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Investigation of the Gelation Potential of Low Molecular Weight Organogelator

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ABSTRACT

In this study, low molecular weight amide compound was employed as the organogelator and its gelation potential was investigated with various solvents. The morphological properties of the obtained gels were investigated. The network structure of the obtained gel was determined by scanning electron microscopy (SEM). Fatty acid esters used in the cosmetic and pharmaceutical industries and also solvents commonly used in the laboratory were employed for gelation. According to this process, the organogelator formed a gel with all the fatty acid esters at very low concentrations and with only anisole, xylene, liquid paraffin and n-dodecane of common organic solvents. Among the gels obtained, those with the lowest concentration were made with isopropyl laurate and isopropyl myristate. It was determined that the melting temperature of the gels prepared with fatty acid esters was higher than those prepared in common solvents. The organogel with the highest melting temperature is the gels made with isopropyl myristate and isopropyl palmitate. In addition, gelation enthalpy values ΔH_g were found. According to the results obtained, it was determined that the highest ΔH_g value belonged to the gel prepared with isopropyl laurate.

1. INTRODUCTION

Gels can be defined as a semi-solid formulation with a solvent phase. They are located in a three-dimensional network structure, either nonpolar or polar [1]. Gels can be classified according to the bonds that hold the existing molecules together in the gelator network. In chemical gels, molecules are held together by covalent bonds while physical gels are joined by weaker physical forces of attraction, such as van der Waals interactions and hydrogen bonds. In many studies, it has been reported that non-polymeric, low molecular weight compounds called organogelators can form networks in hydrophobic solvents as a result of non-covalent interactions [2].

Although a wide variety of gelators have been identified in the gelation process, it is difficult to predict the molecular structure of a potential gelator [3]. Besides that, it may not be possible to predict in advance with which solvent it will form a gel. Currently, the discovery of gelators is still going on by chance. This is followed by screening research, testing different solvents which potentially compatible with the gelator. Estimation of the gelation potential of a molecule may seem possible by investigating its tendency for chemical or physical intermolecular interactions. However, it has not been possible to make generalizations so far. Many factors such as steric effects, stiffness and polarity can inhibit the aggregation tendency of the molecule [4].

In recent years, numerous examples of low molecular weight gels that are very useful as a new drug delivery tool have been shown in the literature [5, 6]. However, until now low molecular weight gels have been used to form gel from organic solvents and to examine the relationship between gelator structure and gelation abilities [7-9]. Organogels can be used in pharmacy, drug and vaccine applications. Low molecular weight gels provide an environment that increases the stability of encapsulated drug molecules, and helps to prevent enzymatic degradation during drug administration. Another benefit of use is that the spontaneous formation of gels takes place during formulation of the drug-loaded material [10]. Organogelator has not been studied much as drug carrier. However, organogels have some advantages as a drug delivery system [11]. Organogels are not affected by moisture and accelerate the penetration to the skin. Due to their organic character, they are also resistant to microbial pollution. The gelation and entrapment procedure as a drug carrier is quite simple and easy to use. Its biocompatibility, biodegradability and non-immunogenic properties eliminate harmful drug effects in long-term applications [12, 13].

2. MATERIALS AND METHODS

2.1. Reagents and materials

The organogelator was synthesized according to the procedure described in the related reference [14] (Figure 1). Fatty acid esters and common organic solvents were chosen as solvents. Ethyl laurate (LEE), ethyl palmitiate (PEE), ethyl myristate (MEE), isopropyl laurate (LIE), isopropyl palmitate (PIE) and isopropyl myristate (MIE) were selected as fatty acids and supplied from Merck Chemical Company. Anisole, xylene, liquid paraffin, n-dodecane, diethylene glycol, 1-decanol, toluene, chloroform was chosen as common organic solvents, and supplied from Merck Chemical Company or Sigma Aldrich Chemical Companies.

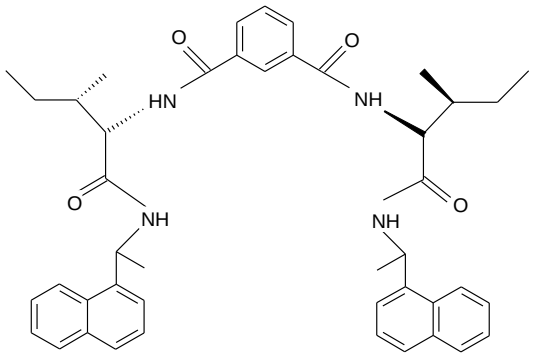

Figure 1. Structure of the organogelator

2.2. Determination of minimum gel concentration (MGC)

1 mg of organogelator was placed in a tube with a 1 cm inner diameter and 1 mL solvent was added. This solution was heated to 20°C below the boiling point of the gelation liquid until the organogelator was completely dissolved. It was then cooled in a thermostated water bath at 25 °C. After about 15 minutes, it was checked whether the solution formed a gel or not. If no gel was formed, 1 mg additional gelator was added and this process was continued until gelation was occurred. The concentration at which gelation occurred was determined as the minimum gelation concentration (MGC mg/mL) [15].

2.3. Determination of melting point of gels (T_g)

A steel ball weighting 0.25 g was carefully placed on the surface of the gels prepared at the minimum gelation concentration. In a temperature-controlled oil bath, the temperature was increased at 1°C intervals until the steel ball dropped to the bottom of the tube. The temperature at which the ball started to fall was determined as the melting point (T_g) of the gelator. This method was repeated with gels prepared at increasing concentrations [16].

2.4. Determination of gelation enthalpy (ΔH_g)

Gelation enthalpy values were calculated via the van't Hoff equation (Equation 1) [17, 18]. The gelation enthalpy values of the organogelator were determined from the slope of the lines found by plotting the $1/T_g$ value against $\ln\%C_g$ (gelator concentration in w%). Here, C_g is the gelator concentration in mol L^{-1}, T_g is the phase transition temperature, and R is the Rydberg gas constant (R = 8.314 J mol^{-1} K^{-1}).

$$d\ln[Cg]/d(1/Tg) = -\Delta Hg/R \quad (1)$$

2.5. Characterization of gel structure by SEM

Gels are formed as a result of the three-dimensional network structure formed by organogelators with solvents [19]. These structures can be characterised by a SEM. Due to the high boiling points of the solvents used in current study, the reprecipitation method was applied while preparing the xerogel [20]. The gels were quickly precipitated in hexane because of insolubility in room temperature. In this way, solvents with high boiling points were transferred to the hexane phase. After the solvents were removed from the gel, the excess hexane was removed by freeze drying process. Thus, the gels were made suitable for SEM analysis.

3. RESULTS AND DISCUSSION

3.1. Determination of the minimum gel concentration

The minimum gelation concentration (MGC) values of the organogelator were determined by performing gelation experiments in ethyl and isopropyl laurate, ethyl and isopropyl myristate, ethyl and isopropyl palmitate, anisole, xylene, liquid paraffin, n-dodecane, diethylene glycol, 1-decanol, toluene and chloroform. Accordingly, the organogelator has a better gel-forming capacity with fatty acid esters than common solvents. It formed a gel with all fatty acid esters at low concentration values. The gels with the lowest minimum gelation concentration are those formed by LIE and MIE. It formed gel with anisole, xylene, liquid paraffin, n-dodecane, which are common solvents (Table I, Figure 2). It did not form gels with diethylene glycol, 1-decanol, toluene and chloroform.

TABLE I
MGC VALUES OF THE ORGANOGELATOR (MG/ML)

Solvents	MGC
Ethyl Laurate	2
Isopropyl Laurate	1
Ethyl Myristate	2
Isopropyl Myristate	1
Ethyl Palmitate	2
Isopropyl Palmitate	2
Anisole	3
Xylene	2
Liquid Paraffin	3
n-dodecane	2
Diethylene glycol	no gelation
1-decanol	no gelation
Toluene	no gelation
Chloroform	no gelation

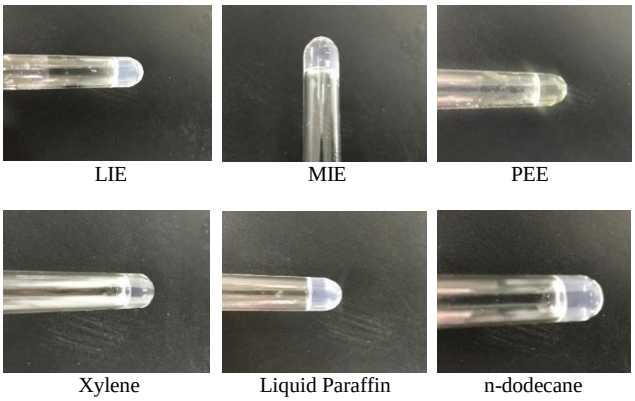

Figure 2. Photographs of gels formed by organogelator with various solvents in MGC

3.2. Determination of melting point of gels (T_g)

The graphs of the melting point (T_g) change values of the gelator against the weight % (C_g) in the gel of the obtained gels are shown in Figures 3 and 4. The T_g values of the gels obtained with fatty acid esters were higher than the gels obtained with common solvents. Accordingly, the organogels with the highest T_g values are the gels made with isopropyl myristate and isopropyl palmitate. The organogel with the lowest T_g value is the gel obtained with n-dodecane. Additionally it was determined that T_g values increased with the concentration of the gel.

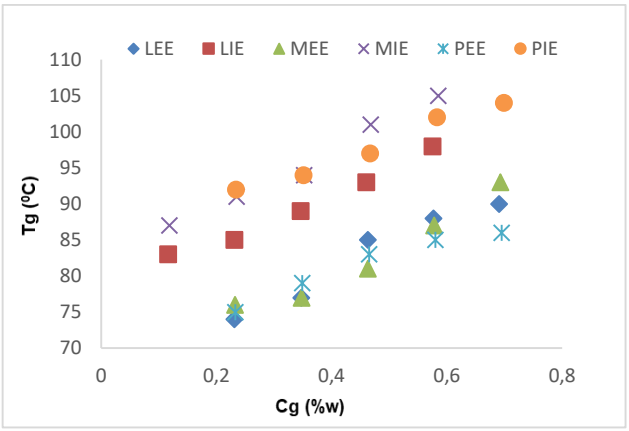

Figure 3. Plot of *Tg* versus the concentration of the organogelator C_g (% w) in fatty acid esters

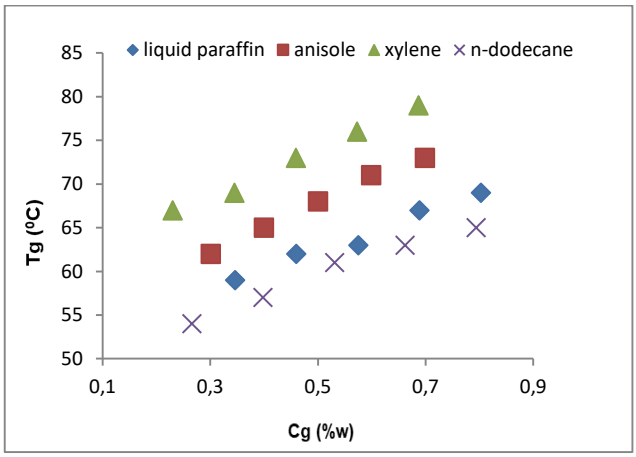

Figure 4. Plot of *Tg* versus the concentration of the organogelator C_g (% w) in common solvents

3.3. Calculation of enthalpy of gelation (ΔH_g)

The graphs of the $1/T_g$ change values of the obtained gels against In C_g are given in Figures 5 and 6. The gelation enthalpy value ΔH_g derived from the slopes of the drawn lines via van't Hoff equation is given in Table II. The high ΔH_g (gel-sol transition enthalpy) indicates that it gives a stable network structure. According to the values shown in Table II, it could be seen that the highest ΔH_g value in fatty acid esters is LIE with 106.91 kj mol^{-1}, and the lowest is MEE with 59.25 kj mol^{-1}. Furthermore it could be seen that the highest ΔH_g value is n-dodecane with 88.61 kj mol^{-1} and the lowest is anisole with 71.92 kj mol^{-1} among common solvents.

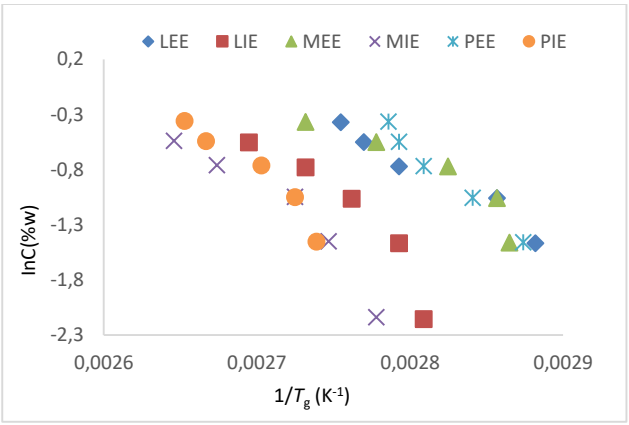

Figure 5. van't Hoff plots of organogelator in fatty acid esters

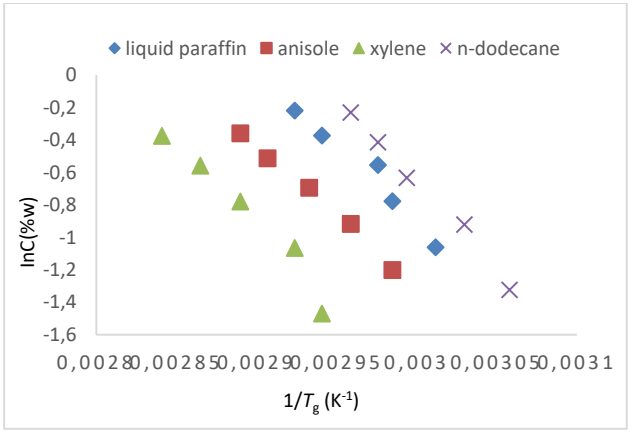

Figure 6. van't Hoff plots of organogelator in common solvents

TABLE II
SOL-GEL TRANSITION ENTHALPY ΔH_g (KJ MOL^{-1}) VALUES FOUND USING VAN'T HOFF PLOTS OF THE ORGANOGELATOR

Solvents	ΔH_G (KJ MOL^{-1})
LEE	63.46
LIE	106.91
MEE	59.25
MIE	93.18
PEE	97.33
PIE	94.01
Anisole	71.92
Xylene	85.44
Liquid Paraffin	76.88
n-dodecane	88.61

3.4. Characterization of gel structure by SEM

Xerogel was created to display the network structures formed by the gels. The solvent was removed by hexane extraction from the gel structure prepared in 1 mL LIE of the organogelator. While doing this, hexane was added and the gels were stirred vigorously, then white precipitate was filtered and washed with hexane. It has been waited for 24 hours under vacuum via freze-dry technique, and xerogel was obtained. The image of xerogel structure is shown in Figure 7. The network structure required for the formation of gels is visible in the photograph.

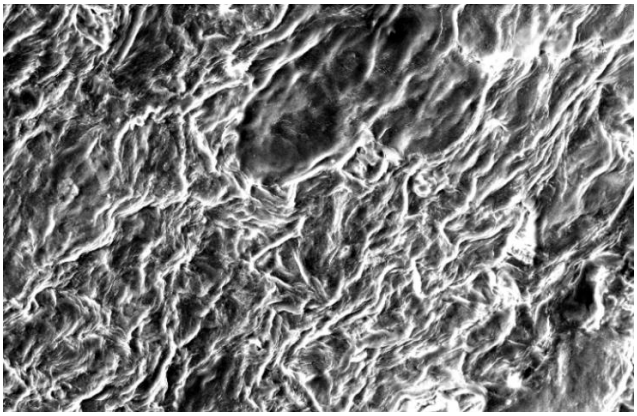

Figure 7. SEM image of gel prepared in LIE of organogelator

4. CONCLUSION AND DISCUSSION

The low molecular weight organogelator that we employed in gelation experiments formed gel with all fatty acid esters. However it formed gel with some of the common solvents. When the investigated organogelator is compared with similar structures in the literature, it could be seen that the gelation potential is good for fatty acid esters. The minimum gelation concentration values of the gels were also found to be quite low. This shows that even a very low amount of organogelator can form the gels while the solvents are fatty acids. In addition, it was determined that the melting temperatures of the gels increased as the concentrations of the prepared gels increased. When we look at the ΔH_g values found using the van't Hoff graphs of the organogelator, it could be seen that the highest result belongs to the LIE fatty acid ester. The solvents employed in this study are liquids used in the pharmaceutical industry such as fatty acid esters and liquid paraffin. Moreover, the organogelator structure contains biocompatible material such as *L*-isoleucine amino acid. Prepared organogels with low MGC values can be used as potential drug carriers.

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BIOGRAPHIES

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