Soft Materials

ISSN: 1539-445X (Print) 1539-4468 (Online) Journal homepage: https://www.tandfonline.com/loi/lsfm20

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To cite this article: Mehmet Çolak, Deniz Barış, Murat Evcil, Nadir Demirel & Halil Hoşgören (2018) Two-component organogelators: combination of N^{ε}-alkanoyl-L-lysine with various N-alkanoyl-L-amino acids: additional level of hierarchical control, Soft Materials, 16:4, 289-302, DOI: 10.1080/1539445X.2018.1517092

To link to this article: https://doi.org/10.1080/1539445X.2018.1517092

SOFT MATERIALS
2018, VOL. 16, NO. 4, 289–302
https://doi.org/10.1080/1539445X.2018.1517092

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Two-component organogelators: combination of N^{ε}-alkanoyl-L-lysine with various N-alkanoyl-L-amino acids: additional level of hierarchical control

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ABSTRACT

Synthesis of two-component organogelation system was performed very easy and concise manner from N^{ε}-palmitoyl-L-lysine ethyl ester and N^{ε}-miristoyl-L-lysine ethyl ester in which they were used as base component and N-lauroyl-L-amino acids (amino acids:, alanine, leucine and phenylalanine as acid components.). And their organogelation properties were examined in different pharmaceutical fluids such as liquid paraffin, fatty acid ethyl, and isopropyl esters. In this way, gelation efficiency was ascertained variations of alkanoyl moieties and combination of different amino acids in the gelator structures. Characterization of gelators was performed via thermal measurement such as Tg and gel–sol enthalpy change; SEM and FTIR as optical methods.

ARTICLE HISTORY
Received 25 June 2018
Accepted 20 August 2018

KEYWORDS
Gels; hydrogen bonds; nanofibers; self-assembly

Introduction

When gelator molecules initially gather into nanofibers and then further arranged into a 3-D network by trapping the solvent within the unoccupied space of the network, gels are formed. When low molecular-weight organic molecules in organic solvent form a gel, they are mostly denoted physical gels or supramolecular gels (1–4). Due to their unsurpassed properties and potential applications for new soft organic materials (5), template synthesis (6), drug delivery (7,8), there have been intensive relevance on supramolecular organogels.

Long nanofibers (supramolecular polymers) that are self-assembled via van der Waals, π-stacking, hydrogen-bonding, coordination, electrostatic, and charge-transfer interactions constitute a great number of supramolecular gels. Non-covalent cross-links and physical complexity between the supramolecular polymers generate a 3D arrangement. As a consequence, the solvent is trapped into sample-spanning network. The LMWGs (low molecular-weight organogelators) produce miscellaneous nano-scaled superstructures as nanoribbons, nanoparticles, nanofibers, bundle, nanosheets, and helical structures in organogels. The chemical structure of LMWGs and the solvent determine the formation of such structures (9). Two-component gelling systems were first reported by Hanabusa et al. and McPherson et al. in 1993 (10,11). In a rigid component system, the individual components have limited gelation ability by themselves, but they can behave as an organogelator when they form two components complex. But, in some two-component system, while one component is an organogelator, gelation process can be changed with the formation of a new two-component complex after the addition of second component. In this sense, physical properties such as minimum gel concentration (MGC), Tg (gel melting point), gel strength, and gelation ability can be fine-tuned. Two-component gel systems are the soft materials with adjustable microscopic and macroscopic properties that spontaneously come together as results of hydrogen bond (12), host–guest interaction (13), metal-ion coordination (14), charge-transfer phenomena (15), and acid–base interactions (16). A stable two-component system is a system that while components have limited gelation abilities separately, this ability increases with the formation of a complex from these two components.

In two-component systems, to make structural modifications on either one of the components introduce functional behaviors to the materials. Finally, to change the materials behaviors and to generate new morphologies, different gelation fluid as another parameter was used. The additional level of supramolecular control in the hierarchical self-assembly of two-component gels gives excellent adjustability and controllability (17).

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Another structural modification is to change the ratio of the two components, Smith, Hirst and co-workers studied on this effect and demonstrated that this provide another possibility for achieving morphological adjustability. They also reported that this additional level of control, not possible with a one-component gelator. It can allow the controlled assembly of completely new nanostructured morphology (17,18). Although there is impressive variety of an organogel system, relatively few have been considered in the field of drug delivery, because there is no enough information on their biocompatibility and toxicity (19). In order to develop the biocompatibility and biodegradability, gelator structure is often bound with a biomolecular precursor (20,21). As a simple strategy, incorporate a biologically relevant molecule/precursor as one of its components (either hydrophobic or hydrophilic) could improve the biocompatibility of an amphiphilic gelator (22). The long alkyl chain of fatty acid ester is an appropriate choice as the hydrophobic domain of the gelator (23).

Amino acids serve a good viewpoint for preparing synthetic organogelators (24,25). As alternative to those naturally occurring ones like lecithin because the production cost is high, and they are not produced in large scale. Their synthetic procedures are relatively simple and well-established. They are used as the main starting materials in development of the gelators because of large quantities of natural abundance. There is prosperity of data explaining supramolecular gels contained amino acid hydrogen-bonding residues functionalized with long alkyl chains (23).

Moreover, L-lysine (26,27) is one of the most versatile building blocks for the construction of organo-and hydro-gelators because of its biocompatibility, high density of functional groups, and easy orthogonal functionalization. As a result, Suzuki, Hanabusa and coworkers have used L-lysine as a key building block to develop functional soft materials in organic solvents (26). Hanabusa group have first reported L-lysine-based organogelators by functionalizing the amines of L-lysine with long chain fatty acids (23).

After this study, they have described the construction of a new two-component gelling system by using N^{ε}-lauroyl-L-lysine ethyl and dodecyl esters as a base component and N-dodecyl-L-amino acids (valine, phenylalanine, alanine, glycine, and lysine) as an acid component instead of employing aliphatic acids and their organogelation properties (9).

In our research both of acidic and basic component were functionalized not only lauroyl group but also palmitoyl and myristoyl groups were introduced into their structures as key attachments. By using N^{ε}-alkanoyl-L-lysine ethyl esters as a base component (alkanoyl groups: palmitoyl, myristoyl) and N-alkanoyl-L-amino acids as an acid component in which alkanoyl groups are lauroyl, myristoyl, palmitoyl subunits on the acidic segments were designed and synthesized to understand the role of lipophilicity of alkanoyl moieties. And also, elucidation of their gelling properties was also checked with respect to the variation of several amino acids (amino acids: alanine, leucine, phenyl alanine). In this way, L-lysine-based comprising different alkanoyl chain as a basic component and various amino acids (aliphatic and aromatic) derivatization with aliphatic chains as an acidic component were designed and synthesized. Thus, introducing those biocompatible moieties and amides functionality can be an effective strategy for decreasing cytotoxicity of the new two-component gelator systems. The development of most of such gelators generally requires multi-step and time-consuming synthesis and tedious purification procedures (28).

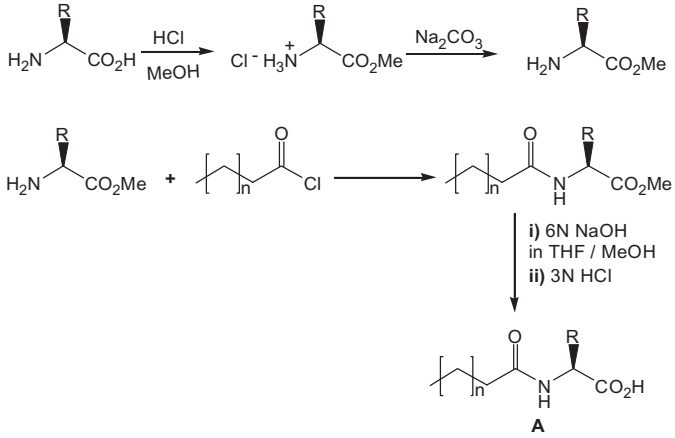
However, in the current study, L-lysine is linked by an amide bridge via N^{ε}-amine heads. This provides an advantage since the synthesis involves a facile and straightforward step and does not require any protection. By expanding the hydrophobic–hydrophilic balance to increase gelling potential, which contains different amino acid and different alkanoyl groups, thus is fine-tuned, BmAn-type 7 gelator compounds were synthesized and evaluated as two-component organogelators (Scheme 1, Scheme 2 and Scheme 3). Also, gelation efficiency was investigated in liquid paraffin, ethyl and isopropyl esters of some fatty acids used in cosmetic and drug industries. In this stage of our study, the characterization of the obtained gelators was performed; *Tg* measurement, MGC, and determination of gel–sol transition enthalpies. On the other hand, elaborative gel characterization was made temperature-dependent IR experiments and SEM visualization techniques.

Results and discussion

Synthesis

Synthesis of N-alkanoyl -l-amino acid ethyl esters (AE1, AE2, AE3, AE4, AE5)

Synthesis of N-alkanoyl-L-amino acid derivatives (A type acid components) was shown in Scheme 1. The synthesis of acid component is easy and forward. In the synthesis, different alkanoyl groups were used. L-Amino acid methyl ester hydrochloride (0.036 mol) (amino acids: alanine, leucine, and phenylalanine) was dissolved in adequate amount of water. $CHCl_3$ (25 mL)



Scheme 1. General synthesis of compounds type A (N-alkanoyl-L-amino acid derivatives).

was added to this solution and Na_2CO_3 was added this two-phase system, at 0°C until solution of pH became 10. To prevent hydrolysis, addition of base should be completed quickly. The solution was extracted with $CHCl_3$ (25 mL) twice and the organic phases were combined and dried over Na_2SO_4; then solvent was evaporated, and the product was recovered as amino acid ester for the second step.

In the second step, L-amino acid methyl ester (0.03 mol) was dissolved in $CHCl_3$ (50 mL) with triethylamine (0.032 mol) and cooled to 0°C. Alkanoyl chloride (0.032 mol) in $CHCl_3$ (10 mL) was added slowly. After completed addition of alkanoyl chloride, the mixture was stirred further 5 h. $CHCl_3$ (50 mL) was added and washed with HCl (3M, 15 mL) three times. Organic phase was washed with water, brain and again water and dried over Na_2SO_4 than evaporated and product dried on a vacuum gives [N-lauroyl-L-alanine methyl ester (AE1), N-lauroyl-L-leucine methyl ester (AE2), N-lauroyl-L-phenylalanine methyl ester (AE3), N-myristoyl-L-phenylalanine methyl ester (AE4), N-palmitoyl-L-phenylalanine methyl ester (AE5) (Scheme 1, Table 1).

Synthesis of N-alkanoyl -L-amino acids (A_1, A_2, A3, A_4, A_5)

N-Alkanoyl-L-amino acid methyl ester (3.5 mmol) [N-lauroyl-L-alanine methyl ester (**AE_1**), N-lauroyl-L-Leucine methyl ester (**AE_2**), N-lauroyl-L-phenylalanine methyl ester) (**AE_3**) and N-Myristoyl-L-phenylalanine methyl ester (**AE_4**), N-Palmitoyl-L-phenylalanine methyl ester (**AE_5**)] was dissolved in the mixture of MeOH:THF (10 mL, 1:1, v/v). The mixture was cooled to the 0°C and NaOH (3.5 mmol, 0.14 g) in water (4.3 mL) was added to this solution and stirred for further 8 h. The organic phase was evaporated and the remaining phase was cooled to 0°C and HCl (6M, 14 mL) added slowly to this solution. The resultant precipitate washed with hexane and water, respectively; and then filtered to give N-alkanoyl-L-amino acids: [N-lauroyl-L-alanine (**A_1**), N-lauroyl-L-leucine (**A_2**), N-lauroyl-L-phenylalanine (**A_3**)], N-myristoyl-L-phenylalanine (**A_4**), and N-palmitoyl-L-phenylalanine (**A_5**) as a white solid. (Scheme 1, Table 1). For the detailed synthetic information was given in the Supporting Information. See **SI** (1–10)

Synthesis of Nε-alkanoyl –L-lysine derivatives (B type basic components) was shown in Scheme 2)

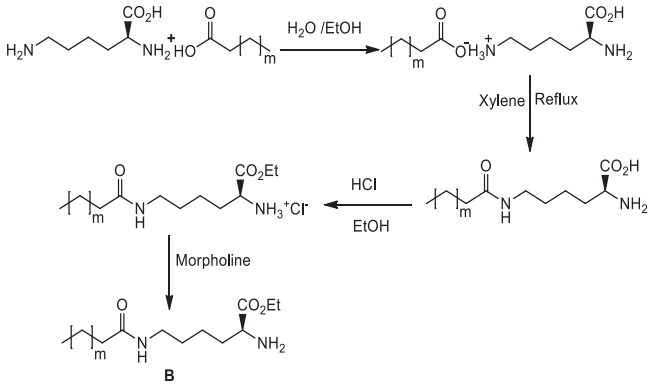
Synthesis of n^{ε}-alkanoate-L-lysine (BS)

L-Lysine (0.1 mol) in distilled water (50 mL) was added to the solution of fatty acids (0.1 mol) in MeOH (20 mL) and stirred at room temperature for 30 min. The mixture was kept at 4°C for a 1 day. The resultant white precipitate was filtered and washed with mixture of H_2O: MeOH (50%, v/v) and then dried on a vacuum gives N^{ε}-alkanoate-L-lysine as a pure, white solid **BS_1** (N^{ε}-palmitoate-L-lysine), **BS_2** (N^{ε}-myristoate-L-lysine), **BS_3** (N^{ε}-laureate-L-lysine) (Scheme 2, Table 2).

The synthesis of N^{ε}-alkanoyl-L-lysine derivatives is the key step because there is very limited literature. Synthesis of N^{ε}-acetyl derivatives of these compounds to be used in the synthesis of target molecules was first made and patented by Takizawa K., Yoshida R., in 1975 (29). The use of these compounds is owned by Japanese

Table 1. Abbreviations list of acidic components and their precursors.

Acid component	Amide ester	n	R
A1	AE1	9	Methyl
A2	AE2	9	Isobutyl
A3	AE3	9	Benzyl
A4	AE4	11	Benzyl
A5	AE5	13	Benzyl



Scheme 2. Synthesis of N$^{\varepsilon}$-alkanoyl-L-lysine derivatives.

Ajinomoto Co., Inc., Tokyo, Japan. Another synthesis method is to convert the Thallium (I) salt of N-hydroxysuccinimide to its corresponding N-hydroxysuccinimide active ester with the corresponding acid chlorides; based on the acylation of the Nε –lysine amino acid with the active esters formed. This method provides a selective (chemoselective) acylation of the amino group in the side chain of basic amino acids such as lysine (30,31). Another method is to form complex between the α-amino group of lysine with the copper (II). Then acylation of N$^{\varepsilon}$ of lysine. The procedure is completed by removal of the copper (II) ion with the 8-hydroxyquinoline from the acylated amino acid complex. In this method, only acetic anhydride is used as an acylating agent. Acetyl lysine ^{15}N labeled was prepared according to this procedure (32). Our method has advantages that the synthesis procedure is simple and forward. And, the synthesis step is short when compared with the literature methods.

Synthesis of n$^{\varepsilon}$-alkanoyl-L-lysine (amide acids: compounds type BAA)

N$^{\epsilon}$-Alkanoates-L-lysine (0.1 mol) was added into xylene (150 mL) in a 250-mL flask attached with Dean-Stark apparatus. Reaction mixture was refluxed at 145°C for 1 day. The mixture was cooled to the room temperature, resultant precipitate was filtered and washed with H_2O: EtOH (50%, v/v) and then dried on a vacuum gives N$^{\varepsilon}$-alkonoyl-L-lysine amide acid: **BAA$_1$** (N$^{\varepsilon}$-palmitoyl-L-lysine), **BAA$_2$** (N$^{\varepsilon}$-myristoyl-L-lysine), **BAA$_3$** (N ε-lauroyl-L-lysine), (Scheme 2, Table 2).

Table 2. Abbreviations list of basic components and their precursors.

Basic component	Salt	Amide Acid	AE.HCl	*m*
B_1	BS_1	BAA_1	BAE_1.HCl	13
B_2	BS_2	BAA_2	BAE_2.HCl	11
B_3	BS3	BAA_3	BAE_3.HCl	9

Synthesis of Nε-alkanoyl-L-lysine ethyl ester hydrochloride (BAE. HCl compounds)

Dry HCl gases were passed from a solution of N$^{\varepsilon}$-alkonoyl-L-lysine (3 mmol) in EtOH (50 mL) until the mixture became a clear solution. The mixture was kept at 4°C for 1 day. The excess HCl was removed by passing N_2 gases from the solution. The solvent was evaporated and the resultant precipitate was washed with THF and mixture of (Et_2O: MeOH) (10:1, v/v); after dried on a vacuum gives N$^{\varepsilon}$-alkanoyl-L-lysine ethyl ester hydrochloride as a white solid: **BAE$_1$.HCl** (N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester hydrochloride), **BAE$_2$.HCl** (N$^{\varepsilon}$myristoyl-L-lysine ethyl ester hydrochloride), **BAE$_3$.HCl** (N$^{\varepsilon}$-lauroyl-L-lysine ethyl ester hydrochloride) (Scheme 2, Table 2).

Synthesis of Nε-alkanoyl-L-lysine ethyl esters (base components: B)

(Method 1): Excess morpholine was added to a solution of N$^{\varepsilon}$-alkanoyl-L-lysine ethyl ester hydrochloride (0.015 mol) in hexane (100 mL). The mixture was stirred at room temperature for 15 min. The mixture was heated, up to 60°C and filtered, then filtrate was cooled and resultant precipitate recrystallized from hexane gives as a white solid of N$^{\varepsilon}$-alkanoyl-L-lysine ethyl ester: **B$_1$** (N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester), **B$_2$** (N$^{\varepsilon}$-myristoyl-L-lysine ethyl ester), **B$_3$** (N$^{\varepsilon}$-lauroyl-L-lysine ethyl ester) (Scheme 2, Table 2).

Synthesis of Nε-alkanoyl-L-lysine ethyl esters (base components: B)

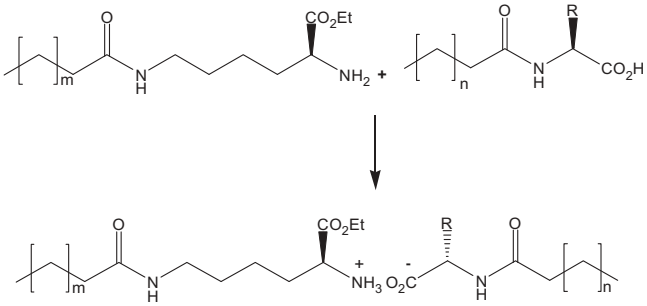
(Method 2): Concentrated K_2CO_3 solution in water (50 mL) was added to a solution of N$^{\varepsilon}$-alkanoyl-L-lysine ethyl ester hydrochloride (0.015 mol) in $CHCl_3$ (50 mL), at 0°C. The water phase was extracted three times with CH_3Cl (50 mL). The organic phases were combined and dried over Na_2SO_4 and then evaporated. The raw material crystallized from hexane and resultant white solid was than dried on a vacuum gives above basic components **B$_1$, B$_2$**, and **B$_3$**. See **SI** (11–25) in the Supporting Information.

Synthesis of B$_1$A$_1$, B$_1$A$_2$, B$_1$A$_3$, B$_1$A$_4$, B$_1$A$_5$, B$_2$A$_3$, B$_2$A$_5$ gelators

N$^{\varepsilon}$-Alkanoyl-L-lysine ethyl ester (1mmol) [basic components: N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester **(B$_1$)**, N$^{\varepsilon}$-myristoyl-L-lysine ethyl ester **(B$_2$)**], and N-alkanoyl-L-amino acid (1mmol): [acidic components: N-lauroyl-L-alanine **(A$_1$)**, N-lauroyl-L-leucine **(A$_2$)**, N-lauroyl-L-phenylalanine **(A$_3$)**, N-myristoyl-L-phenylalanine **(A$_4$)**, and N-palmitoyl-L-phenylalanine **(A$_5$)**] was dissolved in MeOH (10 mL). The mixture was stirred at room

Table 3. List of two-component organogelators.

Gelator	R	*m*	n
B_1A_1	Methyl	13	9
B_1A_2	Isobutyl	13	9
B_1A_3	Benzyl	13	9
B_1A_4	Benzyl	13	11
B_1A_5	Benzyl	13	13
B_2A_3	Benzyl	11	9
B_2A_5	Benzyl	11	13



Scheme 3. Synthesis of two-component gelators.

temperature for 30 min and then was kept at 4°C for a 1 day. The mixture of solvent was evaporated, the resultant precipitate was washed with ether and dried on a vacuum gives two-component gelators (Scheme 3, Table 3): N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester/N-lauroyl-L-alaninate (**B_1A_1**), N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester/N-lauroyl-L-leucinate (**B_1A_2**), N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester/N-lauroyl-L-phenylalaninate (**B_1A_3**), N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester/N-myristoyl-L-phenylalaninate (**B_1A_4**), N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester/N-palmitoyl-L-phenylalaninate (**B_1A_5**), N$^{\varepsilon}$-myristoyl-L-lysine ethyl ester/N-lauroyl-L-phenylalaninate (**B_2A_3**), N$^{\varepsilon}$-myristoyl-L-lysine ethyl ester/N-palmitoyl-L-phenylalaninate (**B_2A_5**), as a pure white solid (yield: quantitative).

Synthesis of two-component gelators: **B_1A_1**, **B_1A_2**, **B_1A_3**, **B_1A_4**, **B_1A_5**,**B_2A_3**, **B_2A_5** [Acid component, N-alkanoyl-L-amino acids and base components, N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester (B_1), N$^{\varepsilon}$-miristoyl-L-lysine ethyl ester (B_2)] was shown in Scheme 3.

Gelation tests

The MGC of gelators in fatty acid esters, squalene, 1, 2-propanediol, water and liquid paraffin was determined and summarized in (Table 4 and Fig. 1).

Gelator prepared from N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester (**B_1**) as base component and N-lauroyl-L-amino acids as acid components with different amino acids segment in derivatization with alanine, leucine, and phenylalanine, give **A_1**, **A_2**, and **A_3** acidic components, respectively. Among them (**B_1A_3**) is the most stable and having low MGC (Table 4). Lauroyl chain in acidic component of gelator (**B_1A_3**) was changed with myristoyl and palmitoyl groups conferred N-myristoyl-L-phenylalanine and N-palmitoyl-L-phenylalanine as acidic components gave (**B_1A_4**) and (**B_1A_5**) gelators, respectively. Total carbon numbers in the gelators **B_1A_3**, **B_1A_4**, and **B_1A_5** are 28, 30, and 32 carbons, respectively.

Among them the best result was obtained with gelator **B_1A_3**, total 28 carbons, in point of MGC values (**Fig. 2**).

For the comparison of gelation efficiency according to the base components was explored with the same acidic component A_3, N$^{\varepsilon}$-palmitoyl-L-lysine ethyl ester (**B_1**) was changed with the myristoyl-L-lysine ethyl ester (**B_2**).

Again, **B_2A_3** gelator with the 26 carbons reveals the similar results and good gelation ability as gelator **B_1A_3** having 28 carbons. For the effect of acidic components chain length on the gelation ability, **B_2A_3** and **B_2A_5** gelators having total 26 and 30 carbons on the alkanoyl chains, respectively were prepared. **B_2A_3** was given good gelation ability as **B_1A_3** (**Fig. 2**). In general, a lyophilic–lyophobic balance of an organogelator molecule is very important factor for the organogelation phenomenon. In a two-component gelator, it is easy to modify the molecular structure either of the two components. Interestingly, the optimal aliphatic chain length of the acidic part had a remarkable effect on the T_{gel} values of the gels in the plateau region. T_{gel} decreased from 103°C

Table 4. MGC of gelators, mg mL^{-1}.

Solvent	(B_1A_3)	(B_1A_4)	(B_1A_5)	(B_2A_3)	(B_2A_5)	(B1A1)	(B_1A_2)
LEE	8 (og)	10 (og)	14 (tlg)	cry	14 (og)	11 (og)	sol
LIE	2 (tlg)	2 (tlg)	cry	4 (tlg)	8 (tlg)	sol	2 (tg)
MEE	13 (og)	8 (og)	16 (tlg)	4 (tlg)	18 (og)	27 (og)	17 (og)
MIE	2 (og)	6 (tlg)	14 (tlg)	2 (tg)	10 (tlg)	sol	11 (og)
PEE	3 (og)	18 (og)	16 (og)	4 (tlg)	18 (og)	5 (og)	17 (og)
PIE	4 (og)	4 (og)	18 (tlg)	4 (tlg)	16 (og)	23 (og)	14 (og)
Liquid paraffin	1 (tg)	1 (tg)	2 (tg)	2 (tg)	2 (tg)	9 (tg)	1 (tg)
Squalene	1 (tg)	6 (tg)	12 (tg)	cry	Not tested	Not tested	Not tested
1,2-propane-Diol	sol	sol	sol	sol	sol	sol	sol
H_2O	ins	ins	ins	ins	ins	ins	ins

PEE: palmitic acid ethyl ester; og: opaque gel; sol: soluble; cry: crystal; tg: transparent gel; N.T: no tested; tlg: translucen gel.

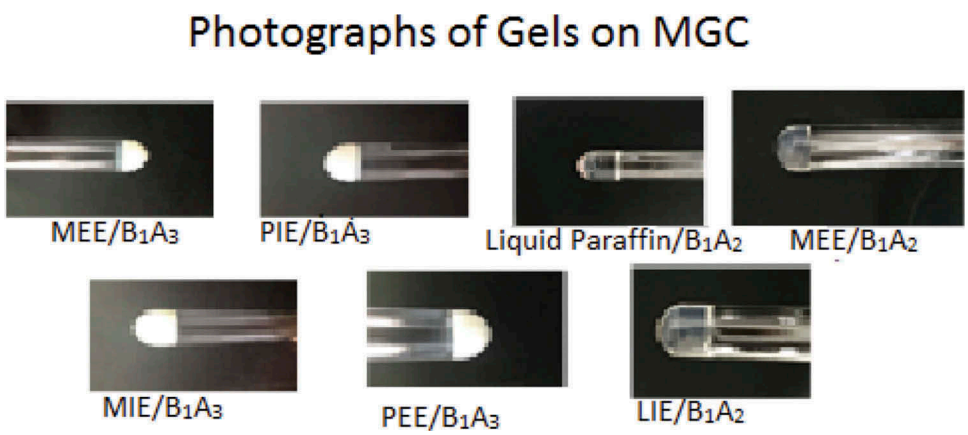


Figure 1. The photographs of gels taken at MGC.

(for gelator $\mathbf{B_1A_4}$, 30 C) to 84°C for $\mathbf{B_1A_5}$ (32 C) and 85°C for $\mathbf{B_1A_3}$ (28 C), respectively. Again $\mathbf{B_2A_3}$ (26 C) and $\mathbf{B_2A_5}$ (30 C) gelators, T_{gel} values in the plateau region decreased from 78°C to 43°C, respectively. And, similar results it was obtained with the basic part chain length of gelator. T_{gel} values in the plateau region decreased from 85°C (for gelator $\mathbf{B_1A_3}$ with 28C) to 78°C (for $\mathbf{B_2A_3}$ with 26 C) and from 84°C (for $\mathbf{B_1A_5}$, with 32 C) to 43°C (for $\mathbf{B_2A_5}$, with 30 C) (**Fig. 2**). From these results, it is obviously seen that variation of amino acid group in the acidic component and chain length of alkanoyl groups in both acidic and basic components have profound effect on their thermal stability. T_{gel} values of gelators $\mathbf{B_1A_4}$ and $\mathbf{B_2A_5}$ show profound difference in the plateau region only replacing of aliphatic chains on the acidic and basic component. T_{gel} decreased from 103°C to 45°C $\mathbf{B_1A_4}$ and 43°C for $\mathbf{B_2A_5}$ gelators, respectively; although both have the same total carbon number (30 C) and same amino acids found at their structure. In general, when the MGC of gelators in the same fatty acid ethyl ester is higher than its isopropyl ester; this situation is attributed to low solubility of gelators in isopropyl ester. Gelator and gelling fluid as a drug carrying matrix is not drug active agent so they should be in a minimum content. And also, another implementation, MGC has an important feature (**Fig. 2**). Because of their higher solubility and MGC values of **(B_1A_1)** and **(B_1A_2)** gelators in tested organic solvents; for this reason their gel–sol transition enthalpy of these gelators did not assigned. They are not convenient their using as a drug carrier matrix and other implementation (Table 4).

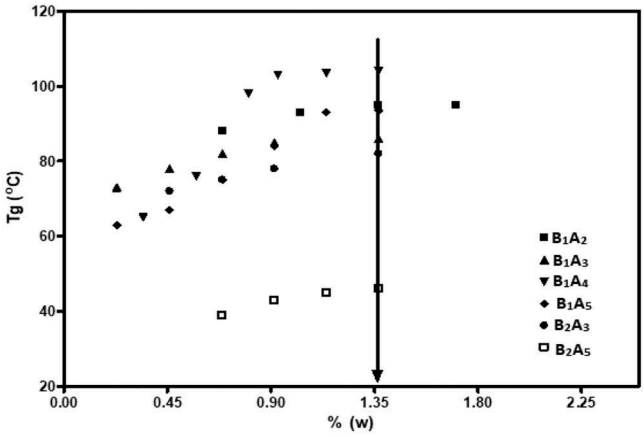


Figure 2. Effect of percentage concentration (as % w/w) on the gel–sol transition temperature of the gel in the liquid paraffin.

Calculation of ΔH_g gelling enthalpies

Enthalpies of the gel–sol transition (ΔH_{gel}) obtained from the slope of van't Hoff plots for gelators **(B_1A_2), (B_1A_3),(B_1A_4), (B_1A_5), (B_2A_3)**, and **(B_2A_5)** in different fluids are summarized in (Table 5) and they are represented in **Fig. 1**. Taking into consideration of MGC and gel–sol transition enthalpy, which is an important factor for the application of gels. **(B_1A_3)** and **(B_2A_3)** are the most sable gelators in liquid paraffin and palmitic acid ethyl ester (PEE). The most problem encountered in the gelator application is their shelf-life. Gel–sol transition enthalpy (ΔH_g) representation of the stability of gelator network is the result of non-bonding interaction between organogelator molecules. For the long-term shelf-life and long-term drug release, the stability of gel in the depot formulation is very important (33).

Table 5. Gel–sol enthalpies ΔH (kJ mol^{-1}) from van't Hoff Equation.

Fluid	(B_1A_3)	(B_1A_4)	(B_1A_5)	(B_2A_3)	(B_2A_5)	(B_1A_2)
LEE	67.7	39.2	89.2	–	48.6	–
LIE	55.7	27.3	–	30	–	49.4
MEE	21.7	14.5	29.0	43	–	–
MIE	136.9	27.8	114.1	56	41.1	–
PEE	100.1	29.8	65.6	173.9	–	–
PIE	81.4	21.7	–	87	–	–
Liquid paraffin	124.5	27	35.8	107	78.3	80.4

Taking into consideration of MGC and gel–sol transition enthalpy **(B_1A_3)** and **(B_2A_3)** have potential applicability in the drug release implementation. The ΔH_g values depend on the chemical structures of L-lysine esters and N-alkanoyl-L-amino acids as well as using of gelling solvents. The gels in liquid paraffin and PEE with **(B_2A_3)** gelator exhibit the highest ΔH_g value (Table 5).

Characterization of gel structure by SEM

The method mentioned above was applied for **(B_1A_3)** gelator prepared in different fluids LEE (Lauric acid ethyl ester), liquid paraffin, and LIE (lauric acid isopropyl ester). And also SEM imaging of xerogels prepared from different gelators, **B_1A_3, B_1A_2, B_2A_3**, in the same fluid (LIE).

In general, it is obviously seen from SEM image, xerogels are in the form of fiber in the gelator's molecules. SEM image of different gelators in the same solvent (LIE) and B_1A_3 gelator in the different solvents has shown that their xerogels morphologies were influenced with gelator structure and also solvent nature in either case. When the SEM images were analyzed carefully, the fiber structure of gel has oriented bend and spiral pattern by the influence of chirality. (**Figs. 3 and 4**)

Temperature-dependent IR studies

The FTIR spectra were measured to clarify the driving forces for the organogelation. In the cases analyzed in this study, hydrogen-bonding and acid–base interactions are very important. FTIR spectra of **(B_2A_5)** gel in liquid paraffin, temperature depending changes were measured at 30°C, 80°C, and 130°C. It is possible to see the changes belonging to free and bounded carbonyl peak of amide I, amide II, and NH stretching peak (**Fig. 6**). The IR spectrum of two-component system in liquid paraffin shows the bands of hydrogen-bonded amides, and the new IR band arising from the carboxylate group appears at 1,589 cm^{-1}. All the samples are in the solution state at 130°C, The IR peak of carboxylate disappears from the IR spectrum of **(B_2A_5)**. In addition, the broadening band at 1,687 cm^{-1} of the non-hydrogen-bonded amide group is observed. In this case, the gel-to-sol transition temperature T_{gel} is 130°C. The IR spectra severely changes at around T_{gel} (**Fig. 5**). The facts indicate that the hydrogen-bonding and acid–base interaction play a crucial role in the organogelation. Similar results were acquired temperature dependent IR spectra of B_1A_3, B_2A_3, and B_1A_5 gelators in liquid paraffin. In this case, the gel-to-sol transition temperatures T_{gel} belonging to B_1A_3, B_2A_3, and B_1A_5 gelators are 100°C, 120°C, and 120°C, respectively. B_1A_3, B_1A_5, B_2A_3, and B_2A_5 gelators have

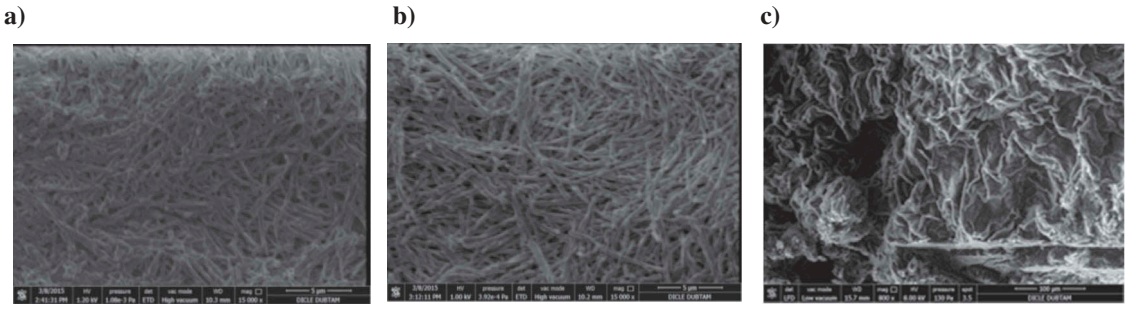


Figure 3. SEM images of B_1A_3 in different solvents (a) 1.5 mg in 1.5 mL liquid paraffin, (b) 8 mg in LEE, and (c) 2 mg in 1 mL LIE.

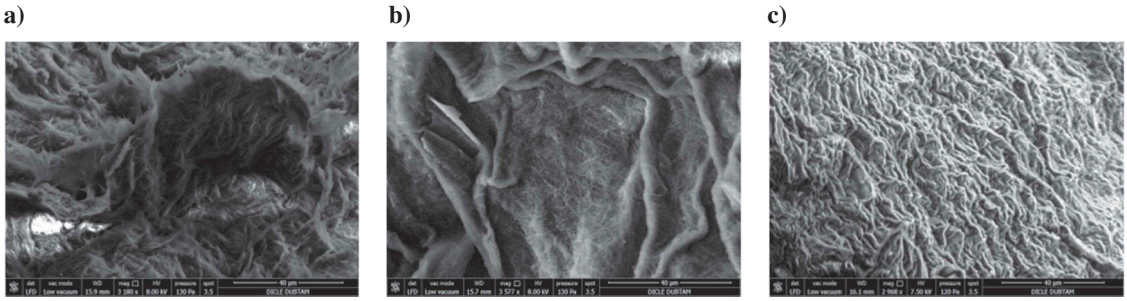


Figure 4. SEM images of different gelators in LIE solvents (a) B_2A_3 4 mg in 1 mL LIE, (b) B_1A_3 2 mg in 1 mL LIE, and (c) B_1A_2 2 mg in 1 mL LIE.

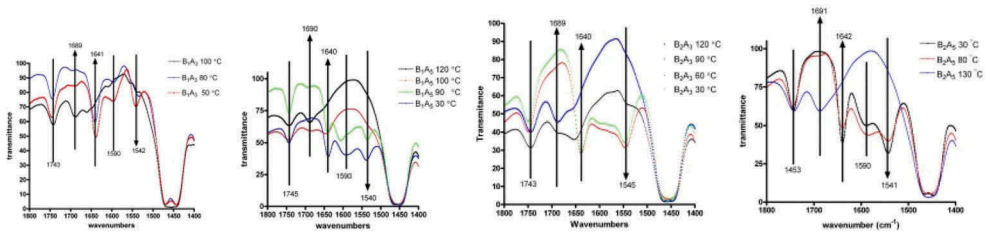


Figure 5. Temperature dependent (25–130°C) FTIR spectra of B_1A_3, B_1A_5, B_2A_3, and B_2A_5 gelators in liquid paraffin. Shifting of wave numbers and intensity changes by temperature increasing. Amide I, and amide II bands.

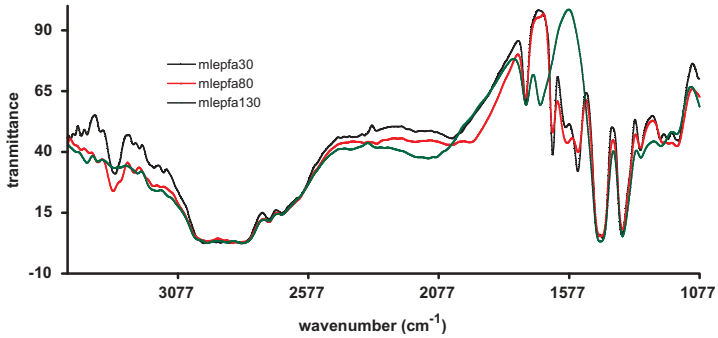


Figure 6. The FTIR spectrum of B_2A_5 gel (MLEPFA in liquid paraffin): Free and bound carbonyl peak of amide I, amide II and NH stretching peak depending temperature.

different alkanoyl chains but possess same amino acids pair on the acidic and basic component (Lysine and phenylalanine); temperature dependent IR spectra don't demonstrate any change (Fig. 5). Length of alkanoyl chains does not have an impact on shifting of hydrogen-bonding wave numbers belonging to amide I and amide II bonds (C = O ….H–N stretching).

These IR results suggest that the gel-to-sol transition is influenced by breaking the hydrogen-bonding interactions and the acid–base interactions. In the case of this study, the two-component system (organic salt compounds) possess two hydrogen-bonding sites (two amide groups) and also two long alkyl chains. Therefore, the driving forces are hydrogen-bonding, acid–base, and van-der Waals interactions that responsible for the self-assembly into the nanofibers (leading to the organogelation).

Conclusions

To enhance the biocompatibility and biodegradability, biomolecular precursor is often inserted in the structure of gelator. And also, synthesis of gelators was performed via very easy, clear, and concise manner according to the literature methods. Thus, introducing those biocompatible moieties and amides functionality can be a useful strategy for diminish the cytotoxicity of the novel designed gelator systems. For this aim gelators and liquid trapped in the gel must be chosen from biocompatible materials, and also fluid and gelator must contain functional groups that recognized from the body are requested properties.

Moreover their modulation have been performed combination of lysine with various naturally occurring amino acids and also different alkanoyl groups were used providing biocompatibility and increasing gelation efficiency. Amino acids and fatty acids parts of gelators, both of them are selected as biocompatible materials These materials have great organogelation ability for pharmaceutical fluids; especially, they can form in fatty acid esters and liquid paraffin below 0.1 wt%. In two-component systems, making modifications on the structure of either one of the two components easily permit the introduction of functional behavior into the materials.

Finally, using of different gelation fluid such as liquid paraffin and ethyl laurate, isopropyl myristate and isopropyl palmitate (oils used widely in pharmaceutical formulation) presents another parameter that can be changed to generate new morphologies and adjust the materials behavior. We expect that this new approach, two-component gel formation, will guide to a broad range of interesting material with adjustable microscopic and macroscopic features and potentially interesting applications such as drug delivery.

Experimental section

Glassware and solvent were dried, and the reactions were performed under high purity argon or nitrogen atmosphere because of substances used in the reaction are very sensitive to air and moisture. All chemicals are reagent grade unless otherwise noted they have quality of reagent grade. All chemicals were obtained from Sigma-Aldrich or Fluka. Silica gel 60 (Merck, 0.040 to 0.063 mm) and silica gel/TLC-cards (F_{254}) were used in flash chromatography and TLC, respectively. Synthetic procedures were monitored by TLC. Melting points were determined by a Gallenkamp Model apparatus with open capillaries and they are uncorrected. Elemental analyses C, H, and N were performed using a Carlo-Erba 1108 Model apparatus; and the results are within ±0.4% of the theoretical values. Mass spectrums were taken with Shimadzu 8040 LC-MS apparatus. Specific tilt angle was measured with polarimetry cell (volume of 1 mL and length of 1dm) at 20°C temperature by using Perkin-Elmer 341 model device. Infrared spectra were recorded on a MATTSON Model 1000 Spectrophotometer. Temperature-dependent IR spectra were taken with a Specac GS20730 model heating jacket. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) Spectra were recorded on a Bruker AV400 High Performance Digital FT-NMR Spectrometer. Chemical shifts (δ) and coupling constants (J) are reported in ppm and Hz. SEM observations were carried out using a FEI Quanta 250 FEG field emission scanning microscope.

Synthesis

Synthesis of Nε-Palmitoyl-L-lysine ethyl ester/ N-Lauroyl-Lalaninate (B_1A_1)

N$^{\varepsilon}$-Palmitoyl-L-lysine ethyl ester (1 mmol, 0.412 g) and N-lauroyl-L-alanine (1mmol, 0.27 g) was dissolved in MeOH (10 mL). The mixture was stirred at room temperature for 30 min then was kept at 4°C for 1 day. The resultant precipitate was filtered and washed with ether, and then dried on a vacuum; gives as a pure white solid (yield: quantitative); m.p. 91–95°C; [α]$_D^{20}$ = ± 12° (c = 5 in ethanol); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 0.88 (t, 6H, J = 6.8 Hz, Lau-CH_2–CH_3, Pal-CH_2–CH_3), 1.25–1.31 (m, 43H, Lau-$(CH_2)_9$, Pal-$(CH_2)_{12}$, OCH_2CH_3), 1.36 (d, 3H, J = 7.2 Hz, CH*CH_3), 1.52–1.60 (m, 8H, Lau-CH_2–CH_2–CH_2–C=O, Pal-CH_2–CH_2–CH_2–C=O, NH–$CH_2CH_2CH_2$), 1.89 (m, 2H, $CH^{\pm}NH_3CH_2$), 2.18 (m, 4H, Lau-CO–CH_2–, Pal-CO–CH_2), 3.22–3.24 (m, 2H, $NHCH_2$), 3.85, (m, 1H, Alanine-CH*), 4.2–4.25 (m, 2H, OCH_2CH_3), 4.30–4.34 (m, 1 H, Lysine-*CH), 6.54 (bs, 1 H, –C=O–NH), 6.76 (bs, 1 H, –C=O–NH), 7.67 (bs, 3H, $NH^{\pm}_3$), ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 14.1, 18.5, 22.2, 22.6, 25.7, 25.9, 28.8, 29.3, 29.4, 29.4, 29.5, 29.6, 29.6, 29.7, 31.1, 31.9, 36.5, 36.6, 38.8, 49.5, 52.9, 62.0, 171.4, 173.3, 173.8, 177.8; IR (KBr): ν = 3,820, 3,780, 3,704, 3,605, 3,500, 3,397, 3,317, 3,140.5, 2,921, 2,853, 1,746, 1,641, 1,540, 1,462, 1,399, 1,220, 1,032, 861; LCMS m/z calcd for $C_{24}H_{49}N_2O_3^{\pm}$ (413.65), $C_{15}H_{28}NO_3^-$ (270.38); found: (ES$^{\pm}$) [m/z] = 413.90, (ES$^-$) [m/z] = 270.30; elemental analysis calcd (%) for $C_{39}H_{76}N_3O_6$ (684.032 gmol^{-1}): C 68.47, H 11.19, N 6.48; found: C 68.27, H 11.12, N, 6.41.

Nε-Palmitoyl-L-lysine ethyl ester/N-Lauroyl-L-leucinate (B_1A_2)

N$^{\varepsilon}$-Palmitoyl-L-lysine ethyl ester (1 mmol, 0.412 g) and N-lauroyl-L-leucine (1mmol, 0.312 g) was dissolved in MeOH (10 mL). The mixture was stirred at room temperature for 30 min and then was kept at 4°C for 1 day. The resultant precipitate was filtered and washed with ether, and then dried on a vacuum; gives as a pure white solid (yield: quantitative). m.p. 97–100 °C; [α]$_D^{20}$ = −9,2° (c = 1 in ethanol); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 0.86–0.93 (m, 12H, $CH(CH_3)_2$, Lau-CH_2–CH_3, Pal-CH_2–CH_3), 1.25–1.30 [m, 43H, Lau-$(CH2)_9$, Pal-$(CH2)_{12}$, OCH_2CH_3], 1.42–1.58 [m, 11H, $CH(CH3)_2$, Lau-CH_2–CH_2–CH_2–C=O,Pal-CH_2–CH_2–CH_2–C=O,NH–$CH_2CH_2CH_2$],1.60–1.62 [m, 2H, CH_2 $CH(NH_3)^{\pm}$], 2.15–2.21 (m, 4H, Lau-CO–CH_2–, Pal-CO–CH_2), 3.23–3.75 (m, 2H, $NHCH_2$), 4.18–4.20 (m, 1H, Leu-CH*), 4.21–4.24 (m, 2H, OCH_2CH_3), 4.36–4.37 (m, 1H, Lys*CH), 6.09 [bs, 3H, $(NH_3)^{\pm}$], 6.46 (bs, 1H, –C=O–NH), 6.57 (bs, 1 H, –C=O–NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 14.0, 14.1, 21.9, 22.0, 22.1, 22.2, 22.6, 22.9, 23.0, 24.7, 24.88, 25.75, 25.78, 25.90, 25.95, 28.77, 28.84, 29.28, 29.34, 29.38, 29.4, 29.5, 29.5, 29.6, 29.6, 29.6, 31.9, 31.5, 31.9, 36.5, 36.7, 38.5, 38.8, 40.8, 41.1, 51.7, 51.9, 52.1, 61.3, 171.9, 172.3, 173.6, 173.8; IR (KBr): ν = 3,912, 3,784, 3,706, 3,653, 3,588, 3,434, 3,322, 3,212, 3,070, 2,922, 2,856, 1,750, 1,641, 1,539, 1,466, 1,397, 1,299, 1,216, 1,032, 859; LCMS m/z calcd for $C_{24}H_{49}N_2O_3^{\pm}$ (413.65), $C_{18}H_{34}NO_3^-$ (312.46); found: (ES$^{\pm}$) [m/z] = 413.20, (ES$^-$) [m/z] = 313.10; elemental analysis calcd (%) for $C_{42}H_{82}N_3O_6$ (729.11 gmol^{-1}): C 69.18, H 11.33, N 5.76; found: C 69.01, H 11.29, N 5.71.

Nε-Palmitoyl-L-lysine ethyl ester / N-Lauroyl-L-phenylalaninate (B_1A_3)

N$^{\varepsilon}$-Palmitoyl-L-lysine ethyl ester (1 mmol, 0.412 g) and N-lauroyl-L-phenylalanine (1mmol, 0.347 g) was dissolved in MeOH (10 mL). The mixture was stirred at room temperature for 30 min and then was kept at 4°C

for 1 day. The resultant precipitate was filtered and washed with ether, and then dried on a vacuum; gives as a pure white solid (yield: quantitative); m.p. 105–109°C; $[\alpha]_D^{20}$ = ± 20,6° (*c* = 1 in ethanol); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 0.89 (t, 6H, *J* = 6.8 Hz, Lau-CH_2–CH_3, Pal-CH_2–CH_3), 1.23–1.31 (m, 43 H, Lau-$(CH2)_9$, Pal-$(CH2)_{12,}$ OCH_2CH_3), 1.52–1.60 (m, 8H, Leu-CH_2–CH_2–CH_2–C=O, Pal-CH_2–CH_2–CH_2–C=O, NH–$CH_2CH_2CH_2$), 1.91 [m, 2H, CH $(NH_3)^{\pm}$ CH_2], 2.15 (m, 4H, Lau-CO–CH_2–, Pal-CO–CH_2), 3.01–3.06 (m, 1H, *CH–CH_2-Ph), 3.19–3.24 (m, 3H, *CH–CH_2-Ph, NHCH_2), 3.86, (m, 1H,Phe-CH*), 4.2–4.25 (m, 2H, OCH_2CH_3), 4.65–4.66 (m, 1H, Lys-*CH), 6.46 (bs, 1H, –C=O–NH), 6.54 (bs, 1H, –C=O–NH), 7.18–7.28 [m, 8H, $(NH_3)^{\pm}$, Ar–H]; ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 14.1, 22.1, 22.6, 25.9, 28.7, 29.2, 29.3, 29.4, 29.4, 29.5, 29.5, 29., 29.6, 29.7, 30.6, 31.9, 36.5, 36.6, 37.6, 38.7, 52.8, 54.4, 62.2, 126.7, 128.3, 129.4, 137.0, 170.9, 173.4, 173.9, 177.2; IR(KBr): ν = 3,906, 33,817, 3,787, 3,682, 3,514, 3,351, 3,286, 3,198, 3,036, 2,920, 2,852, 1,747, 1,640, 1,574, 1,536, 1,468, 1,401, 1,221, 1,131, 1,037, 869; LCMS m/z calcd for $C_{24}H_{49}N_2O_3^{\pm}$ (413.65), $C_{21}H_{32}NO_3^-$ (346.47); found: $(ES^{\pm})$ [m/z] = 413,95, (ES^-) [m/z] = 346,25; elemental analysis calcd (%) for $C_{45}H_{80}N_3O_6$: (760,12 $gmol^{-1}$): C 71.10, H 10.60, N 5.52; found: C 70.89, H 10.55, N 5.51.

Nε-Palmitoyl-L-lysine ethyl ester/ N-Myristoyl-L-phenylalaninate (B_1A_4)

N^{ε}-Palmitoyl-L-lysine ethyl ester (1 mmol, 0.412 g) and N-myristoyl-L-phenylalanine (1 mmol, 0.374 g) was dissolved in MeOH (10 mL). The mixture was stirred at room temperature for 30 mins and was kept at 4°C for 1 day. The resultant precipitate was filtered and washed with ether, and then dried on vacuum; gives as a pure white solid (yield: quantitative); m.p. 112–116 °C; $[\alpha]_D^{20}$ = ± 14,8° (c = 1 in ethanol); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS):δ = 0.89 (t, 6H, *J* = 6.8 Hz, Myr-CH_2–CH_3, Pal-CH_2–CH_3), 1.23–1.31 (m, 47H, Myr-$(CH2)_{10}$, Pal-$(CH2)_{12,}$ OCH_2CH_3), 1.42–1.60 (m, 8H, Myr-CH_2–CH_2–CH_2–CO, Pal-CH_2–CH_2–CH_2–CO, NH–$CH_2CH_2CH_2$), 1.91 [m, 2H, $CH(NH_3)^{\pm}$ CH_2], 2.14 (m, 4H, Myr-CO–CH_2-, pal-CO–CH_2), 3.18–3.20 (m, 1H, *CH–CH_2-Ph), 3.22–3.23 (m, 3H, *CH–CH_2-Ph, NHCH_2), 3.72–3.74 (m, 1H, phenylalanine-CH*), 4.20–4.24 (m, 2H, OCH_2CH_3), 4.61–4.63 (m, 1 H, Lys-*CH), 6.33 (bs, 1 H, –C=O–NH), 6.46 (bs, 1 H, –C=O–NH), 6.74 (bs, 3H, $NH_3^{\pm}$), 7.18–7.28 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 14.1, 22.1, 22.6, 25.9, 28.7, 29.2, 29.3, 29.4, 29.4, 29.5, 29.5, 29.6, 29.6, 29.7, 30.6, 31.9, 36.5, 36.6, 37.6, 38.7, 52.8, 54.47 62.2, 126.7, 128.3, 129.4, 137.0, 170.9, 173.4, 173.9, 177.2; IR(KBr): ν = 3,801., 3,714, 3,502, 3,416, 3,343, 3,061, 2,918, 2,851, 1,746, 1,642, 1,577, 1,534, 1,467, 1,402, 1,223, 1,201, 1,129, 1,072, 1,030, 863; LCMS m/z calcd for $C_{24}H_{49}N_2O_3^{\pm}$ (413.65), $C_{23}H_{36}NO_3^-$ (374.52); found: $(ES^{\pm})$ [m/z] = 413,90, (ES^-) [m/z] = 374.30; elemental analysis calcd (%) for $C_{47}H_{84}N_3O_6$ (788,17 $gmol^{-1}$): C 71.61, H 10.74, N 5.33; found: C 71.78, H 10.69, N 5.29.

Nε-Palmitoyl-L-lysine ethyl ester/ N-Palmitoyl-L-phenylalaninate (B_1A_5)

N^{ε}-Palmitoyl-L-lysine ethyl ester (1 mmol, 0.412 g) and N-myristoyl-L-phenylalanine (1 mmol, 0.403 g) was dissolved in MeOH (10 mL). The mixture was stirred at room temperature for 30 min and was kept at 4°C for 1 day. The resultant precipitate was filtered and washed with ether, and then dried on a vacuum; gives as a pure white solid (yield: quantitative); m.p. 121–126 °C; $[\alpha]_D^{20}$ = ± 13,4° (*c* = 1 in ethanol); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C,TMS): δ = 0.89 (t, 6H, *J* = 6.8 Hz, Pal-CH_2–CH_3, Pal-CH_2–CH_3), 1.23–1.32 [m, 51H, Pal-$(CH_2)_{12}$, Pal-$(CH_2)_{12,}$ OCH_2CH_3), 1.42–1.55 (m,8H, Pal-CH_2–CH_2–CH_2–CO, Pal-CH_2–CH_2–CH_2–CO, NH–$CH_2CH_2CH_2$], 1.92 [m, 2H, $CH(NH_3)^{\pm}$ CH_2], 2.15 (m, 4H, Pal-CO–CH_2–, Pal-CO–CH_2), 3.05–3.08 (m, 1H, *CH–CH_2-Ph), 3.22–3.24 (m, 3H, *CH–CH_2-Ph, NHCH_2), 3.74 (m, 1H, Phe-CH*), 4.20–4.24 (m, 2H, OCH_2CH_3), 4.65–4.67 (m, 1 H, Lys-*CH), 6.28 (bs, 1 H, –C=O–NH), 6.38 (bs, 1 H, –C=O–NH), 6.68 (bs, 3H, $NH_3^{\pm}$), 7.18–7.28 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 14.1, 14.1, 22.4, 22.6, 25.6, 25.8, 28.9, 29.2, 29.3, 29.4, 29.4, 29.5, 29.5, 29.6, 29.7, 31.5, 31.9, 36.5, 36.7, 37.6, 38.8, 53.0, 54.4, 61.9, 126.7, 128.3, 129.4, 137.1, 172.2, 173.4, 173.7, 175.7; IR(KBr): ν = 3,656, 3,567, 3,337, 3,028, 2,918, 2,851, 1,745, 161, 1,535, 1,467, 1,401, 1,294, 1,224, 1,202, 1,130, 1,030, 863; LCMS m/z calcd for $C_{24}H_{49}N_2O_3^{\pm}$ (413.65), $C_{25}H_{40}NO_3^-$ (402.38); found: $(ES^{\pm})$ [m/z] = 413,90, (ES^-) [m/z] = 402.35; elemental analysis calcd (%) for $C_{49}H_{88}N_3O_6$ (816.18 $gmol^{-1}$): C 72.10, H 10.86, N 5.14; found: C 71.88, H 10.89, N 5.11.

Nε-Myristoyl-L-lysine ethyl ester/ N-Lauroyl-L-phenylalaninate (B_2A_3)

N^{ε}-Myristoyl-L-lysine ethyl ester (1 mmol, 0.384 g) and N-lauroyl-L-phenylalanine (1mmol, 0.347 g) was dissolved in MeOH (10 mL). The mixture was stirred at room temperature for 30 min and was kept at 4°C for 1 day. The resultant precipitate was filtered and washed with ether, and then dried on a vacuum; gives as a pure white solid (yield: quantitative); m.p. 108–111°C; $[\alpha]_D^{20}$ = ± 7.2° (*c* = 1 in ethanol); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 0.89 (t, 6H, *J* = 6.8 Hz, Lau-

CH_2–CH_3, Myr-CH_2–CH_3), 1.26–1.31 [m, 39 H, Lau-$(CH2)_8$, Myr-$(CH2)_{10}$, OCH_2CH_3], 1.44–1.61 (m, 8H, Lau-CH_2–CH_2–CH_2–CO, Myr-CH_2–CH_2–CH_2–CO, NH–$CH_2CH_2CH_2$), 1.75–1.85 [m, 2H, $CH(NH_3)^{\pm}CH_2$], 2.14 (m, 4H, Lau-CO–CH_2–, Myr-CO–CH_2), 3.01–3.25 (m, 4H, *CH–CH_2-Ph, $NHCH_2$), 3.67 (m, 1H, phe-CH*), 3.72–3.81 (m, 2H, OCH_2CH_3), 4.21–4.23 (m, 1 H, Lys-*CH), 4.85 (bs, 3H, $NH_3^{\pm}$), 6.1 (bs, 1H, –CO–NH), 6.37 (bs, 1H, –CO–NH), 7.18–7.28 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 14.0, 22.4, 22.6, 25.6, 25.8, 29.0, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 32.3, 36.5, 36.7, 38.9, 52.4, 53.3, 126.6, 128.3, 129.4, 137.2, 172.2, 173.3, 173.5, 175.7; IR(KBr): ν = 3,843, 3,714, 3,335, 3,067, 3,027, 2,920, 2,582, 1,749, 1,644, 1,537, 1,466, 1,402, 1,136, 995; LCMS m/z calcd for $C_{22}H_{45}N_2O_3^{\pm}$ (385.60), $C_{21}H_{32}NO_3^{-}$ (346.47); found: ($ES^{\pm}$) [m/z] = 385.85, (ES^{-}) [m/z] = 346.30; elemental analysis calcd (%) for $C_{43}H_{77}N_3O_6$ (732.08 $gmol^{-1}$): C 70.54, H 10.60, N 5.75; found: C 70.33, H 10.46, N 5.71.

Nε-myristoyl-L-lysine ethyl ester/ N-palmitoyl-L-phenylalaninate (B_2A_5)

N^{ε}-Myristoyl-L-lysine ethyl ester (1 mmol, 0.384 g) and N-palmitoyl-L-phenylalanine (1 mmol, 0.405 g) was dissolved in MeOH (10 mL). The mixture was stirred at room temperature for 30 min and was kept at 4°C for 1 day. The resultant precipitate was filtered and washed with ether, and then dried on a vacuum; gives as a pure white solid (yield: quantitative); m.p. 120–122.7 °C; $[\alpha]_D^{20}$ = ± 14,0° (c = 1 in ethanol); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 0.89 (t, 6H, J = 6.8 Hz, Myr-CH_2–CH_3, Pal-CH_2–CH_3), 1.23–1.31 (m, 47H, Myr-$(CH_2)_{10}$, Pal-$(CH_2)_{12}$, OCH_2CH_3), 1.43–1.60 (m, 8H, Myr-CH_2–CH_2–CH_2–CO, Pal-CH_2–CH_2–CH_2–CO, NH–$CH_2CH_2CH_2$), 1.91 [m, 2H, $CH(NH_3)^{\pm}CH_2$], 2.14 (m, 4H, Myr-CO–CH_2–, Pal-CO–CH_2), 3.04–3.24 (m, 4H, *CH–CH_2-Ph, $NHCH_2$), 3.73 (m, 1H, phenylalanine-CH*), 4.20–4.24 (m, 2H, OCH_2CH_3), 4.62–4.64 (m, 1H, Lys-*CH), 6.32 (bs, 1H, –CO–NH), 6.43 (bs, 1H, –CO–NH), 6.88 (bs, 3H, $NH_3^{\pm}$), 7.18–7.28 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 14.1, 14.1, 22.2, 22.6, 25.7, 25.8, 28.9, 29.2, 29.3, 29.4, 29.4, 29.5, 29.7, 31.6, 31.9, 36.5, 36.7, 37.7, 38.8, 53.0, 54.5, 61.9, 126.6, 128.3, 129.4, 137.2, 172.2, 173.3, 173.7, 175.9; IR(KBr): ν = 3,801, 3,714, 3,502, 3,416, 3,343, 3,061, 2,918, 2,851, 1,746, 1,642, 1,577, 1,534, 1,467, 1,402, 1,223, 1,201, 1,129, 1,072, 1,030, 863; LCMS m/z calcd for $C_{22}H_{45}N_2O_3^{\pm}$ (385.60), $C_{25}H_{40}NO_3^{-}$ (402.38); found: ($ES^{\pm}$) [m/z] = 384.85, (ES^{-}) [m/z] = 402.30; elemental analysis calcd (%) for $C_{47}H_{85}N_3O_6$ (788.18 $gmol^{-1}$): C 71.61, H 10.87, N 5.33; found: C 71.39, H 10.90, N 5.29.

Characterization of organogels

The synthesized organic gelators have been gelated in fatty acid esters. The structural feature of gels was characterized spectroscopic method as FTIR and optical method as SEM imaging. The MGC of gelator was determined as mg mL^{-1} for the measurement of gelation ability. The results were summarized in Table 4. And also by measuring melting point (T_g) was calculated for the estimation of gel–sol transition enthalpy (ΔH_g) using van't Hoff equation for the thermal stability of gelators.

Determination of *MGC*

A typical gelation experiment as mentioned in the literature was carried out for the gelation test (34). In the determination of gelling properties, 1 mg gelator was added to the 1 mL solvent sample. The mixture was heated until 20°C below the boiling point of the solvent. The mixture was putted to cool at 25°C. After about 15 min the gel is removed and checked for gelation. In the lack of gelling, the quantity of gelator was increased each time by 1 mg till to form gel. The appearance of a homogeneous substance was considered as indication of gelation with no gravitational flow upon inversion of the test tube. The MGC is determined as MGC (mg mL^{-1}). This value is important whether gel is the super gel category or not (35). The gelator specified as non-soluble, if 1 mg gelator was not dissolved in the 1 mL of sample solvent during the test. The gelator specified as soluble, if gelator was dissolved in the sample solvent over 10% (w/w) during the test.

Determination of melting point of gel

Gel-to-sol transition temperatures (T_{gel}) were determined using "the dropping ball" method reported in the literature (36). A tube containing gel is immersed in an accuracy thermo regulated oil bath, and the temperature at which, on tube inversion, the gel no longer remains rigid is monitored (18). Gel samples in 1 mL organic solvent were transferred to a small glass tube (12 mm × 75 mm) and 0.25 g the steel ball was putted on the top of gel in the test tube and heated 1°C in a minute. This ensures that stress generated by the gel on the measurement of its melting point is approximately constant in each case. When the steel ball sink to the bottom of the tube, the temperature (T_g) recorded as the melting point of the gel. The process is repeated with the different gel concentration.

Determination of gel–sol transition enthalpies (δh_g)

If gel–sol transition can be compared with the melting of crystal, gel–sol transition enthalpy can be calculated

from the van't Hoff equation (37). Further, van's Hoff relationships were employed to obtain thermodynamic parameters for gel-to-sol transition in order to analyze detailed thermal behaviors of gels (37,38). The melting enthalpy of crystals is estimated by van't Hoff equation (Eq. (1)). This could also apply to obtain the gel–sol transition enthalpy. Gel–sol transition enthalpy is calculated from the van't Hoff equation.

$$\frac{d\ln C_g}{d_1/T_g} = \frac{\Delta H_g}{R} \quad (1)$$

Characterization of gel structure with SEM

Preparation procedure of xerogel. The surface and size of nano structure of organogelators can be imaged by electron microscope. It is impossible to prepare dry sample (xerogel) by direct freeze-drying processing from the prepared gel because the organic fluids (fatty acid, paraffin, and squalene) which have high boiling point used to prepare gels. In such circumstances, the re-precipitation method used to prepare xerogel samples (9).The gelator which is resultant N-alkanoyl-L-lysine ethyl ester/N-alkanoyl-L-amino acid salt is insoluble in hexane at room temperature, so the SEM sample can be prepared by precipitation of gels in high boiling point fluid and extract high boiling fluid to the hexane phase. Although the organogel is destroyed by shaking in hexane, the nano-scaled network is maintained by the quick precipitation. There is some risk and morphological change during this precipitation process. The method mentioned above was applied for **(B_1A_3)** gelator prepared in different fluids LEE, liquid paraffin and LIE to see fluid effect on the gelator morphology. And also SEM imaging of xerogels prepared from different gelators, **B_1A_3, B_1A_2, B_2A_3,in** the same fluid (LIE) to see effect of structure on the gelator morphology. Xerogel forms of gelators were prepared at the MGC. For instance xerogel form **B_1A_3** gel was prepared by which 8 mg gelator was dissolved in 1 mL liquid paraffin. While the gel was stirring fast, hexane was added to the mixture or hexane was added to the gel and stirring fast by vortex. The fluid over precipitated gelator as fiber was extracted by Pasteur pipette. If the phase was not separated well, the centrifuge (6,000 rpm) was used to separate phase. In each case, hexane was added to remove high boiling point gelling fluids from the nano-space of gel completely. The excess hexane was removed by freeze-drying processing after in assurance that liquid paraffin had been completely removed from the gel. The freeze-drying processing was carried out for 24 h to make ready the sample for SEM imaging.

Characterization of gel structure with FTIR

Hydrogen-bonding plays very essential role in the self-assembly of gelators and FTIR spectroscopy is the one of the most powerful tool to study these interactions (39–42). Hydrogen-bonding in the gel network, van der Waals attraction was determined by taking the temperature-dependent IR spectrum. For this purpose, CaF_2 window and Teflon spacer were used. Gel was purged into teflon spacer by the aid of micro spatula and quenched to suffuse to gel between CaF_2 windows. To obtain IR spectra depending on temperature, CaF_2 windows prepared above is placed into GS20730 model Specac heating jacket (jacket heating apparatus). In order to observe interaction in gel networks, the FTIR spectrum of gel (T_g = 120°C) prepared from 14 mg **(B_2A_5)**. Gelator in 1 mL liquid paraffin was recorded between 30 and 130°C temperature range and each time temperature increased 10°C.

To take spectrum, jacket was heated by increment 10°C, interval between 30°C and above 10°C gelator's T_g values. At every turn, the gel was expected to be constant temperature in the heating cell and pulled spectrum. With the temperature rises, hydrogen bonds depending on the gel networks and release hydrogen bonds, amide I and amide II bands and N–H stretching peaks were followed; changes due to temperature are recorded (**Fig. 6**).

Funding

We would like to express our gratitude to The Scientific and Technological Research Council of Turkey (TÜBİTAK) for financially support [grant number: 113Z142] and the Dicle University Research Council [grant numbers: 13-FF-72 and 13-FF-3].

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