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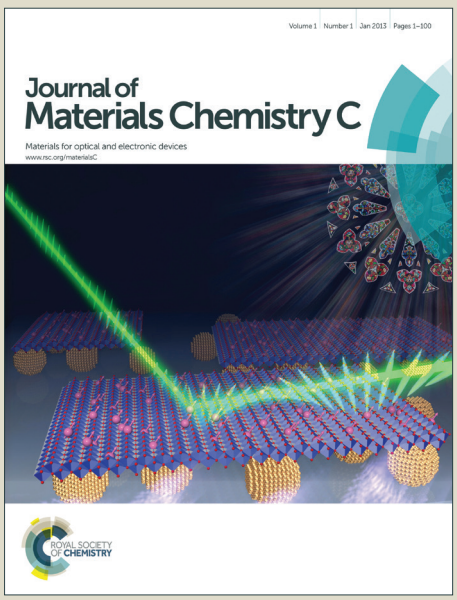

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PAPER

Shape-Selective, Stoichiometric Sensing of Fatty Acids with a Mixed Polydiacetylene Liposome

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Unsaturated fatty acids exert diverse biological processes dependent on their overall shape due to the *cis* and *trans* isomerism. Hence selective detection of fatty acids by their molecular shape is of interest but is a challenging goal. Disclosed here is a polymerized liposome that selectively senses bent fatty acids over linear fatty acids, with turn-on type fluorescence change as well as distinct color change from blue to red. Use of two different liposome components that contain monoamine and triamine moieties is found to be critical for the color change. Furthermore, the color change can be correlated with a distinct stoichiometry between the molar ratio of the total liposome components and an analyte *cis*-fatty acid, oleic aicd, in a ratio of 1:2. The colorimetric response also shows a good linearity up to the equivalent point, which enables monitoring of content change of *cis*-fatty acids in commercial cooking oil upon heating at 200 °C.

1. Introduction

Fatty acids play vital roles in many biological processes, functioning as a cell membrane component and as an energy source, signalling for metabolic regulation, and modulating the gene expression, growth and survival pathways, and inflammatory and metabolic response.[1] Fatty acids can be classified into unsaturated and saturated ones depending on the presence and absence of carbon-carbon double bonds, respectively. Unsaturated fatty acids can have *cis*- or *trans*-configuration according to the geometry of double bonds, and most of the naturally occurring fatty acids contain *cis*-double bonds. *cis*-Fatty acids such as α-linolenic acid and linoleic acid are essential and not synthesized in our body, but they play an important role in the life and death of cardiac cells.[2] *cis*-Fatty acids are also known to activate protein kinase C, a family of enzymes involved in several signal transduction cascades.[3] Furthermore, *cis*-fatty acids such as linoleic and arachidonic acids can be metabolized into a diverse family of bioactive lipid mediators called eicosanoids, which function as pro- and anti-inflammatory mediators.[4] In contrast to the beneficiary effects of *cis*-fatty acids, the consumption of *trans*-fatty acids is known to increase the risk of coronary heart disease.[5]

Considering the distinct biological effects of *cis*-fatty acids from those of *trans*-fatty acids, methods that can discriminate *cis*-fatty acids from *trans*-fatty acids or saturated fatty acids are of significant interest. The discrimination of *cis*-fatty acids from *trans*- or linear fatty acids by artificial receptors, however, is a challenging issue because both have the same functionality such as a hydrophobic alkyl chain and a carboxyl group. The overall geometry, bent or linear, can be the major difference that we may utilize for discriminating *cis*-fatty acids from *trans*- or saturated fatty acids. Conventionally, fatty acid isomers are analyzed, after derivatization to their methyl esters, by gas chromatography (GC).[6] Recently, colorimetric and fluorimetric methods for the determination of fatty acids have received growing interest, as they can provide an easy and convenient assay method. Glass and co-workers reported calix-naphthalene based molecular tubes that tightly bind *cis*-fatty acids with a long straight-chain; the binding resulted in fluorescent quenching.[7] Tolosa and co-workers used a fluorescent fatty acid binding protein (FABP) for the ratiometric fluorescence sensing of oleic acid;[8] the protein system responded to oleic acid in the concentration range of 0.02–4.7 μM, as determined by both steady-state and time-resolved luminescence decay experiments. Ye and co-workers used Ubxd8 protein for the recognition and sensing of unsaturated fatty acids that regulate the triglyceride synthesis.[9]

In spite of those efforts, the detection of fatty acid, in particular, discrimination of *cis* and *trans* isomers by a simple and efficient method remains as a challenging goal. Herein, we report the mixed liposome sensing system as a simple, yet efficient assay tool for the discrimination of *cis*-fatty acids from *trans*- and saturated fatty acids. Yoon and co-workers reported a liposome based sensing system for *cis*-fatty acids for the first time.[10] They demonstrated that an imidazolium-functionalized polydiacetylene (PDA) liposome selectively responded to *cis*-fatty acids with both colour and fluorescence changes; however, its capability of quantification is not shown. Our liposome based sensing system selectively senses *cis*-fatty acids from *trans*- and saturated fatty acids, further with a distinct colour change from blue to red. Our system also enables us to semi-quantify *cis*-fatty acids. Furthermore, we show that the liposome system interacts with fatty acids with a discrete binding

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† Electronic Supplementary Information (ESI) available: The experimental details for the synthesis and characterisation of liposome **3** and dioleyl malonic acid **4**. See DOI:

stoichiometry, a surprising observation with such a macromolecular liposome system.

PDA liposomes can show stimuli-sensitive chromogenic and fluorogenic responses, making them unique and versatile sensing platforms.[11] In solution, blue PDA liposomes turn to red in response to various stimuli such as heat, pH, mechanical stress, and the binding site–analyte interactions. The PDA liposomes in the "red" phase emit fluorescence, thus enabling fluorescence sensing in a turn-on manner. Such stimuli can cause a perturbation in the conjugation length of the polydiacetylene π backbone, leading to the chromogenic and fluorogenic response. With this "built-in" sensing capability, we can develop the PDA liposomes into chromogenic and fluorogenic sensing systems by deliberately introducing recognition units onto the liposome surface.[12] We have particular interest in the "multi-component" PDA liposome systems in which more than two different liposome components are mixed to form the polymerized liposomes. Such a "mixed" liposome approach has been demonstrated to be useful in realizing high analyte selectivity by us,[13] as the integrated recognition units on the liposome surface can provide a rather congested binding pocket/site that selectively accommodates an analyte.

2. Experimental

2.1. Synthetic Procedure

All chemicals were commercially available and used without further purification. Synthesis of liposome component **1** was carried out according to the reported procedure.[13] Syntheses of liposome component **2** and dioleylmalonic acid **4** are described in the Supplementary Information (ESI).

2.2. Preparation of liposome 3

A mixed solution of **1** (2.1 mg, 5 μmol) and **2** (2.5 mg, 5 μmol) in chloroform (1 mL) was prepared in a vial, from a stock solution of each component. The solvent in the vial was evaporated by flushing with a stream of Ar gas, and then filled with deionized water (10 mL). The resultant suspension was sonicated for 25 min at 80 °C (Fisher scientific sonic dismembrator, model 500) and then filtered through a cellulose acetate filter (diameter 0.8 μm) to remove dispersed lipid aggregates. The filtered solution was kept at 4 °C overnight to give a solution of the mixed liposome, which was exposed to 254 nm UV (1 mW/cm^2) for 2 min to give a solution of the polymerized liposome **3**. The concentration of liposome is defined to be the summed concentration of the total liposome components: 10 μmol/10 mL = 1.0 mM.

2.3. Preparation of fatty acids and soybean oil samples

Each fatty acid sample (100 mg) was dissolved in MeOH (5 mL), which was treated with an excess amount of Na_2CO_3 to make the corresponding sodium salt. The solution was filtered to remove residual Na_2CO_3 and concentrated in vacuum to obtain a white powder. Finally, the powder was dissolved in deionized water to make a stock solution (10 mM). The soybean oil samples were saponified with 0.5 N NaOH in MeOH at 100 °C for 10 min r.

2.4. Colorimetric assay of fatty acids with liposome 3

UV-Vis spectral changes were monitored for a solution of liposome **3** by incremental addition of a given fatty acid. For example, to a solution of liposome **3** (50 μM) prepared in HEPES buffer (10 mM, pH 7.4) was added an aliquot of a fatty acid (0, 10, 20, 30, 40, 50, 60, 75, 100, 250, and 500 μM) dissolved in HEPES buffer (10 mM, pH 7.4) in such a way that the total volume remained at 1.0 mL. After addition of a fatty acid, the resulting solution was gently shaken for 10 min and its UV-Vis spectrum was recorded. For the evaluation of the liposome selectivity toward various fatty acids, a small aliquot of each of the fatty acids (200 μM in pH 7.4 HEPES buffer) was added to a solution of liposome **3** (200 μM in pH 7.4 HEPES buffer). The colour change of this solution, after shaking gently for 10 min, was recorded by photography and by UV-Vis measurement.

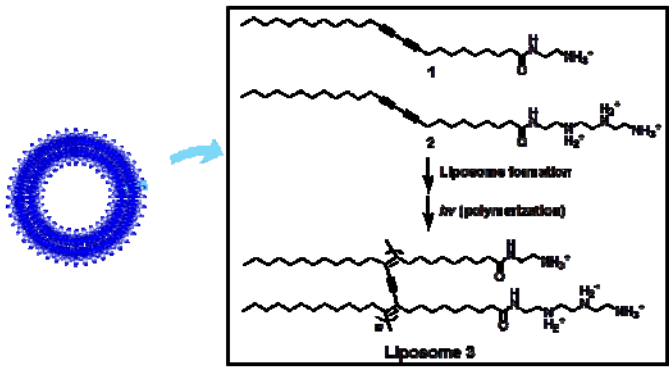
2.5. Dynamic Light Scattering (DLS) Analysis

A dynamic light scattering method was used to determine the average size of liposome **3** in solution. Light scattering was measure using a Zetasizer (Malvern Instruments Co., UK) equipped with a He-Ne layer at a detection angle of 173°. The fluctuation of scattered light intensity was related to the Brownian motion of the liposome **3** and the Stoke-Einstein equation was used to calculate the particle size. The concentration of liposome **3** in the solution was 1.0 μM, and all measurements were carried out at a room temperature.

3. Results and discussion

3.1. Preparation of the mixed liposome sensing system

We reasoned that PDA liposomes with cationic surface groups would recognize fatty acids through two key molecular interactions: 1) electrostatic interactions between the cationic groups and the fatty acid carboxylate groups, and 2) insertion of the fatty acid alkyl chain into the hydrophobic domain of liposome. In the case of *cis*-fatty acids that have a bent geometry, insertion into the liposome chains may distort the poly(enyne) backbone to cause a colour change. A preliminary study with a simple amine-terminated liposome prepared from the liposome component **1**, however, failed to sense *cis*-fatty acids. It seemed that the mono-amine system provided insufficient molecular interactions. Therefore, we prepared a liposome containing three amino units starting from the liposome component **2**; however, this time the liposome underwent precipitation upon treatment with a fatty acid. Based on our experience with the mixed liposome systems,[13] then we prepared a mixed liposome composed of components **1** and **2** in a 1:1 ratio. To our delight, this mixed liposome **3** showed a desirable sensing behaviour with a distinct colour change at physiological pH of 7.4 upon treatment with oleic acid, a *cis*-fatty acid. This result again demonstrates that the recognition and sensing behaviours of PDA liposomes can be tuned by introducing a secondary liposome component.



Scheme 1 Preparation of polymerized liposome **3**, starting from components **1** and **2** in the molar ratio of 1:1.

The PDA liposomes were prepared according to the established procedure, as shown in Scheme 1. A mixed liposome from then irradiated with UV light (254 nm) for 2 min to produce the corresponding polymerized liposome in solution. The polymerized liposome has a size distribution of 68–122 nm, as measured by dynamic light scattering analysis (Fig. S1, ESI†). This PDA liposome solution was stable for months when kept at 4 °C. The concentration of the PDA liposome was defined based on the total moles of the two liposome components used.

3.2. Sensing of *cis*-fatty acids with liposome 3

We evaluated the sensing behaviour of liposome **3** toward various fatty acids: *cis*- and *trans*-fatty acids, saturated fatty acids, and geranic acid. When liposome **3** (200 μM) was treated with various fatty acids (200 μM) in HEPES buffer (10 mM, pH 7.4), a distinct colour change from blue to red occurred within 5 minutes only in the case of *cis*-fatty acids (oleic, linoleic, and palmitic acid), but no colour change resulted in the both cases of *trans*-fatty acids and saturated fatty acids. Geranic acid that has branched alkyl substituents but has overall linear geometry also did not cause colour change. Furthermore, an ester of a *cis*-fatty acid, methyl oleate, did not cause any colour change (Fig. 1). These results indicate that fatty acids having a "bent" shape and in their carboxylate form can distort the polyenyne backbone, thereby causing colour change. In contrast, both *trans*-fatty acids and saturated fatty acids that have overall "linear" shape do not exert steric strain to the polyenyne backbone enough to cause the colour change. It is notable that the present mixed liposome system exhibits much more distinct colour changes toward *cis*-fatty acids than does the imidazolium-based liposome system.[10] The larger changes in the absorption spectra accordingly lead to the higher sensitivity, demonstrating an advantageous feature of our two-component liposome system. It should be noted that most of known liposome sensing systems are fabricated from single recognition component.[14]

3.3. Assay of various fatty acids with liposome 3

We evaluated colorimetric response of liposome **3** toward oleic acid that is chosen as a representative *cis*-fatty acid, by UV-Vis spectroscopy. Spectral changes were followed for a solution of liposome **3** (50 μM) in HEPES buffer (10 mM, pH 7.4) by incremental

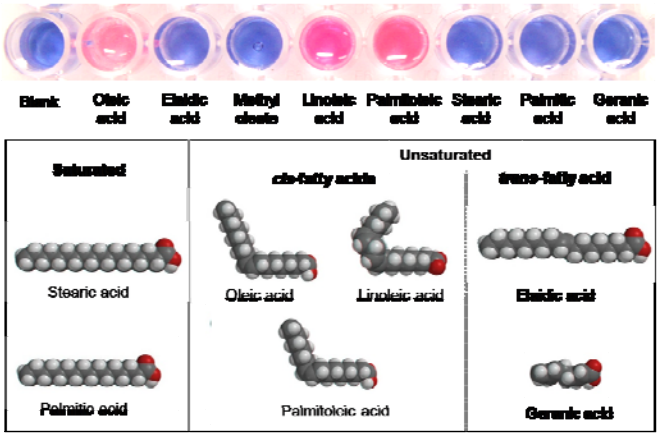


Fig. 1 Colorimetric response of liposome **3** (200 μM) toward the various fatty acids (200 μM) in HEPES buffer (10 mM, pH 7.4).

addition of oleic acid sodium salt (10 mM, 1 mL at a time) dissolved in deionized water. The liposome concentration is expressed as the summed concentration of the two liposome components used for the preparation of the liposome by counting them indiscriminately. The collected absorption titration data (Fig. 2a) show that the absorbance at 630 nm decreases whereas the absorbance at 540 nm increases; these absorption changes correspond to the colour change from blue to red.

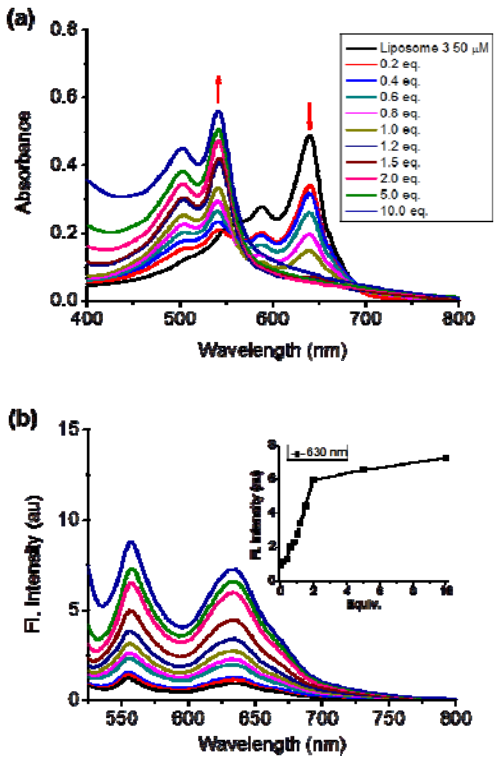


Fig. 2 (a) UV-Vis spectral changes of liposome **3** (50 μM) upon addition of oleic acid (0–10 equiv.) in HEPES buffer (10 mM, pH 7.4). (b) Fluorescent spectral changes of liposome **3** (50 μM) upon addition of oleic acid (0–10 equiv.) in HEPES buffer (10 mM, pH 7.4). Inset is a plot of fluorescence intensity change (the peak height at 630 nm) depending on the molar equivalent of oleic acid with respect to that of the liposome components.

The blue-to-red colour change also can be monitored by the corresponding emission change from the red-phase liposomes, showing turn-on fluorescence increase (Fig. 2b). For a quantification purpose, the colour change that shows ratiometric behaviour is preferred over the fluorescence change.

The absorption spectral changes can be represented by a quantitative parameter, the percent colorimetric response (%CR), defined as Equation 1.[15]

$$\%CR = \left[\frac{\{A_{blue}/(A_{blue}+A_{red})\}_0 - \{A_{blue}/(A_{blue}+A_{red})\}_t}{\{A_{blue}/(A_{blue}+A_{red})\}_0}\right] \times 100 \quad (1)$$

In this equation, "*A*" notes the absorbance either at 630 nm (A_{red}) or at 540 nm (A_{blue}), and the indices "*0*" and "*t*" note the absorbance before and after the addition of the fatty acid solution, respectively. Interestingly, the colorimetric response showed saturation behaviour at two equivalents of oleic acid with respect to liposome **3**, a binding mode of 1:2 liposome **3**/oleic acid. In addition, the %CR value increases quite linearly up to the saturation point (Fig. 3). The fluorescence titration data also show the same stoichiometry (Fig. 2b inset). Such a discrete binding stoichiometry is an unusual result if we consider that the liposome is composed of a large number of recognition components. To the best of our knowledge, such a binding stoichiometry has rarely been observed with a liposome system.

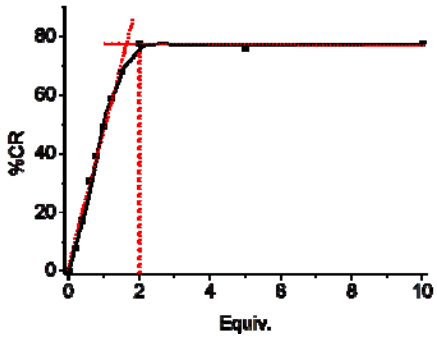


Fig. 3 Plot of the %CR values depending on the molar equivalent of oleic acid (0–10 equiv.) with respect to that of the liposome components, obtained from the absorbance titration data in Fig. 2.

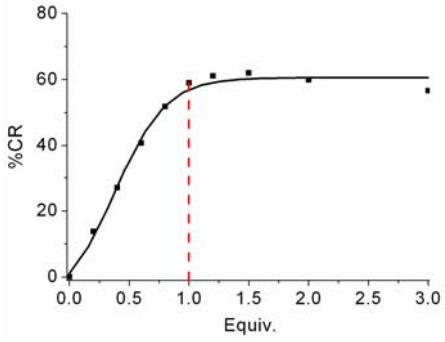


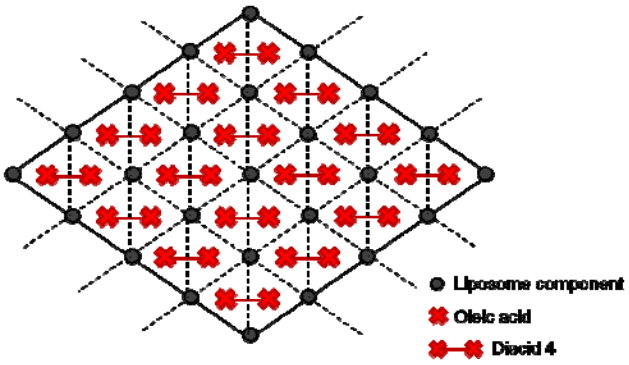
Fig. 4 Plot of the %CR values depending on the equivalent of dioleyl malonic acid **4** (0–3 equiv.). This graph is obtained from the UV-Vis titration of liposome **3** with **4**.

To confirm the 1:2 (liposome components/fatty acid) binding mode, we prepared a dioleyl malonic acid (**4**) and assessed it under the same conditions. The %CR value is saturated with an equivalent of the dioleyl malonic acid, which result supports the 1:2 binding mode observed in the case of oleic acid (Fig. 4).

A diagram to represent the 1:2 binding stoichiometry between liposome **3** and oleic acid or the 1:1 binding mode in the case of dioleyl malonic acid **4** is presented in Scheme 2. Thus, one oleic acid molecule is inserted into a triangle space generated by three adjacent liposome components, or one dioleyl malonic acid molecule is inserted into the space generated by four adjacent liposome components that are arranged in a rhombus shape. Given that such a liposome is composed of a large number of the components (two different components in this study, which are counted indiscriminately), the diagram only represents a portion of the spherical liposome surface. This binding model represents the 1:2 binding stoichiometry between the liposome component (n^2) and the fatty acid $\{2(n-1)^2\}$, which can be readily verified with a limit formulas where n represents the number of liposome component on one side of the rhombus (Scheme 2):

$$\lim_{n\to\infty} \frac{2(n-1)^2}{n^2} = 2$$

When n is 400, the corresponding stoichiometry (the molar ratio of a fatty acid such as oleic acid over the liposome component) is 1.99, approaching 2.



Scheme 2 Diagram to show the binding stoichiometry between oleic acid or dioleyl malonic acid **4** and liposome **3**.

3.4. Competitive binding between a bent fatty acid and a linear fatty acid toward liposome 3

Even though bent *cis*-fatty acids cause colour change of the liposome solution, it does not necessarily mean that only *cis*-fatty acids can be inserted into the liposome hydrophobic region. Therefore, it is interesting to know the relative binding ability among bent and linear fatty acids toward liposome **3**. To this end, we evaluated a competitive colorimetric assay of liposome **3** toward oleic acid (representing a bent fatty acid) and stearic acid (representing a linear fatty acid). Two sets of experiments were conducted. Firstly, a solution of liposome **3** (200 μM) in HEPES buffer (10 mM, pH 7.4) was treated with (**1**) an equimolar mixture of both oleic acid and stearic acid, (**2**) stearic acid only, (**3**) one equivalent of stearic acid for 10 min, followed by one equivalent of oleic acid, and (**4**) one equivalent of oleic acid for 10 min, followed by one equivalent of stearic acid (in all cases 2 equivalents of fatty

acids were added to the liposome), and the resulting colour changes were monitored 10 min after mixing. The results of colour changes are shown in Fig. 5. Similar colour changes were also observed in the second experimental set where we used two equivalents of each acid (400 μM) in each of the experiments (b)–(e) in Fig. 5 (Fig. S2, ESI†). As expected from the above results, linear stearic acid do not cause colour change of the liposome solution. All the other cases, however, show colour changes, from which we can conclude that liposome **3** can accommodate both bent and linear fatty acids. When a pair of linear and bent fatty acids was inserted into the same binding pocket, colour change was also occurred (Fig. 5b). These interesting observations also support the binding mode proposed in Scheme 3. Also, results of the second competition assay suggest that either "homo-pairs" (*cis*-*cis* or *trans*-*trans*) or "hetero-pair" (*cis*-*trans*) can be inserted into the liposome with a comparable efficiency.

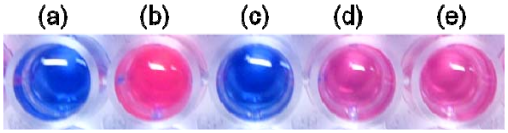


Fig. 5 Competitive colorimetric response of liposome **3** to oleic (bent) and/or stearic (linear) acids in HEPES buffer (10 mM, pH 7.4): (a) liposome **3** only (200 μM), (b) a mixture of stearic acid (200 μM) and oleic acid (200 μM), (c) stearic acid (400 μM), (d) addition of stearic acid (200 μM) for 10 min, followed by oleic acid (200 μM), (e) addition of oleic acid (200 μM) for 10 min, followed by stearic acid (200 μM).

3.5. Monitoring of *cis*-fatty acid contents in commercial oil samples after heating

We applied the liposome sensing system to monitor the concentration change of *cis*-fatty acids in the real soybean oil upon heating. A typical soybean oil is mainly composed of *cis*-fatty acids (ca. 81%), with saturated fatty acids as minor components (ca. 18%).[16] During a cooking process, however, the *cis*-fatty acids can undergo decomposition through thermal oxidation or can be converted to the *trans*-isomers through the heat-induced double bond isomerization.[17] Most commercial cooking oils contain more than one antioxidant such as δ-tocopherol and sesamol (3,4-methylenedioxyphenol), which reduce the thermal oxidation process to a certain extent. Therefore, initially we used oleic acid and linoleic acid samples that do not contain any antioxidant. To reproduce a real cooking situation, we heated each fatty acid sample up to 200 °C under vigorous stirring. As time went on, both the fatty acids turned into brown from initially bright yellow. We collected a small amount of each sample during the heating experiment (0–10 h). Each of the collected samples was dissolved in methanol and then treated with excess sodium carbonate. The residual sodium carbonate was then filtered off and the resulting solution was concentrated in vacuum to afford the corresponding sodium salt of each fatty acid as a white powder. Finally, the white powder was re-dissolved in deionized water to make a 10 mM stock solution, which was analysed using liposome **3** (Fig. 6). In this way, we were able to monitor the concentration change of the *cis*-fatty acid upon heating through the isomerization and decomposition. A slower colour change was observed in the case of oleic acid compared to the case of linoleic acid (Fig. 6a, 6b). The results suggest that linoleic acid, which has two *cis*-double bonds, is more sensitive to the thermal degradation compared with oleic acid, which has one *cis*-double bond.[18] Next, we applied liposome **3** for monitoring of residual *cis*-fatty acids in a soybean oil product after heating at 200 °C. The samples were prepared in a similar manner as described above for pure oleic acid. In this case, as the soybean oil also contains methyl ester of each fatty acid, after heating for the given time each sample was saponified with 0.5 N NaOH in methanol at 100 °C for 10 min. From UV-Vis measurements, we obtained the %CR value for each sample to estimate the residual content of *cis*-fatty acids in the sample. From a plot of the content of *cis*-fatty acids depending on heating time, we were able to estimate that the content of *cis*-fatty acids decreased about 20% from its original value, after heating at 200 °C for 4 h; after that, there was little change in the composition of *cis*-fatty acids (Fig. S6, ESI†). It seems that some antioxidants in the commercial product slow down and reduce the thermal degradation.[17]

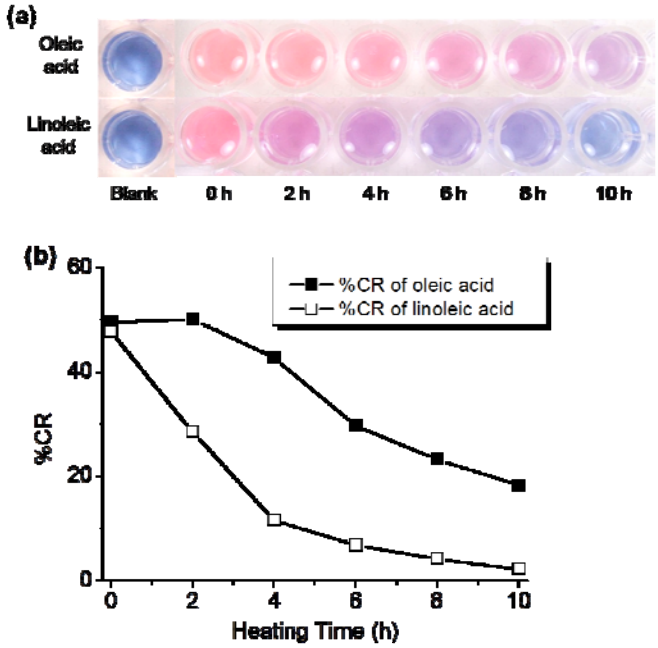


Fig. 6 (a) Colorimetric sensing of oleic acid and linoleic acid with liposome **3** after heating at 200 °C for given times (0–10 h). Each fatty acid sample (50 μM) was treated with liposome **3** (50 μM) in HEPES buffer (10 mM, pH 7.4). (b) Plots of both the %CR value and the residual content of *cis*-fatty acids in each sample with respect to the heating time.

Conclusions

We have disclosed a liposome based sensing system for fatty acids, which is composed of two different amine components that interact with fatty acids both through hydrophobic and ionic interactions. The liposome showed turn-on fluorescence response as well as shape-selective colorimetric response, discriminating *cis*-fatty acids over *trans*- or saturated fatty acids in a ratiometric manner: UV-Vis spectral change with distinct colour change from blue to red was observed in the case of the bent *cis*-fatty acids, which can be explained by the

effective perturbation in the π-backbone of the liposome by the bent fatty acids. The colorimetric response showed a good linearity up to the equivalent point, which enabled us to assess the content of *cis*-fatty acids in commercial cooking oil after heating at 200 °C. The molecular interactions between the liposome and *cis*-fatty acids showed 1:2 and 1:1 (liposome component/fatty acid) binding stoichiometries in the cases of mono- and di-oleyl fatty acids, respectively, indicative of a well-defined binding mode where the fatty acids are inserted into the liposome components. Competition assays demonstrated that liposome **3** can accommodate linear and bent fatty acids or their mixture. The liposome system was used for monitoring of thermal change of *cis*-fatty acids in a commercial oil sample. The discrete binding stoichiometry observed and distinct colorimetric response dependent on the overall shape of fatty acids would make such a liposome based sensing system to be an attractive tool in analyzing fatty acids and related compounds.

Acknowledgements

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Graphic Abstract

A mixed polymerized liposome discriminates fatty acids depending on their overall shape and with a discrete binding stoichiometry.