

Electronic Supplementary Information

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

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Materials and Methods

Stearamide (C18Am, 90%), hexadecanamide (C16Am, 95%), octanamide (C8Am, 98%), and antipyrine (99%) 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. Water was deionised with an Elix UV 3 Milli-Q integral water purification system (Nihon Millipore K.K).

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.

The thixotropic behaviour was evaluated using the vial inversion method. The alkylamide organogel in vial was shaken and collapsed by a vortex genie (Scientific Industries, Inc). Then the obtained sol was left for the set time at room temperature, the recovery of the gel state from the sol state was checked with naked eyes by inverting the vial.

The organogel was observed 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 a Ag-made closable sample pan. $T_{\text{gel} \rightarrow \text{sol}}$ and $T_{\text{sol} \rightarrow \text{gel}}$ 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). 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.

X-ray diffraction data were recorded on a D8 Discover X-ray diffractometer (Bruker AXS K.K.) with CuK α at 26 °C (the sample was filled in a quartz glass capillary tube of 1 mm diameter).

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 cm² 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 (1 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 $\lambda_{\text{max}} = 250$ nm in aqueous solution ($\epsilon = 9380$) 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.

Figs. S1 and S2

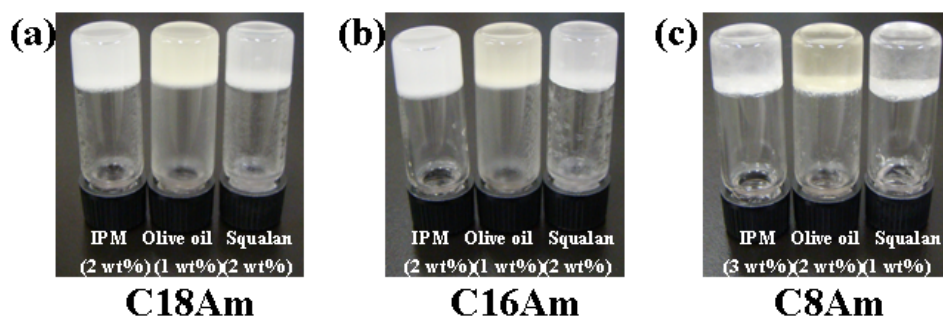


Fig. S1 Photographs of single component alkyl amide gels in isopropyl myristate (IPM), olive oil, and squalane. (a) C18Am gels, (b) C16Am gels, (C) C8Am gels.

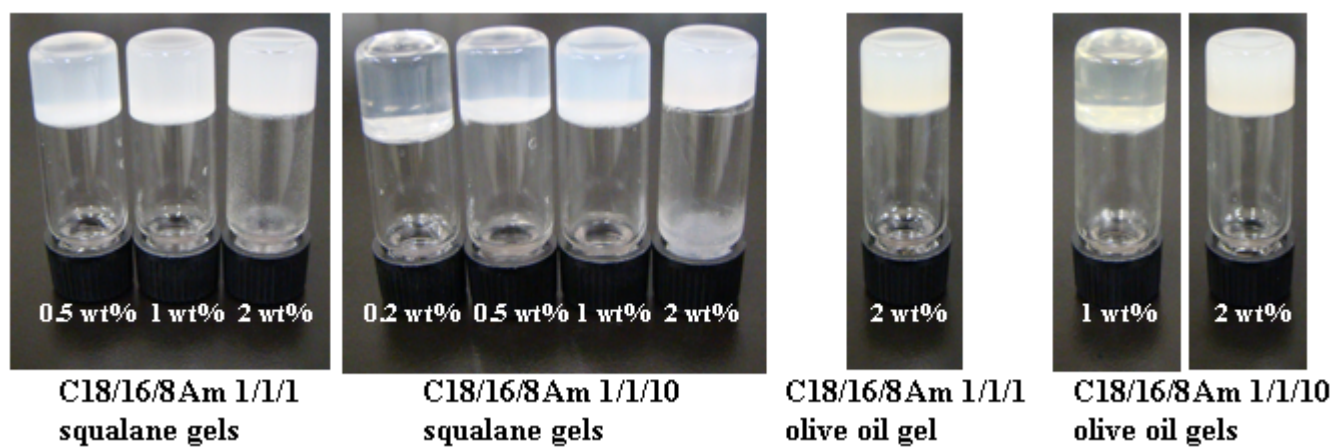


Fig. S2 Photographs of multicomponent alkyl amide gels in squalane and olive oil at different C18Am/C16Am/C8Am mixing ratios (w/w/w).

Table S1 and Fig. S3

Table S1 DSC transition temperatures of organogels in squalane (heating and cooling rates: 2 °C/min and 5 °C/min).

Sample	$T_{\text{gel} \rightarrow \text{sol}} / ^\circ\text{C}$	$T_{\text{gel} \rightarrow \text{sol}} / ^\circ\text{C}$	$T_{\text{sol} \rightarrow \text{gel}} / ^\circ\text{C}$	$T_{\text{sol} \rightarrow \text{gel}} / ^\circ\text{C}$
	$(\Delta H/\text{mJ mg}^{-1})$	$(\Delta H/\text{mJ mg}^{-1})$	$(\Delta H/\text{mJ mg}^{-1})$	$(\Delta H/\text{mJ mg}^{-1})$
	Rate: 2 °C/min	Rate: 5 °C/min	Rate: 2 °C/min	Rate: 5 °C/min
C18Am 2 wt% gel	83 (4.9)	83 (2.8)	92 (5.1)	82 (2.8)
C16Am 2 wt% gel	78 (4.7)	78 (5.0)	82, 88* (4.8)	82, 86* (4.9)
C8Am 1 wt% gel	83 (2.6)	81 (5.8)	85 (2.5)	91 (5.7)
C18Am/C16Am/C8Am 1/1/1 0.5 wt% gel	50 (0.6)	52 (0.6)	55 (0.6)	55 (0.6)
C18Am/C16Am/C8Am 1/1/10 0.2 wt% gel	43 (0.3)	50 (0.3)	64 (0.3)	53 (0.3)

* Bimodal peak (peak temperatures).

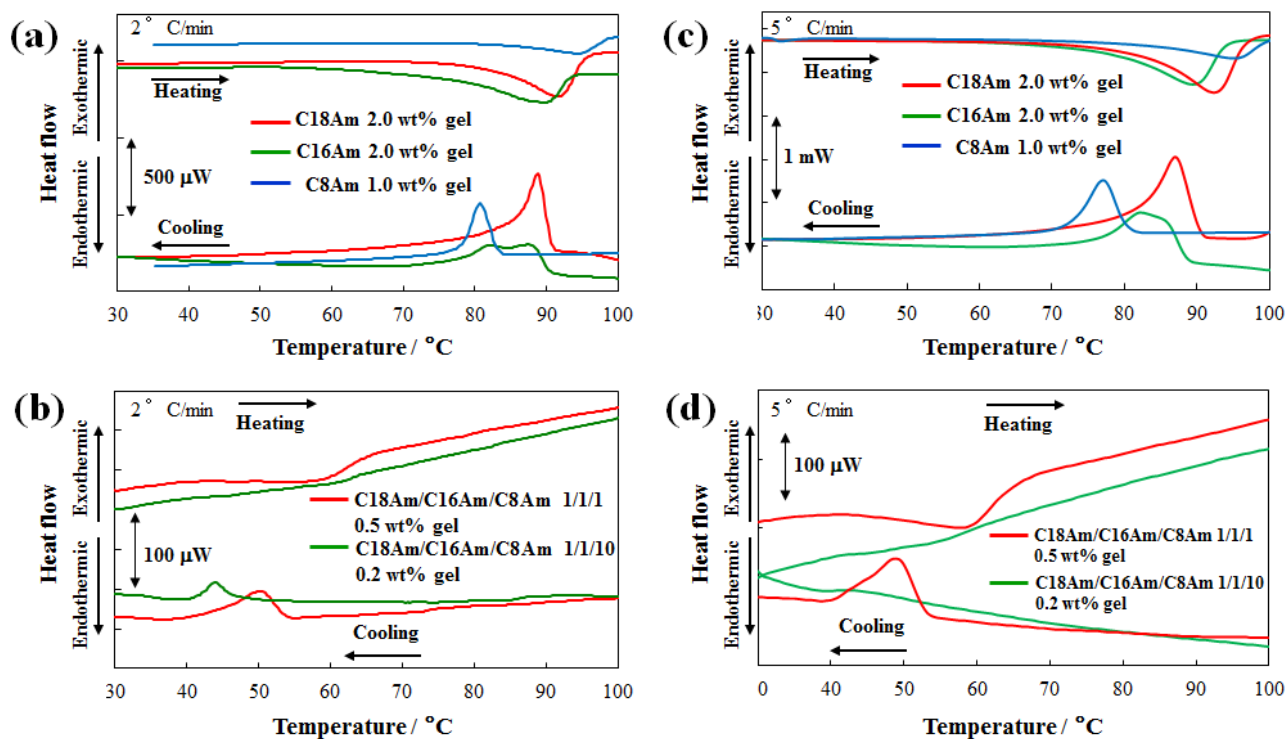


Fig. S3 DSC curves of CnAm organogels in squalane (a, b: 2 °C/min, c, d: 5 °C/min); (a, c) CnAm organogels in squalane (C18Am: 2.0 wt% gel, C16Am: 2.0 wt% gel and C8Am: 1.0 wt% gel), (b, d) mixed C18Am/C16Am/C8Am organogels in squalane with mixing ratio denoted as w/w (C18Am/C16Am/C8Am 1/1/1 0.5 wt% gel and C18Am/C16Am/C8Am 1/1/10 0.2 wt% gel).

Table S2

Table S2 Recovery time of multicomponent alkyl amide gels in olive oil and squalane after shaking.

Sample	C18Am/C16Am/ C8Am (1/1/1)	C18Am/C16Am/ C8Am (1/1/10)
Olive oil 1.0 wt%	No gelation	5 min
Olive oil 2.0 wt%	-(24 h)*	3 min
Squalan 0.5 wt%	-(24 h)*	-(24 h)*
Squalan 1.0 wt%	-(24 h)*	10 min
Squalan 2.0 wt%	-(24 h)*	5 min

* No gel recovery after shaking and 24 h of rest.

Figs. S4 and S5

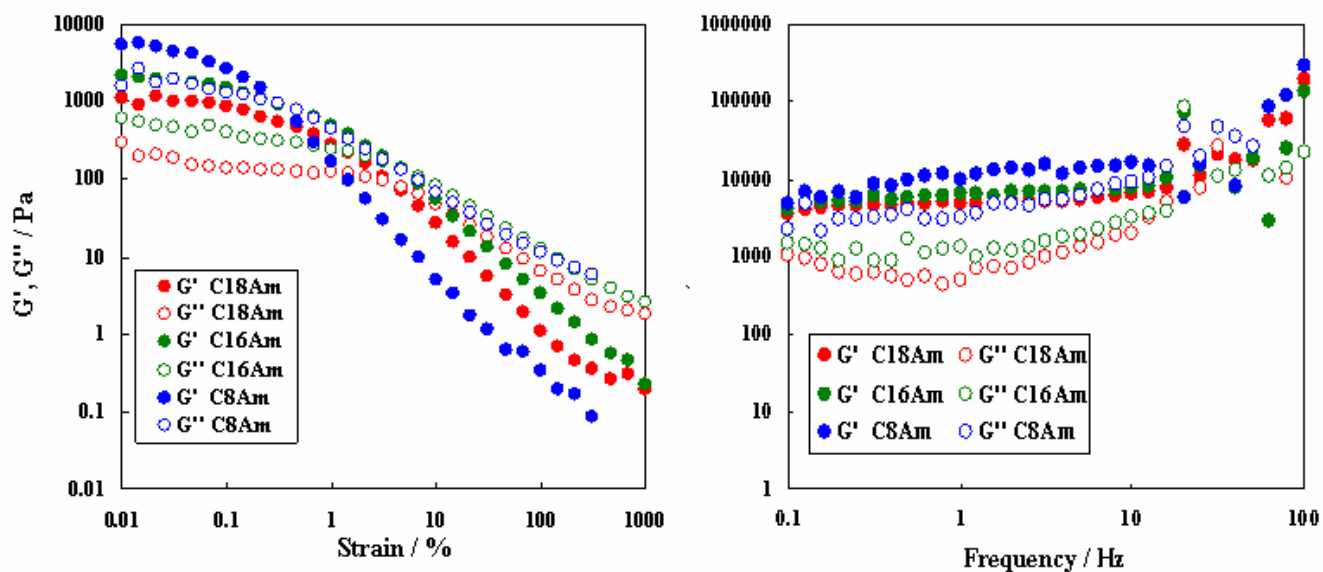


Fig. S4 Dynamic rheological properties of single component CnAm-squalane gels. Frequency sweep (left) and strain sweep (right).

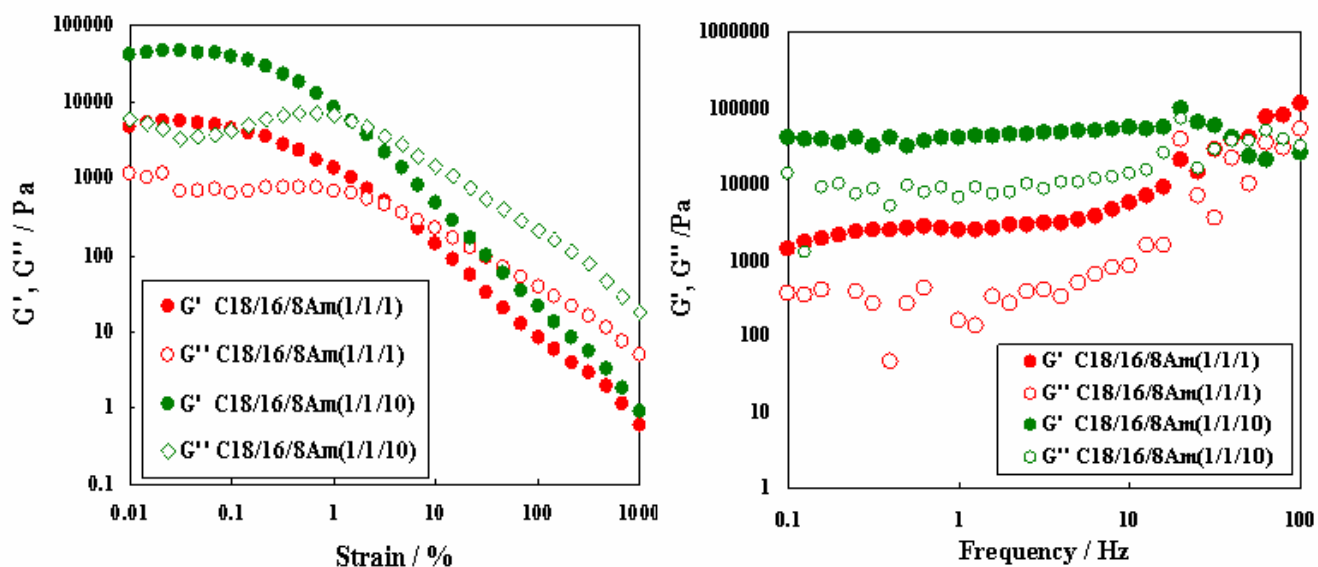


Fig. S5 Dynamic rheological properties of multicomponent CnAm-squalane gels. Frequency sweep (left) and strain sweep (right).

Acknowledgments

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