Chapter 3

Stable Gel from Volatile Solvents at Ambient Condition

3.1 INTRODUCTION

Chapter 2 focuses on the strategic design and synthesis of *bis*-urea-functionalized LMWG **G1**. Gel screening results revealed that **G1** responded to multiple stimuli and heat-cool stimuli gelled maximum numbers of solvents. Heat-cool is the most convenient process used for gel preparation by changing the gelator's solubility in the gelling solvent [1]. However, it was observed that heat-cool stimuli has certain limitations when it dealt with low boiling solvents. During gel screening process, heating was used to dissolve the gelator in the solvent. But this resulted in rapid increase the solvent evaporation rate which caused complete evaporation of the solvent. Use of tightly sealed container might reduce the evaporation problem however it again raise safety concern as heating may create high pressure inside the container. Moreover, there is always a risk of reproducibility associated with the heat/cool stimuli as heating/cooling rates may vary in during the gel preparation [2].

Solvent plays an important role in the gelation efficiency of gelators [3,4]. Gelator's solubility in the gelling solvent is very delicately balanced to facilitate the formation of the gel fibre networks [5-7]. In most cases, a stimuli is required to start the gelation process and the stimuli do so by changing the gelator's solubility in the solvent [8]. Stimuli like sonication, shaking, rapid change in pH of the gelling solvent, solvent addition to alter polarity, addition of salt(s), UV radiation have been employed as alternative to heat-cool strategy for gel formation at ambient conditions [9]. For example, Yamanaka *et.al* reported a C_3-symmetrical *tris*-urea LMWG that responded to heat-cool to form gel in 1,1,2-trichloroethane but failed to form gel in $CHCl_3$ or 1,1,2,2-tetrachloroethane. Instead sonication was found suitable for these solvent to prepare gel [10]. Shaking were also used as stimuli for gel preparation under ambient conditions but also useful to make gel at the M.G.C. (minimum gelator concentration) by initiating the nucleation of the gel fibres and the consequent gelation of the solution [11]. Altering the pH of a micellar solution is an effective means of controlling hydrogelation and pH of water can easily change by means adding simple acid or base [12,13]. Gelators having functional groups such as carboxylic or amine are prone to show pH responsiveness. Adams and his co-workers demonstrated a new approach of pH triggered gel to produce homogeneous and reproducible hydrogels using the controlled hydrolysis of glucono-δ-lactone (GdL) [14]. However changes in the method of gel preparation may lead to change in the gel properties. Colquhoun *et al.* reported three different method for gel

preparation for a gelator which failed to form gel by simple heating-cooling cycle. They prepared the gels by adding a salt or by adding an acid to gelator solution at high pH. They also form gels by adding water to a solution of the gelator in an organic solvent. Gels made from these methods have different mechanical properties which attributed to their network type and fibrous structure [15]. Therefore, gel that does not form by heat-cool can be prepared by other methods which also enlarge the scope of getting different gels from a single gelator.

Although diethyl ether (DEE) has been utilized in gel formation via the heat-cool method in certain instances, it's low boiling point (34.6 °C) presents challenges in handling. As a result, it is less frequently employed as a gelling solvent in practical applications. Sugar-based gelator formed gel in DEE by heating the mixture of gelator in solvent in a septum-capped test tube until the solid was dissolved and subsequent cooling resulted gel formation in DEE [16]. Similarly many other LMGW were used to form gel in other volatile organic solvents using heating-cooling methods [17-19]. This chapter delves into the multi-stimuli responsiveness of **G1** gelator to find alternative route for gel making in volatile organic solvents under ambient conditions by avoiding heat-cool stimuli.

3.2 RESULT AND DISCUSSIONS:

G1 was synthesized and all three polymorphs were isolated following the procedures described in experimental section 2.4 of Chapter 2. In the chapter 2, preliminary gel screening for **G1** was performed using the heat-cool method, resulted in the identification of 10 gelling solvents. Subsequent gel screening studies utilization of other stimuli were restricted to these 10 solvents only. However, heat-cool method was unable to apply in case of highly volatile solvents like hexane, diethyl ether as it failed to solubilize **G1** and evaporated easily during the gel screening process itself. Also, heating at high temperature was restricted due to low boiling point of these solvents. Therefore, the use of heat-cool as a stimulus has limitations in gel preparation for low-boiling solvents. Since **G1** responds to other stimuli such as sonication, shaking, and grinding, which do not involve heating, these methods might be helpful for gelation of these solvents at ambient conditions. With this view, gel screening was performed first with **G1** Form I using sonication, shaking and grinding and the results are tabulated in Table 3.1. From the gel screening results, it was observed that **G1** forms gels in diethyl ether and di-isopropyl ether (IPE) at room temperature itself when sonication and shaking

were used as stimuli. While grinding was used as stimuli, a small gelatinous precipitate formed at first but rapid solvent evaporation before the gel formation resulted only precipitatation at the end. **G1** failed to form gel in other low boiling solvents like hexane, petroleum ether due poor solubility even after application of stimuli.

Table 3.1 Gel screening results of **G1** Form I under sonication, shaking and grinding as stimuli

Sl.No.	**Name of Solvent**	**Stimuli**		
		Sonication	**Shaking**	**Grinding**
01	Ethanol	CS	CS	CS
02	Methanol	CS	CS	CS
03	Propanol	CS	CS	CS
04	2-Propanol	CS	CS	CS
05	Butanol	CS	CS	CS
06	2-Butanol	CS	CS	CS
07	t-Butanol	CS	CS	CS
08	Pentanol	CS	CS	CS
09	Water	P	P	P
10	Acetic acid	CS	CS	CS
11	Dimethylformamide (DMF)	CS	CS	P
12	Dimethylsulfoxide (DMSO)	CS	CS	P
13	Acetonitrile	CS	CS	CS
14	Dioxane	CS	CS	CS
15	Dichloromethane (DCM)	CS	CS	CS
16	Diethyl ether (DEE)	**G**	**G**	P
17	Di-isopropyl ether (IPE)	**G**	**G**	P
18	n-Hexane	P	P	P
19	n-Heptane	P	P	P

20	Cyclohexane	P	P	P
21	Hexadecane	P	P	P
22	Petroleum ether	P	P	P

*G= gel, CS= clear solution, P= precipitate

The gel state of the **G1** Form I ether gels was investigated by determining M.G.C., T_{gel}, and viscoelastic nature as well as the stability of the gels. Gel fiber morphology of the xerogels were also investigated using scanning electron microscopy. Both sonication and shaking stimuli require different M.G.C. of **G1** Form I for gelation of these two ether solvents (Figure 3.1). Gel formation in DEE required lower gelator concentrations (0.2% w/v for sonication and 0.7% w/v for shaking) compared to IPE (0.5% w/v for sonication and 0.8% w/v for shaking). These values suggest that the solubility of **G1** Form I in these solvents, potentially influenced by the stimuli used to form gel. Stimuli played a crucial role in M.G.C. requirement for gelation. Based on M.G.C. value, shaking is found to be a more effective stimulus than sonication for gelation in both DEE and IPE.

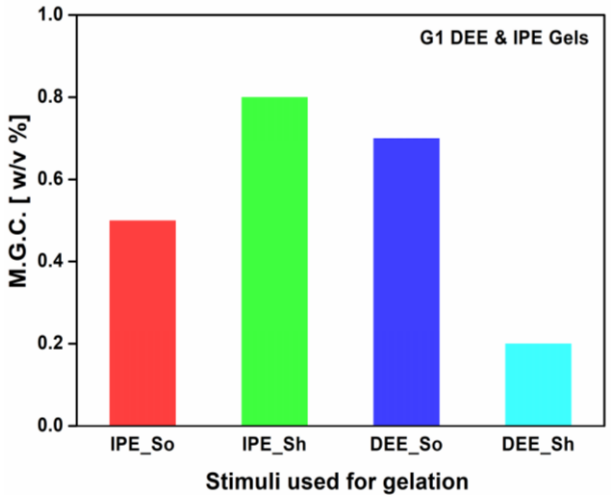

Figure 3.1 M.G.C. of **G1** Form I for diethyl ether (DEE) and di-isopropyl ether (IPE) gels under sonication (So) and shaking (Sh) as stimuli

T_{gel} measurements were carried out for all gels at difference concentrations. No gel-to-sol transition was observed in DEE gels due to solvent evaporation from the vials before reaching the transition point. The boiling point of DEE is 34.6 °C, thus evaporated rapidly even at room temperature when kept uncapped. However, in the gel state, DEE evaporation is significantly reduced even at 70°C. IPE gels exhibited a gel-to-sol transition, and the transition temperature (T_{gel}) increased with increasing gelator

concentration, consistent with general observations. A summary of these results is presented in Table 3.2. Comparison between the stimuli revealed that gels prepared by shaking exhibited higher T_{gel} compared to those prepared by sonication.

Table 3.2 T_{gel} values of DEE and IPE gels prepared through sonication and shaking

Sl. No.	Concentration (g/ml)	Diethyl ether (DEE)*		Di-isopropyl ether (IPE)	
		Sonication (°C)	Shaking (°C)	Sonication (°C)	Shaking (°C)
01	1	63	70	45	55
02	1.5	70	72	60	63
03	2	71	74	72	75
04	3	NP	NP	75	83

*No T_{gel} was observed as above this temperature solvent evaporated completely. NP: Not performed as very minimal changes observed between 1.5 and 2 % w/v gels

Rheological experiments were performed to evaluate the viscoelastic nature and the stability of the gels. Rheology graph of the amplitude sweeps are shown in figures 3.2 (a) and (c). Results confirm that each gel show more solid-like (G') compared to liquid-like characteristics (G") which reveal the viscoelastic nature of the gels. The viscoelastic properties of gels prepared by shaking stimuli are noticeably higher than those of sonication gels, as reflected by their G' (storage modulus), G" (loss modulus), and yield stress (γ) values. Frequency sweep results showed IPE gels are stable in the frequency range of 0.1 to 100 rad/s (as shown in Figure 3.2 (d)). However frequency sweep results for DEE gels suggest that these gels are stable only at higher frequency (in Figure 3.2(b)). In low frequency range, the values of G' and G" became dependent on the frequency used. The reason for this instablility at low frequency linked to the solvent evaporation during the rheological experiments. Frequency sweep experiments start with the highest frequency value and gradually reached the lowest value. Frequency sweep experiments required longer run time based on frequency range and numbers of measuring points in the experiment. DEE evaporated from the gel state due to deformation caused in gel state during frequency sweep experiment for a long time (it was about 15-25 minutes per sample depending the parameters set for the experiment).

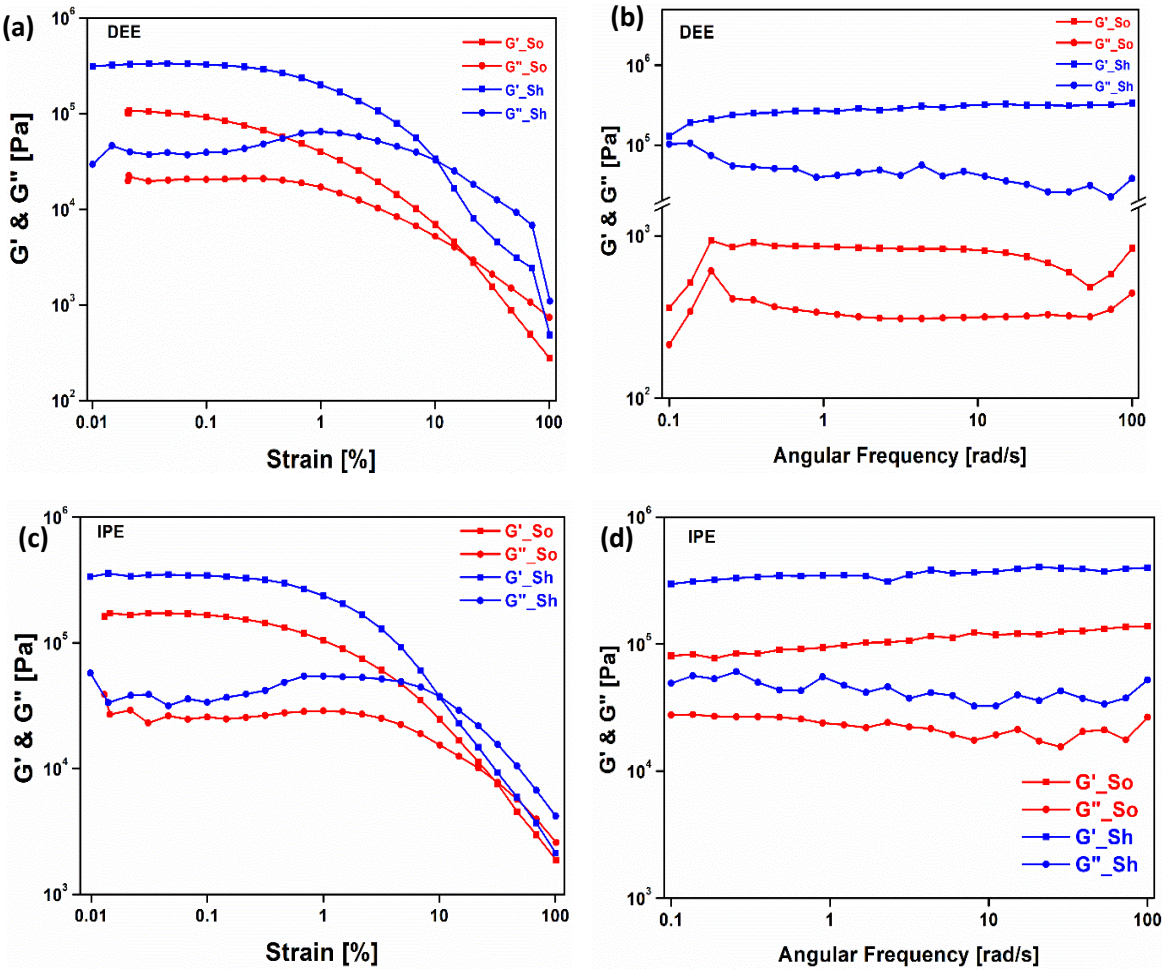

Figure 3.2. Amplitude sweep (graphs a, and c) and frequency sweep (graphs b and d) graphs of DEE and IPE gels prepared by sonication(So) and shaking (Sh) as stimuli

Given the observed differences in M.G.C. requirement and viscoelastic properties among the gels prepared using the two stimuli, the morphology of these gel fibers was examined using electron microscopy. FESEM images of xerogels all four gels reveals distinct morphologies for gel fibers formed in DEE and IPE solvents, as shown in Figure 3.3. **G1** Form I gels in DEE by sonication and shaking exhibited bundled fibres that formed a network-like structure, with the primary difference observed in their uniformity. Whereas **G1** Form I gels prepared in IPE exhibited a rod-like morphology in the xerogels state. This result contrasts significantly with the morphologies observed in **G1** gels prepared under other conditions. It was observed that during the xerogel preparation, solvent evaporation was slow, leading to gel shrinkage without break down of the gel to sol phase. However, in the case of IPE gels, the gel broke down into a sol phase as soon as solvent evaporation started. Subsequent drying of this sol resulted in the isolation of a precipitate. The observation of crystalline morphology in IPE xerogels is linked to this observation. During xerogel preparation from IPE, the gel initially broke

down, leading to the solubilization of gel fibers. Subsequently, these fibers recrystallized from the solution. This explains the observation of the crystalline fibre morphology.

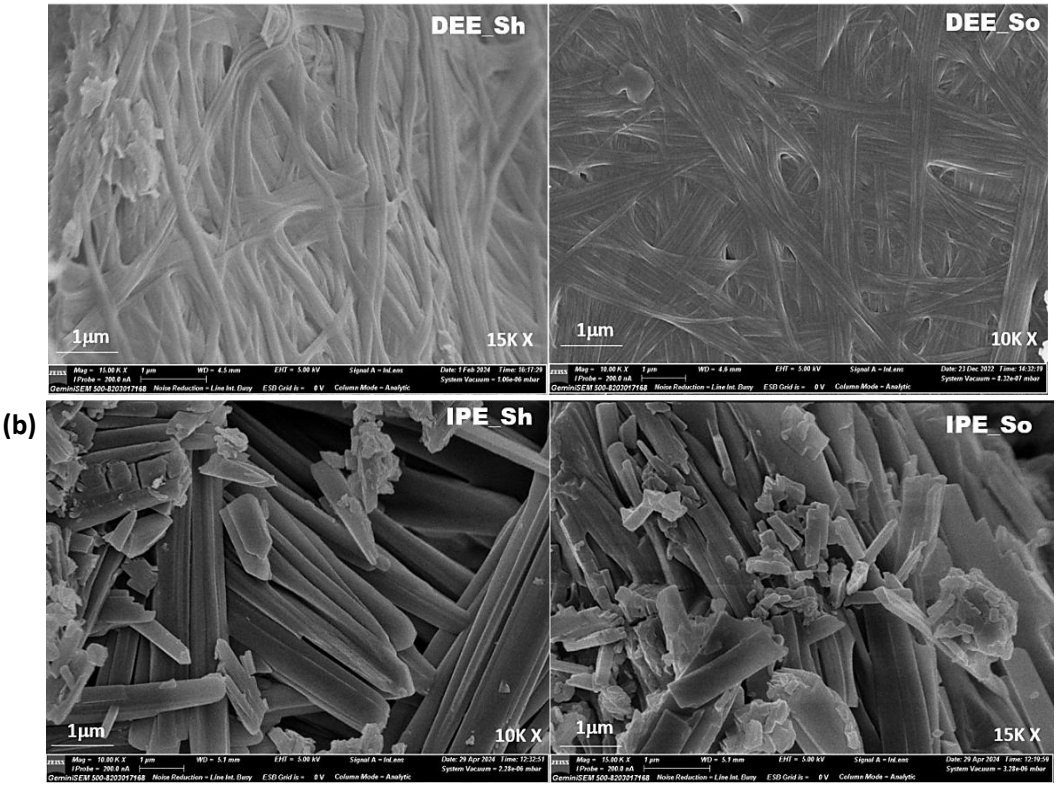

Figure 3.3. FESEM images of xerogels of **G1** in DEE and IPE (So: sonication, and Sh: shaking)

Further PXRD and DSC analysis of these xerogels were conducted to investigate any phase changes in **G1**. Peak around 6° (2θ value) in the PXRD pattern of DEE xerogels shown in Figure 3.4(a) confirm that **G1** retained its phase as **G1** Form I during xerogels preparation. However disappearance of peak around 6° (2θ value) in the PXRD pattern of IPE xerogels shown in Figure 3.4(b) suggest that the polymorphic phase of **G1** was changed to other form. The polymorphic phase of **G1** in xerogels were further investigated by DSC experiments. DSC endotherms of DEE xerogels have only one endothermic peak in the range of 184-186°C which is the melting point of **G1** Form I. Both PXRD and DSC results confirm that **G1** maintained its original phase in DEE gels. However, DSC endotherms of IPE xerogels have two endothermic peaks. First peak at around 158-163°C signify the polymorphic transition from **G1** Form III to I and second peak correspons to melting of **G1** Form I. These results indicate a phase transformation of **G1** in IPE gels from **G1** Form I to III during xerogel preparation.

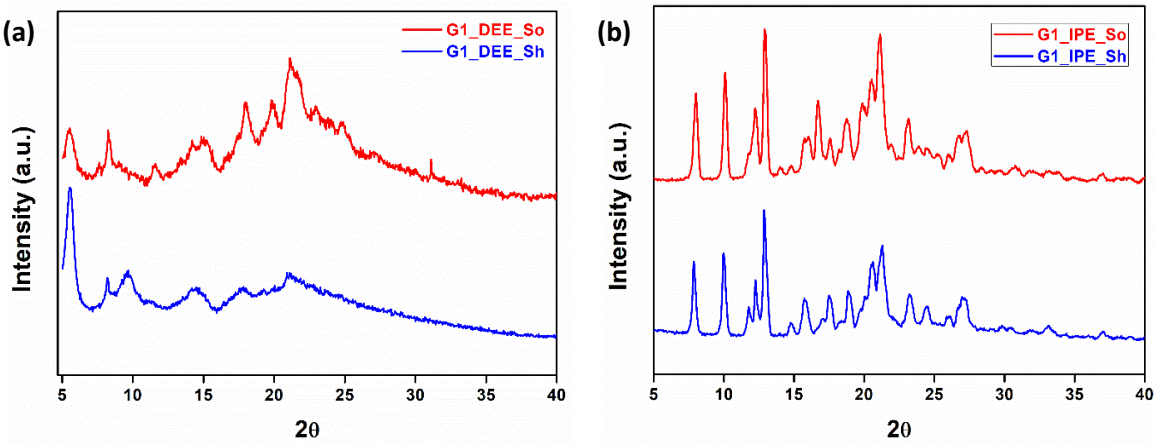

Figure 3.4. PXRD of xerogels of **G1** in (a) DEE and (b) IPE So: sonication, and Sh: shaking)

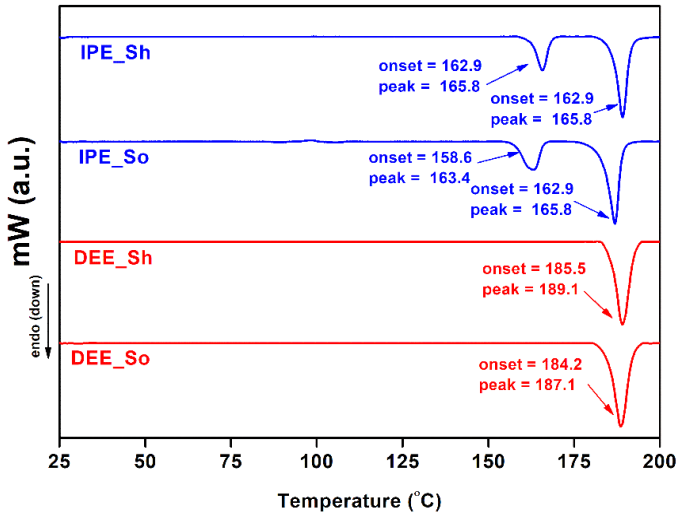

Figure 3.5 DSC endotherms of xerogels of **G1** DEE and IPE gels. (So: sonication, and Sh: shaking)

Gel screening was performed only for **G1** Form I and screening of other two forms were done to know about the role of polymorphism in the gelator's efficiency. As discussed in the chapter 2, three polymorphs of **G1** have difference in their solubility property and thus these polymorphs may behave differently in the gelling solvents: DEE and IPE. Gel screening was performed in both DEE and IPE solvents using all three polymorphs of **G1**, with sonication and shaking employed as stimuli. As expected only the Form I resulted gels and other two forms precipitated or form a dispersed solution (Figure 3.5). This explains the importance of gelator's solubility and if the solubility is balanced in such a manner that slight change in the environment may change the solubility parameter of the gelator. Then those gelators have potential to show multi-stimuli responsiveness.

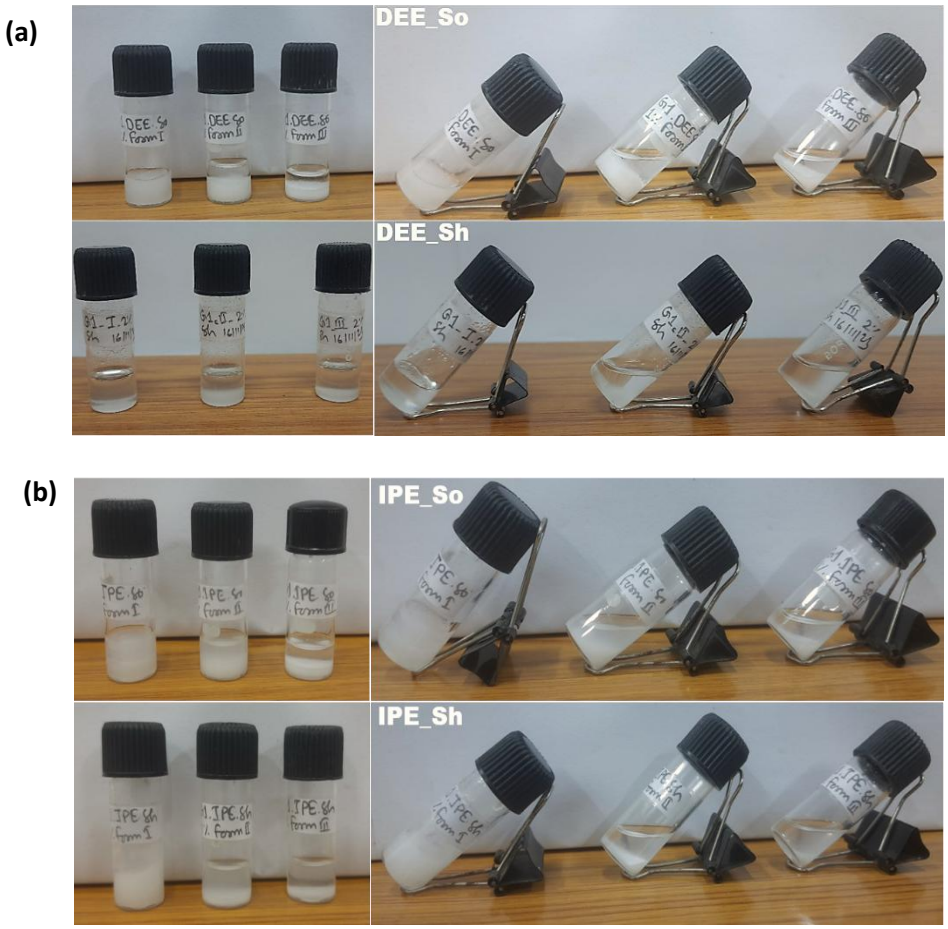

Figure 3.5 Picture of 'vial inversion' test for gel screening using all three polymorphs of **G1**; (a) DEE and (b) IPE as solvents using sonication and shaking as stimuli

3.3 SUMMARY

This chapter explores alternative gel preparation methods for volatile solvents (DEE and IPE) using **G1**, addressing the challenges associated with use of heat-cool as stimuli. Gels were readily prepared using shaking and sonication at room temperature and exhibited stability up to at least 60 °C even at 1% w/v concentration . M.G.C. values are below 1 wt.%, these gels demonstrate potential for practical applications and shaking stimuli required lowest M.G.C. of 0.2% w/v. A distinct morphological change was observed in the gel fibers formed in IPE, compared to the morphologies observed in other **G1** gels. On further investigation using PXRD and DSC analyses, revealed a polymorphic transition of **G1** Form I to III in the xerogels . This transformation is likely attributed to the disruption of the gel structure during the xerogel preparation process and subsequent recrystallization from the sol phase. However, among the three polymorphs of **G1**, only **G1** Form I able to form gel in DEE and IPE. Other two polymorphs failed to form any gel due to poor solubility in these solvents.

3.4. EXPERIMENTAL SECTION

3.4.1 Materials:

All the chemicals used were brought from standard commercial sources and were used as such without further purification (exceptions were mentioned in the procedures). Aminoacetaldehyde diethyl acetal and 1, 3-bis (2-isocyanto-2-propyl) benzene were purchased from TCI. All solvents used in experiments are of laboratory grade and purchased from SRL.

3.4.2 Isolation of G1Polymorphs

All the three polymorphs (**G1** Form I, II, and III) of **G1** were isolated by recrystallization from chloroform, mixture of glycerol/t-butanol/water (GBH) in the ratio of 1:2:1, and DMF respectively.

3.4.3 Procedures for gel preparation:

Glass vial size: 5 ml; Solvent purity: Reagent grade; Concentration: % of w/v. Time required to form gel reduces with increase in the gelator concentration. Gelation at M.G.C. required time to form a stable gel. At M.G.C., sonication and shaking formed the gel fastest.

I. Sonication process:

Required concentration of the mixture of **G1** and solvent was made in a glass vial. After closing the cap of the vial, vial was subjected to sonication (using Ultrasonicator bath) for 10 minutes to obtain a homogenous mixture. Then the vial was kept undisturbed and allowed the solution to form gel.

II. Shaking process:

Required concentration of the mixture of **G1** and solvent was made in a glass vial. After closing the cap of the vial, vial was subjected to shaking using vortex (shaker, make:IKA) for 10 minutes to obtain a homogenous mixture. Then the vial was kept undisturbed and allowed the solution to form gel. Shaking of the mixture can be performed by using hands.

III. Grinding process:

In this process, required amount of **G1** taken in a mortar, solvent was then added and then grounded using the pestle for 5 minutes until the mixture turned into a viscous solution. Then this viscous solution transferred into the vial and kept undisturbed to allow the viscous solution to form gel.

3.4.4 Determination of T_{gel} and M.G.C. of gels:

I) T_{gel} measurement:

T_{gel} of gels with different concentrations are determined by 'ball drop' method. A small steel ball (0.118g ,d ≈ 2 mm) was place on the top of the gel prepared (2mL) in a glass vial (5mL size) and the vial placed in an oil bath whose temperature increase at 1° C per minute. As the temperature increases, ball slowly went inside into the gel and the temperature at which the ball touches the bottom of the vial was recorded as T_{gel} of the gel. Measurements were repeated thrice for accuracy and average value of them was taken as the final value of T_{gel}.

II) M.G.C. measurement:

For measuring M.G.C., at first initial screening was done at 0.5, 1 and 2 w/v % and then screening process was narrow down towards a lower concentration range. Then M.G.C. was evaluated by checking the minimum concentration below which it failed to form gel and that minimum concentration was essential to form the gel was recorded as the M.G.C. value.

3.4.5 Gel screening:

a) Initial screening of solvents using G1 Form I:

Initial screening was done by adding 20 mg/mL of **G1** in respective solvent in a glass vial. Then the vial was subjected different stimuli like sonication, shaking, and grinding. Above mention procedures for gel preparation were used for the screening.

b) Gel screening for all three polymorphs (G1 Form I, II and III) using three stimuli:

Above mention procedures for gel preparation using different stimuli were applied for gel screening.

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