structure. These results suggest that the CnAm–oil gels display a lamellar (dimer) structure in the tape-like crystals, as previously observed in the corresponding alkylamide–toluene gels.[8c]

As described in alkylamide–toluene gel and alkylurea–toluene gel systems, [8b,c] it may be possible that our thixotropic multicomponent organogels composed of mainly C8Am fibres reinforced by C18Am and C16Am fibres. In this speculation, C8Am fibre and/or network is extended by an addition of C18Am and C16Am fibres to C8Am fibre, then this might enable to make effective crosslinking of fibres and/or network resulting in thixtroic behaviour and a decrease of CGC of multicomponent organogels. To explain the mechanism of mixed induced thixotropy and gelation ability in our studies, we need to carry out further study.

Finally, the performance of the multicomponent organogels as drug release materials was assessed through diffusion tests of an encapsulated drug. The non-steroidal anti-inflammatory drug 2,3-dimethyl-1-phenyl-5-pyrazolone (antipyrine), which is soluble in olive oil but insoluble in squalane, was selected as a guest drug in this experiment. Figure 5 shows the cumulative release curve of antipyrine to aqueous media (deionised water) from the 1/1/10 C18Am/C16Am/C8Am gel (w/w/w) in olive oil at 37 °C. The amount of antipyrine released gradually increased during the first few hours to reach a total cumulative value of 20 wt% after 7 h (Fig. 5a). The diffusion test results were analysed using Higuchi (Fig. 5b) [13a] and Korsemeyer–Peppas[13b] theoretical drug release equations (Fig. 5c).[14] The obtained diffusion data displayed a high linearity using models, suggesting that the cumulative release of antipyrine from the organogel to aqueous media was consistent with these models. Therefore, the antipyrine-containing multicomponent organogel is governed by the diffusion kinetics of the drug but not by anomalous mass transport kinetics. These results demonstrate that this organogel may a good candidate as a host material for gradual drug release.

In conclusion, thixotropic organogels composed of a set of alkyl amides and non-volatile oils were created using our mixing method. In addition, investigations of the drug release behaviour of the multicomponent alkylamide organogel suggested that this organogel may be appropriate as new host material for medicinal ointments. Other molecular organogels are currently being studied for controlled drug release applications using this simple mixing method.

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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