Chapter 6

Role of Drug Mimetic Organogels in Nucleating Pure Polymorphic Phases of Drug

6.1 Abstract

This chapter demonstrates a systematic approach to investigate the role of drug mimetic organogels to control concomitant polymorphs of active pharmaceuticals. Three new drug mimetic organogels comprised with imide functional groups have been designed synthesized and characterized using thermal, microscopic, and spectroscopic techniques. Gelation behaviour has been confirmed by rheological analysis or the vial inversion test. Morphological analysis by SEM also supports the gelation behaviour of the synthesized gelators. The gelators are further used as crystallization media for drug with imide functionality. (±) Thalidomide and barbital were chosen as model drug compounds for crystallization experiments. The crystals obtained from both solution crystallization and gel phase crystallization have been analysed by microscopy, FT-IR, PXRD and/or single crystal unit cell determination for output suitable crystals. Interestingly these organogels control the concomitant crystallization of drug barbital and (±) thalidomide. Such role on drug polymorphism by targeted organogels has been emphasised herein.

6.2 Introduction

Molecular gels are semi-solid like material comprising of gelator in low concentrations (<15% by mass) in a particular solvent [1,2]. The gelator molecules are self-assembled via different intermolecular interactions such as van der Waals interaction, hydrogen bonding, π–π stacking etc. to form extensive fibre networks, thereby reducing the flow of solvent [1,2]. Gels can be distinguished in various classes. Organogel is a distinct class of gel, comprising essentially an organic liquid continuous phase, confined by a three-dimensional fibrous network [2–4]. Based on the gelator molecule type, organogels can be further stratified as polymeric and low molecular weight organogelators (LMWGs, gelators which molecular mass is typically ≤3000) [3,5–10].

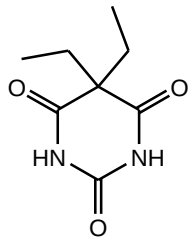
The design and synthesis of LMWGs are gaining substantial attention from the supramolecular research community in last two decades owing to their versatile

applicability in diverse fields ranging from nanomaterial, catalysis, biomedical research, drug delivery to pharmaceutical crystallization such as polymorph screening/ control [11–16]. LMWGs are advantageous, as they provide a mode to design gelators with desired functionalities with specific properties [10]. Generally, they are thermally reversible as they are formed via self-assembled small covalent building blocks through different non-covalent, weak and reversible interactions such as hydrogen bonding, π–π stacking etc. Because of the existence of these weak interactions, gelation behaviour can be manipulated by altering the experimental conditions [5,17,18]. Due to the reversible nature of low molecular oranogels it emerges as an effective template for pharmaceutical crystallization as the separation of crystal is easier [16,19,20]. Gelation behaviour can be achieved in different solvents by changing the medium and experimental conditions [5]. Thus, it offers a range of solvents to perform crystallization experiments, offering the prospect of precise gel–solute interactions. The potential nucleation sites offered by the gelators may further influence the crystal nucleation process and facilitate the occurrence of different solid forms which sometime may not be obtainable from the conventional crystallization method [16,20].

Drug polymorphic form screening/control and separation are of key industrial significance [21,22]. The crystal nucleation control has vital importance in the pharmaceutical industry as different polymorphs of same drug exhibit different physiochemical properties such as solubility, tablability, melting behaviour, hydration stability, bulk density and permeability, which can have overall effects on drug efficacy [23]. Besides this, factors like crystal morphology and particle size also need substantial attention as they can influence the drug physiochemical properties [24]. Functionalized gel surfaces can offer potential alternate nucleation site, subsequently, it can influence the crystallization results such as crystal nucleation time, crystal habit, crystal polymorphism etc. Techniques self-assembled monolayer (SAM), polymer assisted crystallization etc. are also being practices to screening and control of drug polymorphism [25].

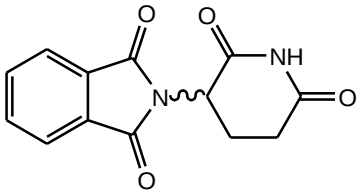
Concomitant polymorphism is a common phenomenon in crystallization [26]. When a compound crystallizes simultaneously in different polymorphic phases, from the same crystallization batch then it is termed as concomitant polymorphism [22,26,27]. The

appearance of concomitant polymorphism is expected for a system when the polymorphs structures differ only in weaker intermolecular interactions and the crystal packing energies are comparable [28]. This phenomenon has been of interest for researchers as it may affect the quality of a crystalline product. Controlling the concomitant polymorphism and selective crystallization of the desired polymorph has paramount importance in drug efficacy and formulation prospect [29]. Understanding the occurrence of concomitant crystallization is vital as it provides insight into nucleation and crystal growth. Though there are reports available on concomitant crystallization, approach to control it is rare. In this work, a gel phase crystallization approach is applied to control the concomitant crystallization of drug barbital (BAR) and (±) thalidomide (THL) anticipating that the tailored imide group in the synthesized gelators will act as a potential nucleation site for their crystallization. BAR is highly polymorphic with six known polymorphs. Crystal structures of three polymorphs of BAR i.e. I, III and V have been reported, which exhibit packing polymorphism [30]. Moreover, BAR is one of the typical examples of molecules that exhibit concomitant polymorphism.



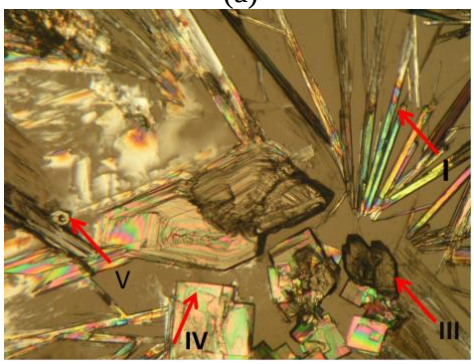
Barbital (BAR)

(a)

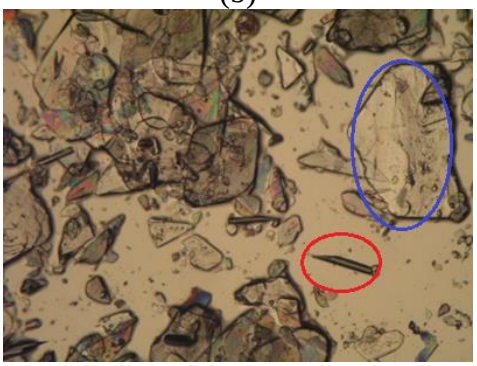


± Thalidomide (THL)

(b)

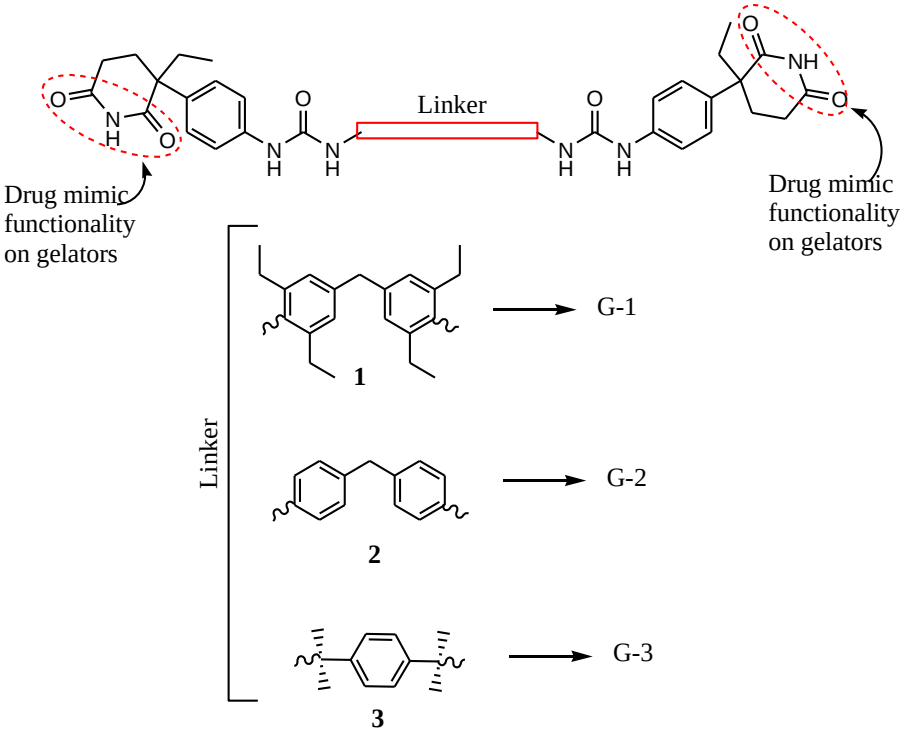


(c)



(d)

Scheme 6.1 Chemical structures of drug (a) barbital and (b) (±) thalidomide; (c) concomitant polymorph appeared from solution crystallization of barbital in cyclohexanone and (d) appearance of concomitant polymorphs of (±) thalidomide from solution crystallization in nitromethane. Red circles signify β form and blue shows plate-shaped α form of (±) thalidomide.



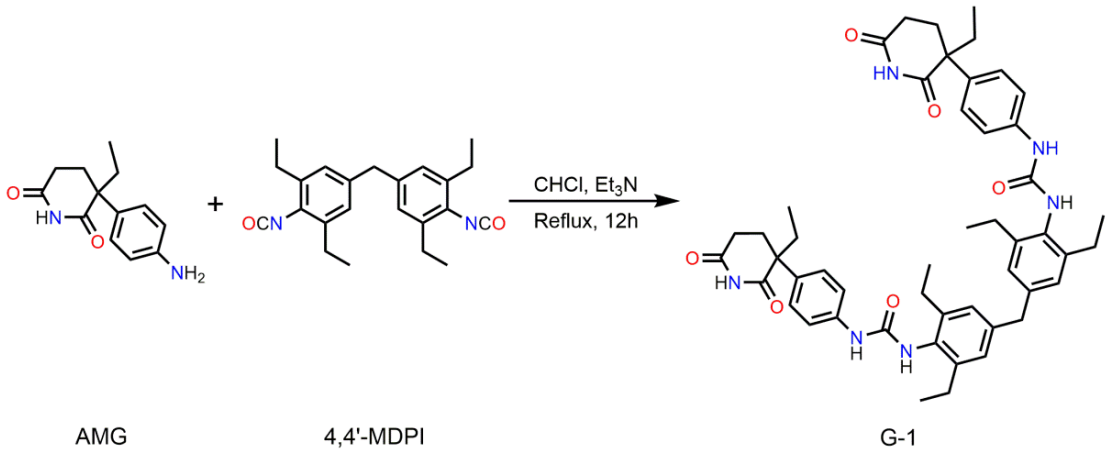
Scheme 6.2 Design of drug mimetic gelators G-1, G-2 and G-3

Three new imide tailored bis-urea based LMWGs were synthesized relying on drug mimetic approach. The intention is to use these gelators as a potential heteromeric nucleation site to grow polymorphs of imide functionalized drugs. Usually, the discovery of gelators is serendipitous; however, bis-urea is one of the favourable motifs for gel formation as they often aggregate via hydrogen bonding to form highly anisotropic morphologies that are essential for gelation [7,10]. Besides the formation of fibre networks, the structures of the gelators, solvent polarity and experimental conditions also play a major role in determining the gelation behaviour. Gelations of the synthesized compounds are expected based on the possibility to form extensive hydrogen bonding networks via the formation of N–H···O synthon. It was anticipated that the drug molecules will interact with the gel functionality via hydrogen bonding which might influence the crystallization outcome. Compared to the conventional crystallization approach this approach is expected to lead to crystallization of different phases of a drug, which further helps in preventing concomitant polymorphism. Considering these aspects the aim of this work is to investigate the crystallization BAR and THL on prepared gel surfaces in order to control the nucleation of concomitant polymorph.

6.3 Results and Discussion

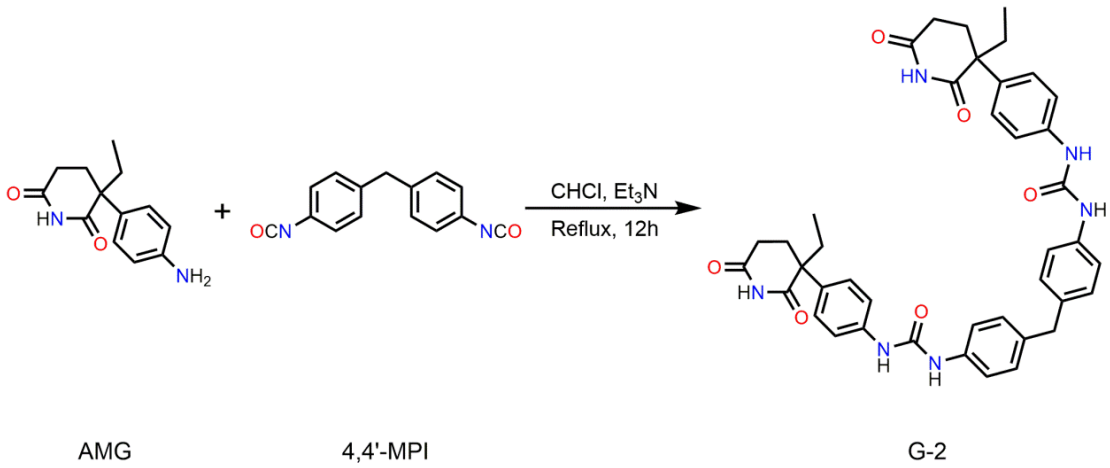
6.3.1 Synthesis

Gelator G-1: Bis-urea based gelator G-1 has been synthesized in good yield (85%) via nucleophilic addition reaction of (±) aminoglutethimide [AMG] and 4,4′-methylenebiz(2,6-diethylphenylisocyanate) [4,4′-MDPI] (Scheme 6.3). Details are available in the experimental section. The synthesized gelator G-1 is characterized by using NMR, FT-IR, mass spectroscopy and elemental analysis.



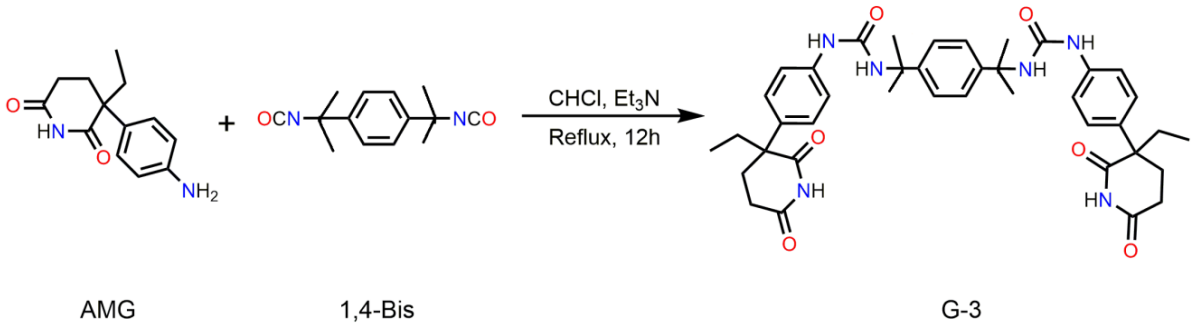
Scheme 6.3 Synthesis of gelator G-1from AMG.

Gelator G-2: Gelator G-2 is synthesized by refluxing AMG with 4,4′-Methylenebis(phenyl isocyanate) [4,4′-MPI] (Scheme 6.4). Detail procedure is available in the experimental section. Gelator G-2 is also further characterized by using NMR, FT-IR, mass spectroscopy and C, H, N elemental analysis.



Scheme 6.4 Synthesis of gelator G-2 from AMG

Gelator G-3: Gelator G-3 is prepared by using the similar procedure as G-1 and G-2 and synthesized from 1,4-Bis-(1-isocyanato-1-methyl-ethyl)-benzene and AMG as shown in Scheme 6.5. Gelator G-3 is characterized by the techniques as mention above.



Scheme 6.5 Synthesis of gelator G-3 from AMG

6.3.2 Characterization

Initial indication over the formation of gelator compounds is evidenced from FT-IR spectrum (Figure 6.1). The significant absorption bands at 3341, 3337 and 3320 cm^{-1} respectively for gelators G-1, G-2 and G-3 are assigned for N-H stretching vibration. The stretching peaks appearing at 1695, 1691 and 1692 cm^{-1} for these compounds advocates the formation of urea linkage.

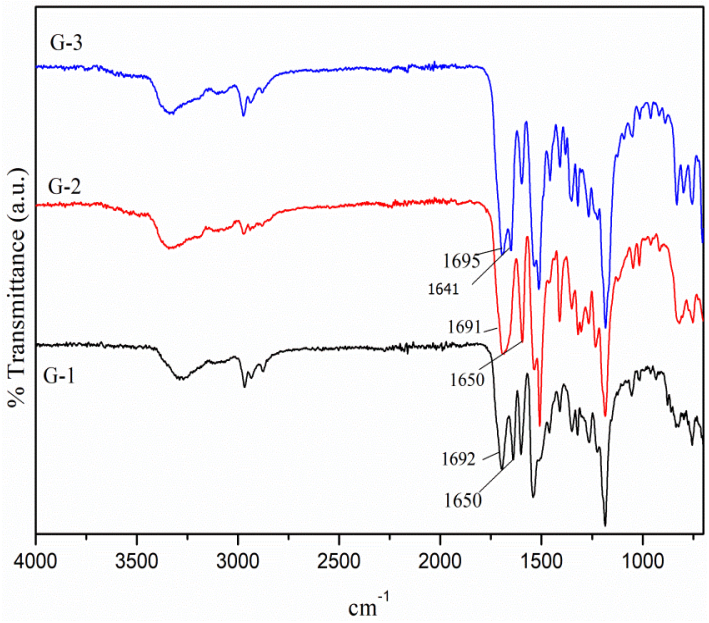


Figure 6.1 Stacked FT-IR spectra of gelators G-1, G-2 and G-3

The synthesised G-1 is further confirmed by ^{1}H- and ^{13}C- NMR spectrum analysis. The singlet at 10.83 and 8.82 ppm for urea NH protons and the singlet peak appears at 3.81 ppm for $–CH_2$ in the spectrum decisively guarantee the formation of gelator G-1 (Figure 6.2).

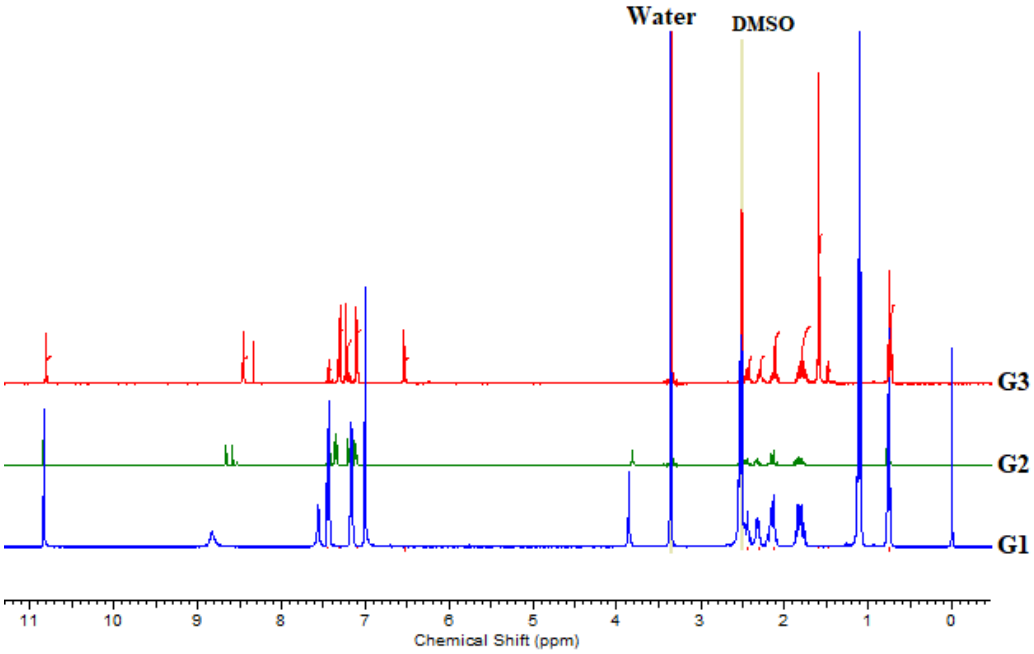


Figure 6.2 Stacked ^{1}H NMR spectra of gelators G-1, G-2 and G-3. The extra peak appeared at 8.32 is identified as residual $CHCl_3$.

The ^{13}C chemical shift appears for G-1 also indicates the formation of the gelator. Especially, the ^{13}C chemical shift peaks at 176.3 and 154.3 responsible for imide carbonyl and substituted urea carbonyl carbon signifies the formation of the gel. Furthermore, mass spectra and elemental analysis also confirm the formation of G-1. A representative ^{1}H NMR stacking plot of the gelators G-1, G-2 and G-3 is shown in Figure 6.2, whereas the ^{13}C NMR and mass spectra are available in Appendix Figure A.10.

6.3.3 Gel screening

It was expected that the targeted gelators will form gel in different solvents through self-assembly via hydrogen bonding in urea base gelators G-1, G-2 and G-3. Gel screening of the synthesized compounds is carried out by varying the concentration of gelators using a

wide range of solvents (Table 6.1). 10 mg of samples are dissolved in 0.5 mL of a respective solvent by gentle heating followed by sonication until full dissolution. Gel formation is observed within a few minutes, whereas in some cases precipitation of the compounds is observed. The formation of the gel is further tested by sample vial inversion test. Compound G-1 is found to be robust gelator as it exhibits gelation in more than ten solvents. G-1 gives robust, stable gel in a wide range of solvents such as ethanol, 1-butanol, 1, 4-butanediol, nitromethane, 1,4-dioxane, nitrobenzene, 1-pentanol, cyclohexanone, cyclopentanone etc. as shown in Figure 6.3.

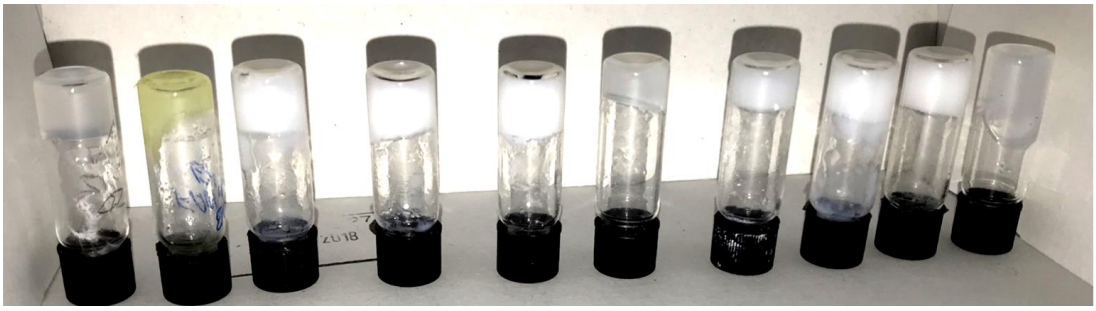
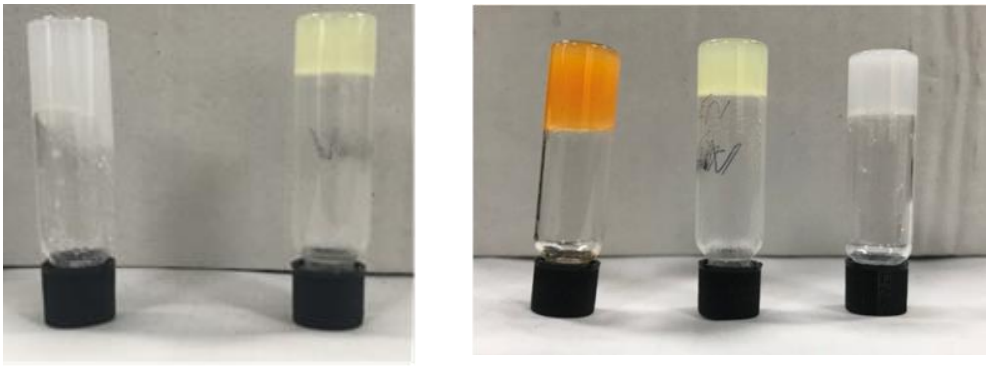


Figure 6.3 Photograph demonstrating reverse sample vial test of the gel of G-1 at wt. 2% in (from left to right) nitromethane, nitrobenzene, ethanol, 1-butanol, tetrahydrofuran, diethylene glycol, 1,4-dioxane, cyclopentanone, cyclohexanone.

However, the lower solubility of gelator G-1 prevents the formation of gel in most alcoholic solvents like methanol, 1-propanol etc. due to the presence of undissolved compounds. A few drops of DMSO readily forms gel in all the common alcoholic solvents. The minimum concentration for the formation of gel i.e. critical gelation concentration (CGC) is important in the context of gelation behaviour. The lowest possible concentration CGC for G-1 at various solvent system is evaluated and found to be in the range of 1.7-2 wt. % for alcoholic solvents, while in the case of a solvent system like nitrobenzene, cyclohexanone, cyclopentanone, 1,4-dioxane, tetrahydrofuran lower CGC (0.8-1 wt. %) has been observed.



(a) (b)

Figure 6.4 Photograph demonstrating the inversion vial test for (a) gels of G-2 in solvent system ethanol: cyclohexane (3:1) and nitrobenzene and (b) gels of G-3 in solvent nitromethane, nitrobenzene and toluene: ethyl acetate (2:1)

Although, gelator G-1 is found as effective gelator which forms gel in more than 10 solvents, other two gelators G-2 and G-3 form gel only in two and three different solvents including a mixture of solvents (Table 6.1). Gelator G-2 forms gels in nitrobenzene, 3:1 mixture of ethanol: cyclohexane (Figure 6.4a). The critical gelation concentration for this gelator has been found as 0.8 and 0.9 wt. % in nitrobenzene and 3:1 mixture of ethanol: cyclohexane respectively. Gelator G-3 gives gel in three different solvents like nitrobenzene, nitromethane and 2:1 toluene: ethyl acetate mixture (Figure 6.4b). The critical gel concentration for this gelator is found to be 0.8 wt. % in each solvent system.

Table 6.1 Gelators G-1, G-2 and G-3 are screened for testing gelation behaviour in a range of solvents by heating 2 % w/v of the gelator compound until completely dissolved in corresponding solvents followed by sonication.

Solvent	**G-1 2% w/v**	**G-2 2% w/v**	**G-3 2% w/v**
1,2,4-trichlorobenzene	P	S	S
Ethylene glycol	G	S	S
2-propanol	PG	PG	S
Acetone	P	S	S
Ethanol	G	PG	PG
Methanol	PG	PG	PG
Methanol+ DMSO (1 drop)	G	PG	PG
1-Pentanol	G	PG	PG

1,4-Butanediol	G	PG	PG
1-Propanol	PG	PG	PG
1-Propanol+ DMSO (1 drop)	G	PG	PG
1-Butanol	G	S	PG
2-Butanol	PG	IS	PG
2-Butanol+ DMSO (1 drop)	G	S	PG
Benzyl Alcohol	PG	S	S
Chloroform	IS	IS	IS
Dimethyl sulfoxide	S	S	S
Dimethylformamide	S	S	G
Ethyl Acetate	IS	IS	S
Nitrobenzene	G	G	G
Nitromethane	G	PG	G
1,4-Dioxane	G	S	S
Tetrahydrofuran	G	S	S
Cyclohexanone	G	S	P
Cyclopentanone	G	P	P
Toluene	P	P	S
H_2O	P	S	S
EtOH: Cyclohexane (3:1)	PG	G	PG
Toluene: Ethyl acetate (2:1)	PG	PG	G

P= Precipitate, G= Gel, PG= Partial Gel, I= Insoluble with heating.

6.3.4 Gel Characterization

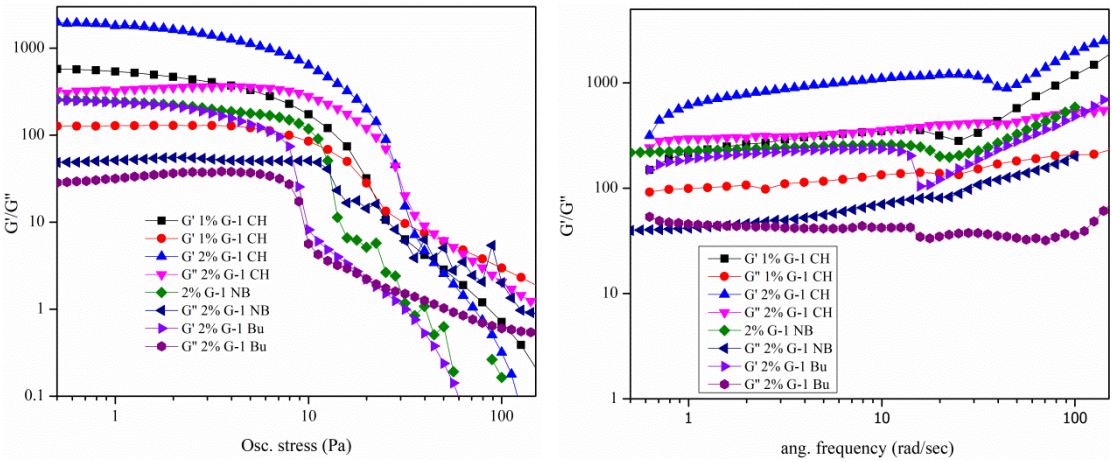
To understand the thermal stability of the gels, dropping ball method is used to determine the sol phase transition temperature, commonly known as T_{sol}, the temperature at which gels are broken down to give solution [31]. G-1 gels found to be stable, emphasizing the case of cyclohexanone with a T_{sol} of 97 degrees at a concentration of 2% wt. (Table 6.2). It has been observed that the thermal stability of the gels improves with the increase in concentration.

Table 6.2 T_{sol} of G-1 at different concentrations considering different solvent systems.

Solvent	Concentration (wt. %)	T_{sol} (°C)
ethanol	2	67
1-butanol	2	64
nitrobenzene	2	78
nitromethane	2	51
cyclohexanone	2	97
cyclohexanone	1	88
cyclopentanone	2	95
cyclopentanone	1	89
1,4-dioxane	2	77
THF	1	53
1-pentanol	1	77
1,4-butanediol	2	63

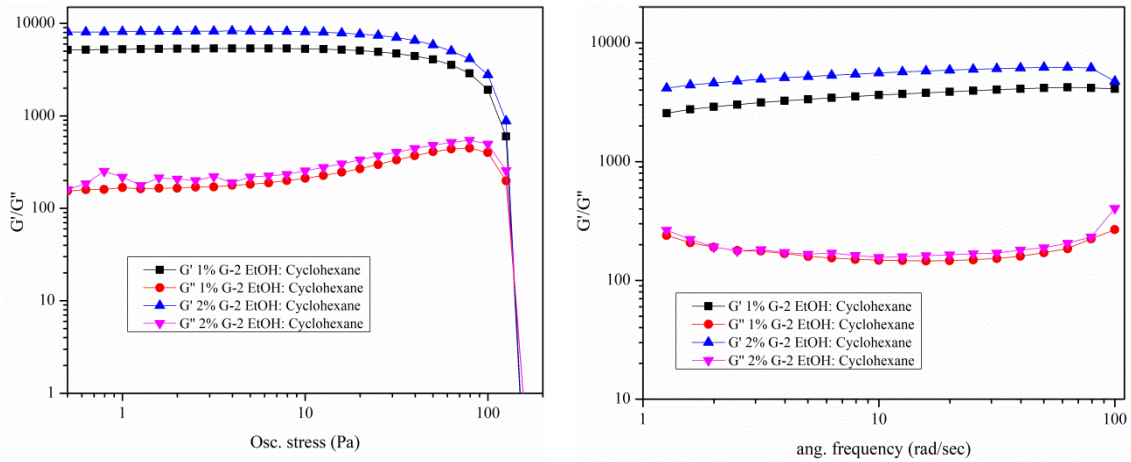
Similarly, the T_{sol} for G-2 and G-3 is also determined. The T_{sol} for G-2 has been observed at 71 and 74 °C in nitrobenzene and EtOH: cyclohexane (3:1) respectively. The gel of G-2 in nitromethane is found considerably weak with T_{sol} only 45 °C for 2 wt. % gel. In nitrobenzene and toluene: ethyl acetate (2:1) the T_{sol} for G-3 is 101 and 83 °C respectively.

To confirm the gelation behaviour of the synthesized gelators rheological measurements has been performed considering different solvent systems and concentration of the gelators [32,33]. The oscillatory rheological experiments confirm the typical viscoelastic properties of the pure gels. In all cases, the storage modulus (G′) is found to be at least 1.5 magnitudes greater than the loss modulus (G″), supporting the gelation properties for all the acquired gels (Figure 6.5a, 6.6a, 6.7a). The relatively large value of G′ confirms that G-1 forms strong gels. The frequency sweep measurements also support the gelation behaviour of all the three gelators as G′ is much higher than G″ in all cases, and they remain almost constant over the entire angular frequency range (Figure 6.5b, 6.6b, 6.7b).



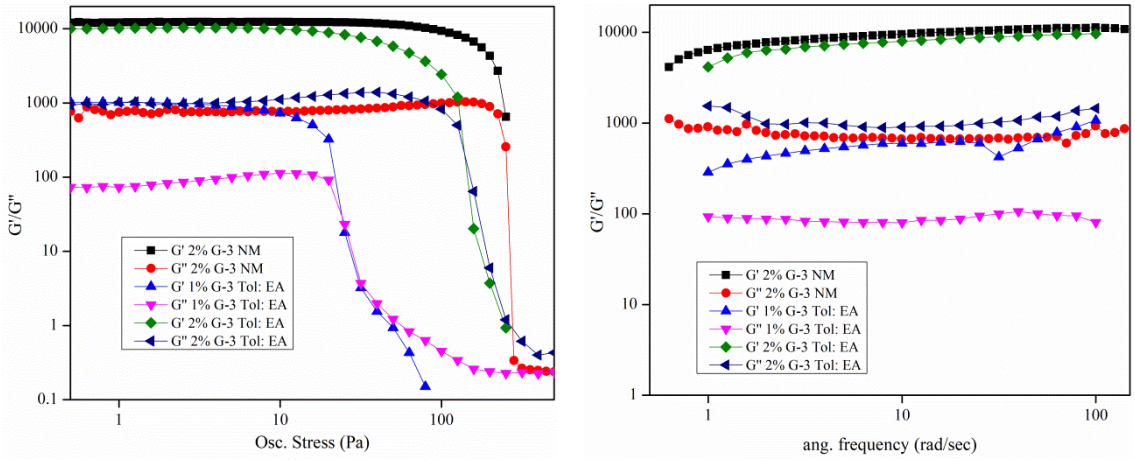
(a) (b)

Figure 6.5 (a) Oscillatory stress sweep comparisons of G-1 considering solvent system cyclohexanone (CH), Nitrobenzene (NB), 1-butanol (1-Bu) at constant frequency of 1 Hz and (b) frequency-sweep rheology of G-1 in nitrobenzene solvent system cyclohexanone (CH), Nitrobenzene (NB), 1-butanol (1-Bu) at constant stress of 10 Pa



(a) (b)

Figure 6.6 (a) Stress Sweep and (b) frequency sweep of gelator G-2 at 1 wt. % and 2 wt. % with solvent system ethanol cyclohexane (1:1).

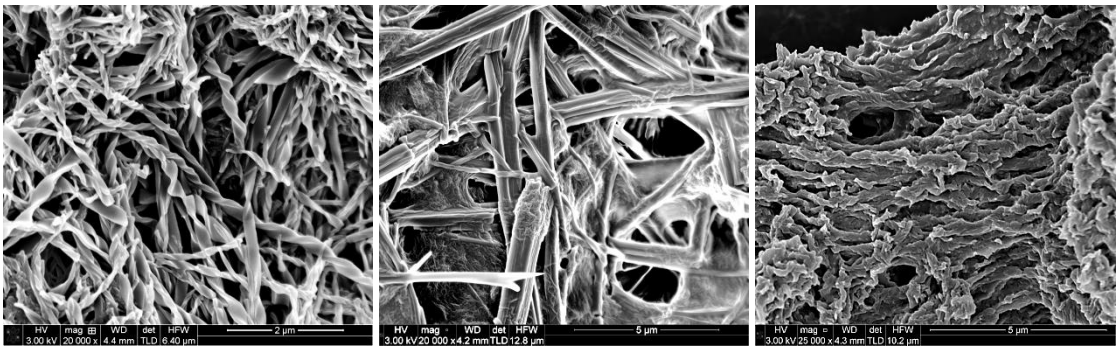


(a) (b)

Figure 6.7 (a) Stress Sweep and (b) frequency sweep of gelator G-3 at 1 wt. % with solvent system toluene ethyl acetate (2:1); (c) Stress Sweep and (d) frequency sweep of gelator G-2 at 2 wt. % with solvent system toluene ethyl acetate (2:1)

6.3.5 Gel Morphology

Scanning electron microscopy (SEM) is used to examine the morphology of the supramolecular aggregates of the gelators. It is expected that low molecular weight organogels should exhibit fibrous morphology [34]. The fibrous nature of these gels is remarkably evident as shown in Figure 6.8 in each case. SEM image of G-1 is obtained from drying a 2 wt. % gel of G-1 in ethanol showing helical twist kind morphology (Figure 6.8a). Cylindrical ribbon type morphology is observed for a 1 wt. % xerogel of G-2 in nitrobenzene (Figure 6.8b). Dense helical morphology is observed for 1 wt. % xerogel of G-3 in nitromethane (6.8c).



(a) (b) (c)

Figure 6.8 SEM images of the xerogels of gelator (a) G-1, (b) G-2 and (c) G-3 demonstrates the fibrous nature of the gelators.

6.3.6 Crystallization of Barbital

To optimize the suitable crystallization conditions a series of crystallization experiments have been done. As BAR has considerably higher solubility in most organic solvents, samples that crystallize at a lower concentration than 100 mg/mL take longer duration for crystallization. The crystallization condition optimized for BAR crystallization is the addition of 20 mg of gelator in 1 mL solution of BAR comprising 100 mg of it in respective solvent. The solution is then warmed followed by sonication to achieve gelation, and then the vials are capped and kept undisturbed for crystallization. Crystals of BAR are obtained in 3-4 days. To draw a comparison between solution crystallization and gel crystallization outcome, identical conditions are maintained for both the procedures.

The crystals that are obtained from control solution crystallization from alcoholic solvents produced concomitant crystal of polymorph I, III, IV and V of BAR and identified by unit cell determination, PXRD, DSC and FT-IR analysis. It is easy to identify the polymorphic form of BAR crystal because of their characteristic FT-IR peaks [30]. Under the same experimental condition, gels of G-1 in alcoholic solvents like 1-butanol, 1-pentanol, 1, 4-butanediol, produced only kinetic form III of BAR. However, in case of ethanol along with polymorph III crystals trace amount of crystals of another kinetic form V is also observed. The solution crystallization of BAR from nitromethane at a concentration of 100 mg/mL resulted in a dense network of needle-shaped crystals. These crystals are analysed by FT-IR and unit cell determination and found to be a mixture of polymorph III and V. Whereas, 2 wt. % gels of G-1 produced large prism-shaped crystals of polymorph III in nitromethane. In the case of nitrobenzene, no difference between crystals obtains from the solution or gel phase crystallization has been observed. In contrast to solution crystallization method, gel phase crystallization of BAR using the gelator G-1 exhibits high selectivity for the kinetic polymorph, form III. This selectivity sustains across a range of solvents for all the three gelators and a comparison between gel phase and solution phase crystallization outcome depicted in Figure 6.10

As G-2 and G-3 give only partial gels in alcoholic solvents, these gelators were used for seeding crystallization. For seeding crystallization, 10 mg of gelator is added in a 1 mL

saturated solution of BAR in a respective alcoholic solvent. The crystals that are obtained from seeding crystallization in alcoholic solvents are characterized by unit cell determination, PXRD, DSC and FT-IR analysis. In seeding crystallization gel fibres selectively induces the polymorphic form III of BAR. A visual comparison of polymorphic form obtained in solution crystallization and seeding crystallization is drawn by taking polarizing microscope images and to be found in Appendix (Figure A.12).

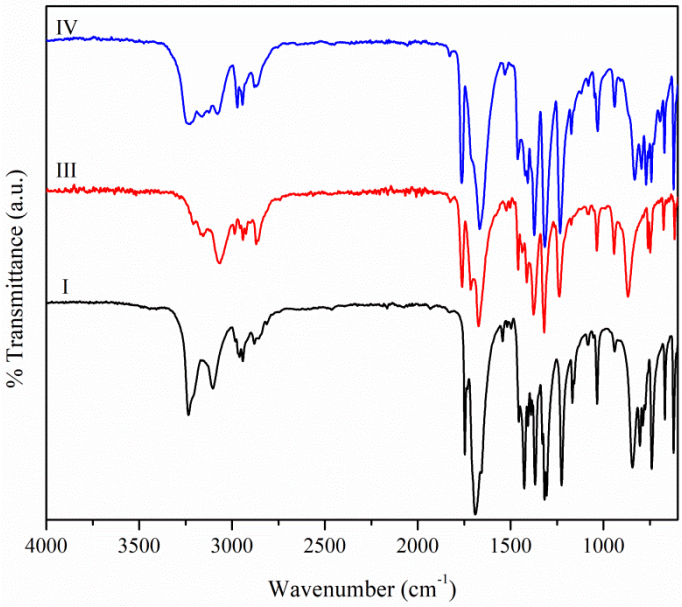
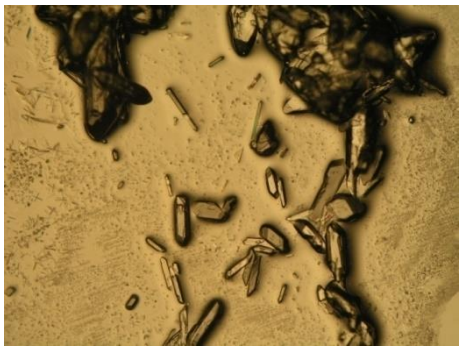
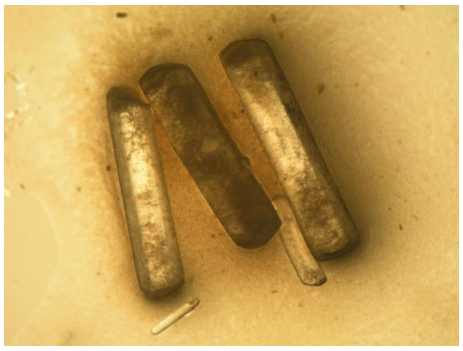


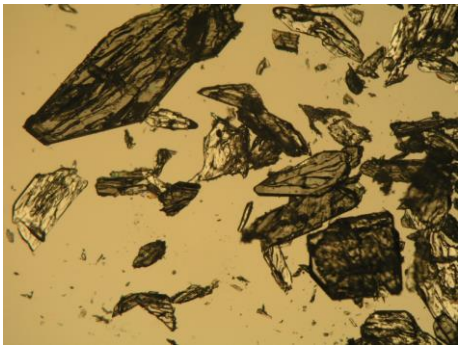
Figure 6.9 FT-IR spectra comparisons of barbital (BAR) polymorphs.



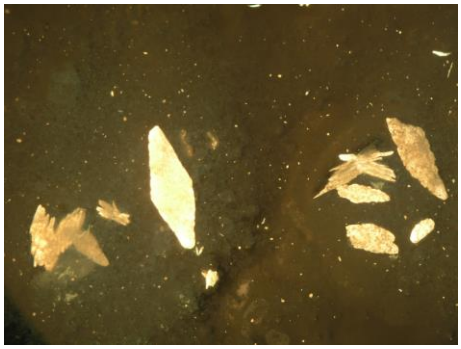
(a) Mixture BAR form I, III, IV, V



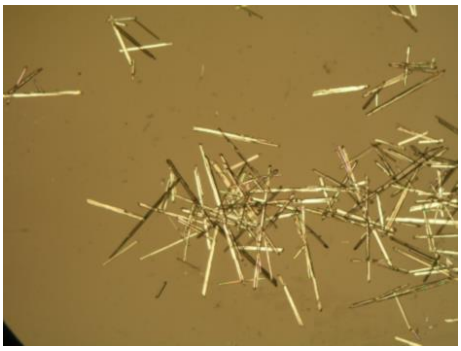
(b) BAR form III



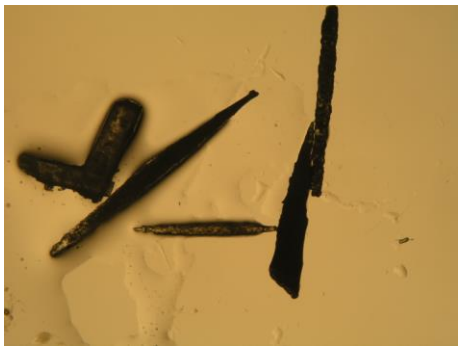
(c) Mixture BAR form I, III, IV, V



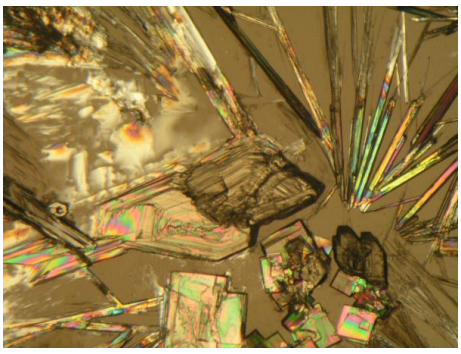
(d) BAR form III and V



(e)) Mixture BAR form III and V



(f) BAR form III



(g) Mixture BAR form I, III, IV, V

(h) BAR form III

Figure 6.10 Comparison of crystallization outcome of BAR from solution and gel crystallization of BAR. Crystal obtained from solution crystallization in (a) 1-butanol, (c) ethanol, (e) nitromethane and (g) cyclohexanone respectively. Crystal obtained inside the gel G-1in (b) 1-butanol, (d) ethanol, (f) nitromethane and (h) cyclohexanone respectively.

Table 6.3 Comparison of crystallization outcome from solution and Gel crystallization of barbital.

Solvent	Crystal forms in pure solvent	Crystal forms from G-1	Crystal forms from G-2	Crystal forms from G-3
Ethanol	I, III, IV, V	III (prism), V	III#	III#
1-butanol	I, III, V	III (rod)	III#	III#
1,4-butane-diol	I, III, V	III (prism)	III#	III#
1-pentanol	I, III, IV, V	III (prism)	III#	III#
Nitrobenzene	III	III	III	III
Nitromethane	III (needle)	III (large Prism)	N/A	Gel Unstable
Cyclohexanone	I, III, IV, V	III (prism)	N/A	N/A
Toluene : ethyl acetate (2:1)	III and V	N/A	III (prism)	N/A
EtOH: Cyclohexane (3:1)	III and V	N/A	N/A	III (prism)
Cyclohexanone	I, III, IV, V	III (prism)	N/A	N/A

#Crystal obtained from seeding crystallization.

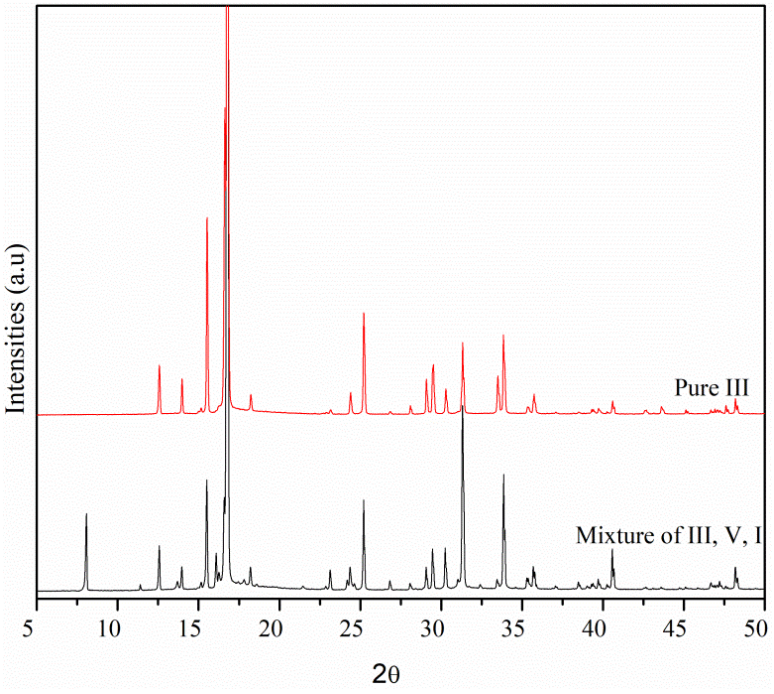
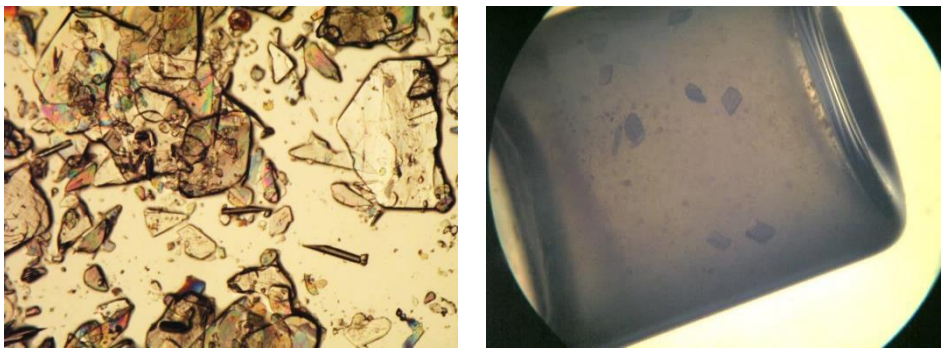


Figure 6.11 PXRD stacked comparison of BAR polymorph III obtained inside gel and mixture of polymorphs obtained from solution crystallization

6.3.7 (±)Thalidomide Crystallization

(±)Thalidomide has very low solubility in most organic solvents and is practically insoluble in alcoholic solvents. So, the crystallization of this drug has to be restricted for only four different solvents like nitromethane, 1,4-dioxane, nitrobenzene, cyclohexanone. There is no report available about concomitant polymorphism of drug THL. Interestingly, the two polymorphs of it, α and β Form crystallize concomitantly upon solution crystallization from nitromethane at concentration 20 mg/mL (Figure 6.12a). From the solution crystallization in nitromethane large plate and small needle-shaped crystals are observed. The plate and needle-shaped crystals are further characterized by FT-IR, PXRD, and unit cell parameter determination and confirmed as α and β form respectively [35]. The polymorphs can be easily distinguished by FT-IR comparison in which the α polymorph exhibit the N-H absorption at 3193, 3098 cm^{-1} and whereas the β polymorphs show absorption peak at 3278 and 3111 cm^{-1} as shown in Figure 6.13. The gel phase crystallization with G-1 in nitromethane prevents the concomitant crystallization and only result in the kinetic Form α of THL (Figure 6.12b). To confirm the phase purity of the polymorphs obtained inside the gel the experimental powder X-ray pattern is compared with that simulated from the single-crystal structure and they are found to be an exact match thus indicating that none of the β Form crystallised (Figure 6.14).



(a) (b)

Figure 6.12 Concomitant crystals plate (α) and needle (β) of THL obtained from solvent evaporation in nitromethane and (b) crystal of polymorph α grown inside the gel G-1 in nitromethane.

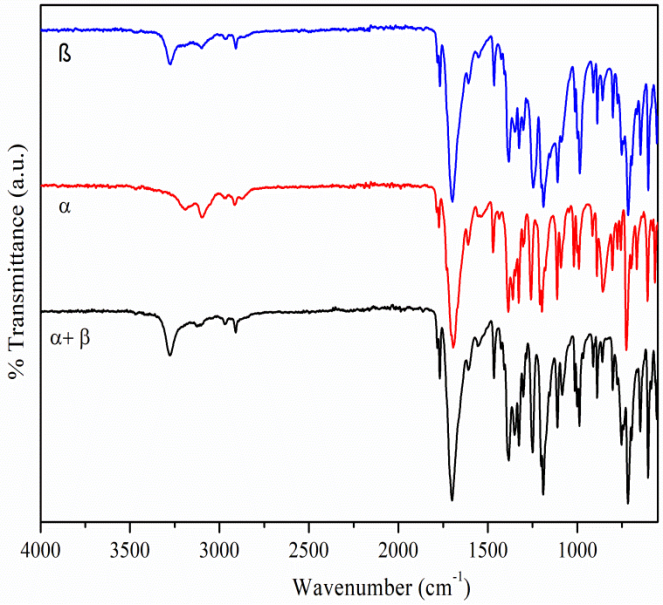


Figure 6.13 FT-IR spectra comparisons of (±) thalidomide (THL) polymorphs.

Under same control condition no substantial changes on crystallization result have been observed among gel (G-1) and solution phase crystallization in solvent nitrobenzene, 1,4-dioxane and cyclohexanone. However, gel phase crystallization results in comparatively larger crystal than solution crystallization in 1, 4-dioxane. A comparison is drawn between gel phase crystallization and solution crystallization results in Table 6.4.

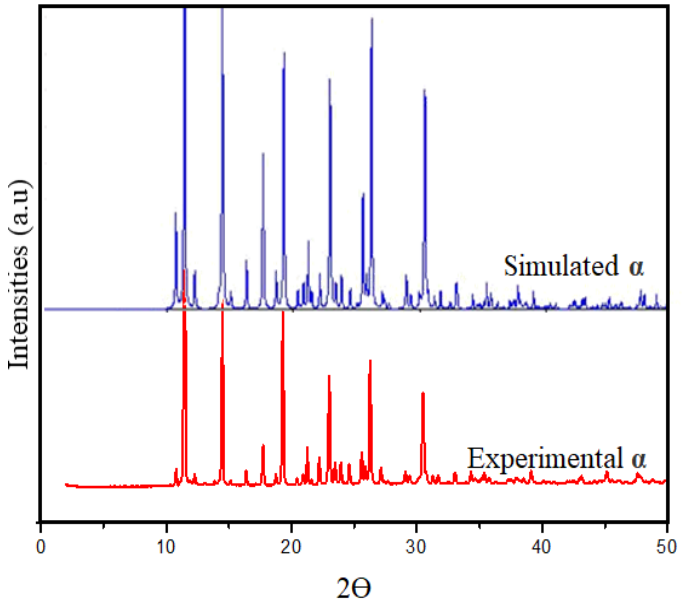


Figure 6.14 Comparison of experimental PXRD of (±) thalidomide (THL) polymorph α obtained inside the gel with simulated from corresponding crystal structure.

Table 6.4 Comparison of crystallization outcome from solution and Gel crystallization of THL

Solvent	Crystal forms in pure solvent	Crystal forms from gel G-1	Crystal forms from gel G-2	Crystal forms from G-3 gel
Nitromethane	α and β	α	N/A	Gel not stable
1,4-dioxane	α	α (comparatively large needle)	N/A	N/A
Cyclohexanone	No crystals	α	N/A	N/A
Nitrobenzene	No crystals	Very tiny crystals of α	Very tiny crystals of α	No crystals

6.4 Summary

Three new bis-urea based drug mimetic molecular organogels are synthesized by nucleophilic addition reaction of (±) aminoglutethimide and isocyanates. Products are characterized by using analytical techniques such as NMR, FT-IR, MS and elemental analysis. Synthesized gelators are subjected to gel screening considering different gelator concentrations and solvent systems. Rheological analysis and vial inversion test have been performed to confirm the gelation behaviour of the gelators. The gels demonstrate high thermal stability and significant mechanical property. G-1 is found to be a robust gelator as it generates gels in more than ten different solvents. The gelators have been used as crystallization media for crystallization of imide functionalized drug THL and BAR. Compared to solution crystallization method, gel phase crystallization using these gelators displays high selectivity towards the kinetic polymorphic form of BAR, form III. Similarly, in the case of THL, the gel G-1 selectively crystallizes the kinetic form α, thus, preventing the concomitant crystallization that is observed in solution crystallization. Thus gelators are found to be effective in preventing the concomitant crystallization of both the drug BAR and THL. These gels are instrumental in providing relief from current confusion about polymorph control method by introducing drug mimetic functionality as potential nucleation sites for crystallization.

6.5 Experimental Section

6.5.1 Materials

All the chemicals used are brought from standard commercial sources and were used as such without further purification. (±) aminoglutethimide (AMG) was purchased from TCI. All solvents of HPLC grade, triethylamine, and chloroform used in the experiments were procured from Merck. The isocyanates were purchased from Sigma Aldrich.

6.5.2 Synthesis and Characterization of Gelators

Gelator G-1: 0.50 g of aminoglutethimide (AMG) was dissolved in 30 mL of chloroform in round bottom flask and an excess amount of triethylamine added drop wise with continuous stirring. A solution of 4,4′-methylenebiz(2,6-diethylphenylisocyanate) (0.42 g) in 20 mL chloroform was added drop wise to the above solution and the reaction mixture was then left stirring at 70 °C for 12 h. The resulting white precipitate was isolated by filtration followed by continuous washing with chloroform. Yield=85%, MP > 300 ºC

FT-IR: 3320 (N–H), 1692 (C=O), 1650 (N–$H_{bending}$) cm^{-1}

^{1}H-NMR: (DMSO-$d_{6,}$ 400MHz): 0.73–0.77 (t, *J*=7.6 Hz, 6H) 1.08–1.12 (t, *J*=8 Hz, 12H), 1.75-1.87 (m, 4H), 2.11–2.20 (m, 4H), 2.40–2.47 (m, 4H) 2.55-2.53 (q, 4H), 3.85 (s, 2H), 7.00 (s, 4H), 7.15-7.17 (d, *J*=8 Hz, 4H), 7.43-7.45 (d, *J*=8 Hz, 4H), 7.56 (s,2H), 8.82 (s, 2H), 10.83 (s, 2H)

^{13}C-NMR: (DMSO-$d_{6,}$ 100 MHz): δ 176.3, 173.2, 154.3, 142.3, 140.1, 139.7, 132.6, 132.2, 127.0, 126.7, 118.2, 50.0, 32.6, 29.5, 26.4, 24.9, 15.1, and 9.3

MS calculated for M+H is 828.02, experimental 828.00. Elemental analysis: C, 71.18; H, 7.11; and N, 10.03.

Gelator G-2: AMG (0.50 g) was dissolved in 30 mL of chloroform in round bottom flask and an excess amount of triethylamine added drop wise with continuous stirring. A solution of 4,4′-methylenebis(phenyl isocyanate) (0.22 g) in 20 mL chloroform was added drop wise to the above solution and the reaction mixture was then left stirring at

70°C for 12 h and the resulting white precipitate isolated by filtration followed by continuous washing by chloroform. Yield=90%, MP > 300 ºC

FT-IR: 3337 (N–H), 1691 (C=O), 1650 ($N–H_{bending}$) cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.74–0.78 (t, *J* = 7.4 Hz, 6H), 1.76–1.88 (m, 4H), 2.09–2.19 (m, 4H), 2.31–2.48 (m, 3H), 3.81(s, 2H), 7.10–7.12 (d, *J*= 8 Hz, 4H), 7.42–7.44 (d, *J*= 8 Hz, 4H), 7.34–7.36 (d, *J*= 8 Hz, 4H), 7.42–7.44 (d, *J*= 8 Hz, 4H), 8.58 (s, 2H), 8.66 (s, 2H), 10.83 (s, 2H).

^{13}C-NMR: (DMSO-d_6, 100 MHz): δ176.3, 173.2, 152.9, 139.1, 137.9, 135.5, 133.1, 129.3, 127.1, 118.84, 118.8, 50.1, 32.6, 29.6, 26.4, and 9.3

MS calculated for M+2H is 357.16, experimental 357.39. Elemental analysis: C, 68.29; H, 5.81; and N, 11.65.

Gelator G-3: AMG (0.5 g) dissolved in chloroform (20 mL) and an excess amount of triethylamine added to it. 0.4 mL of 1,4-Bis-(1-isocyanato-1-methyl-ethyl)-benzene added dropwise to the above solution with continuous stirring. The reaction mixture was refluxed overnight and the precipitate obtained was filtered, washed with chloroform and air dried to get a white solid. Yield=87%, MP > 300 ºC.

FT-IR: 3341 (N–H), 1695 (C=O), 1641 ($N–H_{bending}$) cm^{-1}

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.72-0.75 (t, *J*=8 Hz, 6H), 1.40–1.53 (m, 2H), 1.58(s, 12H), 1.73–1.85 (m, 4H), 2.06–2.16 (m, 4H), 2.45–2.84 (m, 4H),6.53 (s, 2H), 7.23 (s, 2H), 7.29–7.31 (d, *J*=8 Hz, 4H), 7.43 (s, 2H), 8.45 (s, 2H), 10.80 (s, 2H).

^{13}C-NMR: (DMSO-d_6, 100 MHz): δ 176.3, 173.2, 154.8, 148.3, 139.9, 132.2, 128.0, 126.9, 122.9, 121.7, 118.1, 55.0, 50.0, 46.1, 32.6, 30.2, 29.5, 26.4, 12.1, and 9.3

MS calculated for M+H is 709.36, experimental 709.55. Elemental analysis: C, 67.39; H, 6.62; and N, 11.56

6.5.3 Vibrational Spectroscopy

FT-IR spectra of the gelators and the obtained polymorphic form of the drug BAR and THL were recorded in the frequency range of 600–4000 cm^{-1} in a Perkin Elmer Spectrum 100 ATR instrument.

6.5.4 Powder X-ray diffraction

Powder diffraction patterns were recorded on a PANalytical Empyrean diffractometer using Cu Kα radiation (λ = 1.54Å), tube voltage of 40kV and 40mA current. Intensities were measured from 5° to 50° 2θ with 0.04 rad. Soller silts and an incident beam divergent slit of 1/8°, antiscatter slit of 1/4° and diffracted beam anti-scatter slit of 7.5mm (PIXcel).

6.5.5 NMR spectroscopy

All NMR spectra were recorded using a Varian Mercury 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometer at room temperature using deuterated solvent DMSO-d_6.

6.5.6 Mass spectroscopy

Mass spectroscopies of the compounds were collected using a Thermo-Finnigan LTQ FT mass spectrophotometer. Samples were dissolved in methanol and mass spectra are collected in positive electron spray (ES) mode in case of G-2 and G-3, whereas matrix-assisted laser desorption/ionization (MALDI) was used for G-1. Mass spectra of the gelators are in Appendix (Figure A.11)

6.5.7 Elemental Analysis

Elemental analysis is performed by using an Exeter Analytical Inc. CE-400 elemental analyser. Typical sample size 5-7 mg was used to calculate the C, H and N percentage of the prepared compounds.

6.5.8 Rheology

Rheological experiments were performed using advanced rheometer AR 2000 from TA Instruments. The rheometer was equipped with a chiller (Julabo C). Stainless steel 20 mm plain plate geometry was used to perform the experiments. Samples of the gels were

prepared in different concentration using different solvents in 7 mL glass vials. The obtained gels were transferred on to the centre of the plate of the rheometer using a spatula to minimise shear. The strain sweep measurements were performed to estimate the strain at a constant frequency of 1 Hz. Next, frequency sweep measurements and time sweep measurements are performed in the range 0.1 to 4000 Pa. at a constant stress.

6.5.9 Scanning Electron Microscopy (SEM)

SEM images are obtained on a Hitachi S-5200 field emission scanning microscope. The samples were prepared by applying directly to silicon wafer chips (Agar Scientific) using a stick. Then the samples were kept in vacuum for slow evaporation of solvents. All three samples were coated with 2 nm of Pt and were imaged at 3 KeV and 0.34 nA.

6.5.10 Gel Screening

A typical gel screening of the prepared compounds was carried out at a concentration of 0.5-2 wt. % using a wide range of solvents. Samples were dissolved in 0.5 mL of respective solvent through gentle heating followed by sonication roughly for 1 min. Gels formation observed within a few minutes, but sometimes required several hours, whereas in some cases precipitation of the compounds observed.

6.6 References

[1] Osada, Y. and Khokhlov, A. R. *Polymer gels and networks*. Marcel Dekker, 2002.

[2] Weiss, R. G. *Molecular Gels*. Royal Society of Chemistry, Cambridge, 2018.

[3] Abdallah, D. J. and Weiss, R. G. Organogels and low molecular mass organic gelators. *Advanced Materials*, 12(17):1237-1247, 2000.

[4] Lan, Y., Corradini, M. G., Weiss, R. G., Raghavan, S. R., and Rogers, M. A. To gel or not to gel: correlating molecular gelation with solvent parameters. *Chemical Society Reviews*, 44(17):6035-6058, 2015.

[5] Hirst, A. R., Coates, I. A., Boucheteau, T. R., Miravet, J. F., Escuder, B., Castelletto, V., Hamley, I. W., and Smith, D. K. Low-molecular-weight gelators: Elucidating the principles of gelation based on gelator solubility and a cooperative self-assembly model. *Journal of the American Chemical Society*, 130(28):9113-9121, 2008.

[6] Steed, J. W. Supramolecular gel chemistry: Developments over the last decade. *Chemical Communications*, 47(5):1379-1383, 2011.

[7] Steed, J. W. Anion-tuned supramolecular gels: A natural evolution from urea supramolecular chemistry. *Chemical Society Reviews*, 39(10):3686-3699, 2010.

[8] Draper, E. R. and Adams, D. J. Low-Molecular-Weight Gels: The State of the Art. *Chem*, 3(3):390-410, 2017.

[9] Sangeetha, N. M. and Maitra, U. Supramolecular gels: Functions and uses. *Chemical Society Reviews*, 34(10):821-836, 2005.

[10] Dastidar, P. Supramolecular gelling agents: Can they be designed? *Chemical Society Reviews*, 37(12):2699-2715, 2008.

[11] Das, D., Kar, T., and Das, P. K. Gel-nanocomposites: Materials with promising applications. *Soft Matter*, 8(8):2348-2365, 2012.

[12] Miao, R., Peng, J., and Fang, Y. Molecular gels as intermediates in the synthesis of porous materials and fluorescent films: Concepts and applications. *Langmuir*, 33(40):10419-10428, 2017.

[13] Babu, S. S., Praveen, V. K., and Ajayaghosh, A. Functional π-gelators and their applications. *Chemical Reviews*, 114(4):1973-2129, 2014.

[14] Hirst, A. R., Escuder, B., Miravet, J. F., and Smith, D. K. High-tech applications of self-assembling supramolecular nanostructured gel-phase materials: From regenerative medicine to electronic devices. *Angewandte Chemie - International Edition*, 47(42):8002-8018, 2008.

[15] Serban, B., Stipe, K., Alverson, J., Johnston, E., Priestley, N., and Serban, M. A Controlled Antibiotic Release System for the Development of Single-Application Otitis Externa Therapeutics. *Gels*, 3(2):19, 2017.

[16] Foster, J. A., Piepenbrock, M. O. M., Lloyd, G. O., Clarke, N., Howard, J. A. K., and Steed, J. W. Anion-switchable supramolecular gels for controlling pharmaceutical crystal growth. *Nature Chemistry*, 2(12):1037-1043, 2010.

[17] Zhu, G. and Dordick, J. S. Solvent effect on organogel formation by low molecular weight molecules. *Chemistry of Materials*, 18(25):5988-5995, 2006.

[18] Terech, P. and Weiss, R. G. Low Molecular Mass Gelators of Organic Liquids and the Properties of Their Gels. *Chemical Reviews*, 97(8):3133-3160, 1997.

[19] Foster, J. A., Damodaran, K. K., Maurin, A., Day, G. M., Thompson, H. P., Cameron, G. J., Bernal, J. C., and Steed, J. W. Pharmaceutical polymorph control in a drug-mimetic supramolecular gel. *Chemical Science*, 8(1):78-84, 2016.

[20] Kumar, D. K. and Steed, J. W. Supramolecular gel phase crystallization: Orthogonal self-assembly under non-equilibrium conditions. *Chemical Society Reviews*, 43(7):2080-2088, 2014.

[21] Hilfiker, R. *Polymorphism: In the Pharmaceutical Industry*. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, 2006.

[22] Brittain, H. G. Polymorphism Solvatomorphism 2008. *Journal of Pharmaceutical Sciences*, 99(9):3648-3664, 2010.

[23] Bond, A. D. Polymorphism in molecular crystals. *Current Opinion in Solid State and Materials Science*, 13(3-4):91-97, 2009.

[24] Su, C. S., Liao, C. Y., and Jheng, W. De Particle size control and crystal habit modification of phenacetin using ultrasonic crystallization. *Chemical Engineering and Technology*, 38(1):181-186, 2015.

[25] Chen, J., Sarma, B., Evans, J. M. B., and Myerson, A. S. Pharmaceutical Crystallization. *Crystal Growth & Design*, 11(4):887-895, 2011.

[26] Bernstein, J., Davey, R. J., and Henck, J. O. Concomitant polymorphs. *Angewandte Chemie - International Edition*, 38(23):3440-3461, 1999.

[27] Munshi, P., Venugopala, K. N., Jayashree, B. S., and Guru Row, T. N. Concomitant Polymorphism in 3-Acetylcoumarin: Role of Weak C−H···O and C−H···π Interactions. *Crystal Growth and Design*, 4(6):1105-1107, 2004.

[28] Nangia, A. Conformational Polymorphism in Organic Crystals. *Accounts of Chemical Research*, 41(5):595-604, 2008.

[29] Jiang, S., Ter Horst, J. H., and Jansens, P. J. Concomitant polymorphism of o-aminobenzoic acid in antisolvent crystallization. *Crystal Growth and Design*, 8(1):37-43, 2008.

[30] Zencirci, N., Griesser, U. J., Gelbrich, T., Apperley, D. C., and Harris, R. K. Crystal polymorphs of barbital: News about a classic polymorphic system. *Molecular Pharmaceutics*, 11(1):338-350, 2014.

[31] Torres-Moya, I., Saikia, B., Prieto, P., Carrillo, J. R., and Steed, J. W. High thermal stability, pH responsive organogels of 2 H -benzo[d]1,2,3-triazole derivatives as pharmaceutical crystallization media. *CrystEngComm*, DOI: 10.1039/C8:2019.

[32] Yount, W. C., Loveless, D. M., and Craig, S. L. Strong Means Slow: Dynamic Contributions to the Bulk Mechanical Properties of Supramolecular Networks. *Angewandte Chemie International Edition*, 44(18):2746-2748, 2005.

[33] Cai, X., Liu, K., Yan, J., Zhang, H., Hou, X., Liu, Z., and Fang, Y. Calix[4]arene-based supramolecular gels with unprecedented rheological properties. *Soft Matter*, 8(14):3756-3761, 2012.

[34] Byrne, P., Lloyd, G. O., Applegarth, L., Anderson, K. M., Clarke, N., and Steed, J. W. Metal-induced gelation in dipyridyl ureas. *New Journal of Chemistry*, 34(10):2261-2274, 2010.

[35] Reepmeyer, J. C., Rhodes, M. O., Cox, D. C., and Silverton, J. V. Characterization and crystal structure of two polymorphic forms of racemic thalidomide. *Journal of the Chemical Society, Perkin Transactions 2*, 0(9):2063, 1994.