Chapter 5

In-Situ Gelation as Selective Drug Crystallization Strategy

5.1 INTRODUCTION

The *In-situ* preparation of gels at room temperature by mixing of gelator precursors represents is a promising strategy in the development of the field of low molecular weight gels (LMWG). For most of the LMWGs, use of a stimuli is required to make gels. The most common stimuli involves heating and subsequent cooling, resulting in the formation of a gel during the cooling phase [1]. This requirement criteria of stimuli may create practical challenges for their practical applications. For example, using LMWG systems in oil-spill remedies that require heat-cool as stimuli would not be ideal [2]. Moreover, their always risk of reproducility associated with conditions of stimuli used for gelation. In contrast, the *in-situ* gelation technique provides an efficient alternative route with fewer hurdles and less procedural steps, making it economically viable and beneficial for industries [3].

Weiss group reported a new reversible organogelation process based on the rapid and isothermal uptake of CO_2 by an amine at room temperature to form gels. The process involves bubbling CO_2 through an amine solution for several minutes to form the gel, and can be reversed to solution by bubbling N_2 through the heated gel. The gelator ammonium carbamate was formed *in-situ* during the process [4-5]. Another example of preparing organogelations at room temperature by mixing methyl 2,6-diisocyanatohexanoate and alkylamines as precursors of gelators [6]. In fact, organogels prepared by this *in-situ* approach gelled acetone, ethyl acetate, and acetonitrile that failed to form gel through conventional procedure [7]. Another example of *in-situ* gelation in halohydrocarbon solvents at room temperature uses sodium salt as stimuli [8]. Coupling conventional gel making procedures with *in-situ* gelation strategy widen up the solvent scope of a gelator. At the same time, it provides a unified approach toward dealing with a particular problem.

Use of gels for crystallization dates back to 1896 when Liesegang first observed the periodic precipitation of slightly soluble salts in gelatin [9]. Since then this technique has evolved into a modern tool for controlling the crystallization processes [10-15]. Among other gel systems, there has been a rapid rise in the interest in applying LMWG as crystallizing matrices. This rise is attributed to their simple preparation, ease of recovering the crystallised substrates, and significant influence on controlling nucleation event. Notably, Steed's research group reported the application of LMWG in

pharmaceutical crystallization and highlighted the potential uses of this new versatile tool in pharmaceutical polymorph screening and solid form discovery [16]. In conventional gel crystallisation in LMWG, the drug and the gelator are first dissolved by warming them in the gelling solvent. The clear solution is then cooled to room temperature. During this cooling process, both the gelation and crystallization events start. However, gelation occurs first, forming a gel that subsequently acts as a crystallization matrix, thereby controlling the crystallization outcomes [17-19]. Both the gelation and crystallization events are closely related orthogonal processes, often kinetically resolved because of their different time scale [20]. The gelator-drug interaction is a crucial parameter that determines the crystallization outcomes. For example, at a critical gelator to CBZ (Carbamazepine) ratio the effect of CBZ on gel structure was maximum and fiber bundling in the gel was found to be critically affected [21]. Buendía *et.al* examined the the synergistic and antagonistic effects of the functionalities of drugs on gelation and crystallization in a gel phase crystallization process. Presence of strong interactions among the drug molecules and gelators inhibited both the gelation and crystallization process [22]. Therefore, it is necessary to carefully consider the interactions among the gelator and the drug in prior hand.

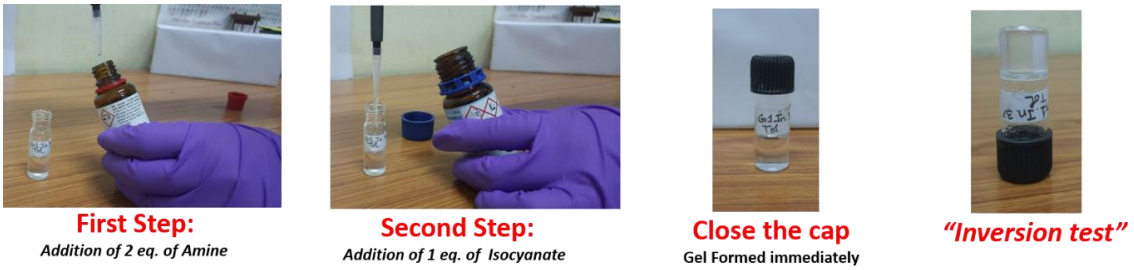
However to deal with this situation where the drug molecules disrupt the gelation process, *in-situ* generation of the gelator in the drug solution might reduce the risk. Moreover, gel preparation at room temperature could be a significant advantage in the gel phase crystallization technique. By eliminating the need for separate gelator preparation, extraction, and use of stimuli for gel making, *in-situ* approach will simplify the process. This work presents an alternative route toward gel phase crystallization for drug molecules.

5.2 RESULT AND DISCUSSIONS:

The synthesis of **G1**, as described in Chapter 2 (ref. to section 2.4.3), involves a simple procedure. It requires the addition of two precursors; aminoacetaldehyde diethylacetal (ADA) and 1,3-bis(2-isocyanatopropan-2-yl)benzene) (ISB) in chloroform at room temperature. In *in-situ* gel synthesis procedure, the solvent used in conventional route is replaced by a suitable gelling solvent. For **G1**, chloroform was replaced with toluene. Gel formation was observed immediately upon mixing the reactants (ADA and

ISB) in the solvents (as shown in Scheme 5.1 5.1 and for details refer to the experimental section 5.4).

It was observed that **G1** require an external stimuli that solubilized it in the gelling solvent to form gel. However, *in-situ* gel synthesis, **G1** is directly prepared in the gelling solvent in solution state. Therefore, dependency of **G1** on stimuli for gel preparation is avoided. Gel screening for the *in-situ* gelation was performed first with those solvents where **G1** form gel using a stimuli. It forms gel in six out of 10 gelling solvents. This results suggest that stimuli have a different role apart from solubilizing **G1** in the gelling solvent.



Scheme 5.1 Pictorial representation of *in-situ* **G1** gel preparation steps

Gel screening was expanded further to explore more solvents that may form gel and the results are tabulated in Table 5.1. Surprisingly, the *in-situ* process forms gels in solvents where **G1** previously failed to form gels using various stimuli (heat-cool, sonication, shaking, and grinding). This is because **G1** has poor solubility in these solvents, and the applied stimuli (heat-cool, sonication, shaking, and grinding) were insufficient to enhance its solubility. However, in the in-situ gelation process **G1** is generated directly in the solvent and due to poor solubility **G1** tried to come out from the solution. This is the driving force for *in-situ* gelation in these solvents. Gel screening results confirm that **G1** does not require any external stimuli for gelation when synthesized *in-situ* in the gelling solvents. A total of 12 different solvent form gel using *in-situ* process. Six of them are new solvents that **G1** failed to form gel using stimuli. This widen up the solvent scope for **G1** from 10 to 16 solvents in total.

Formation of **G1** via *in-situ* process in toluene was confirmed from the ^{1}H and ^{13}C NMR spectra analysis (Figure 5.1). **G1** prepared by *in-situ* process was further characterized by DSC and PXRD to identify the polymorphic phase of **G1**. Characterisitic peak at 5.6° in PXRD pattern and melting peak at 185.1°C in DSC

endotherm of **G1** confirm that **G1** exist as G1 Form I in *in-situ* gel (shown in Figure 5.2 (a) and (b) respectively).

Table 5.1 Gel screening result of *in-situ* gelation process for Gel at 3% w/v

Sl. No.	Name of Solvent	Remark	Sl. No.	Name of Solvent	Remark
1	Toluene	G	6	Acetone	CS
2	o-Xylene	G	7	Acetonitrile	CS
3	m-Xylene	G	8	Dioxane	CS
4	p-Xylene	G	9	Dichloromethane(DCM)	CS
5	Ethyl acetate (EA)	P	10	1,2-Dichloroethane (1,2-DCE)	CS
11	Ethanol	CS	25	Nitromethane (NM)	CS
12	Methanol	CS	26	Nitrobenzene (NB)	G
13	Propanol	CS	27	Ethylene glycol (EG)	P
14	2-Propanol	CS	28	Mesitylene	G
15	Butanol	CS	29	Glycerol	CS
16	2-Butanol	CS	30	Diethyl ether	P
17	t-Butanol	CS	31	Di-isopropyl ether	P
18	Tetrahydrofuran(THF)	P	32	n-Hexane	G
19	Benzyl alcohol	CS	33	n-Heptane	G
20	Pentanol	CS	34	Cyclohexane	G
21	Propane-1,2-diol	CS	35	Cyclohexene	G
22	Acetic acid	CS	36	Hexadecane	G
23	Dimethylformamide (DMF)	CS	37	Petroleum ether	G
24	DMSO	CS	38	Chloroform	CS

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

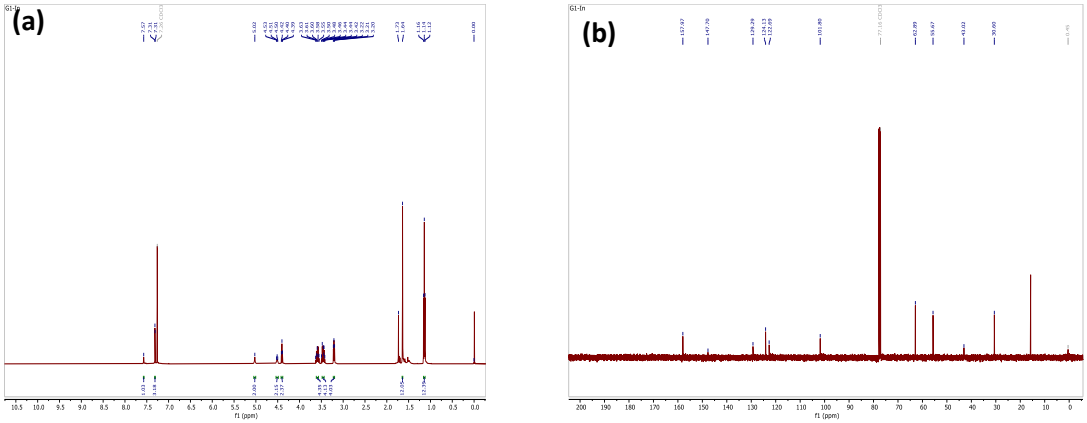


Figure 5.1 ^{1}H (a) and ^{13}C (b) NMR spectra of **G1** obtained from *in-situ* toluene gel

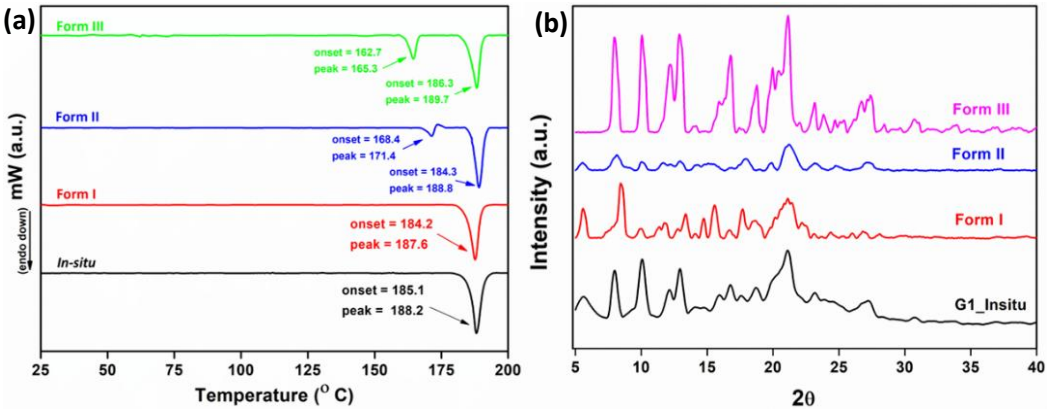


Figure 5.2 DSC endotherm (a) and PXRD pattern (b) of **G1** obtained from *in-situ* approach

Toluene was considered as the gelling solvent for further investigation of the gel state by measuring T_{gel}, and also examine the morphology of gel fibres. T_{gel} of the *in-situ* gel was found to be lower than the stimuli triggered gels (except shaking) at lower concentrations but at higher concentration T_{gel} is comparable with the heat-cool gels (Figure 5.3 a). This observation signifies that concentration gradient (solubility of **G1** Form I is 6.67 mg/ml in toluene) play a deciding role in *in-situ* gelation process. Xerogel of **G1** *in-situ* gel was prepared to investigate the gel fibre morphology. Xerogel was investigated using scanning electron microscopy, FESEM images revealed networks structure of gelator fibres and gels fibres form bundles and these bundles were intertwined by thin fibres of gelator (Figure 5.3 b).

Several attempts were made to measure the M.G.C. of the *in-situ* gel, however, precise determination proved challenging due to various limitations. However, it was observed that gels were stable even at 0.5% (w/v) of **G1**.

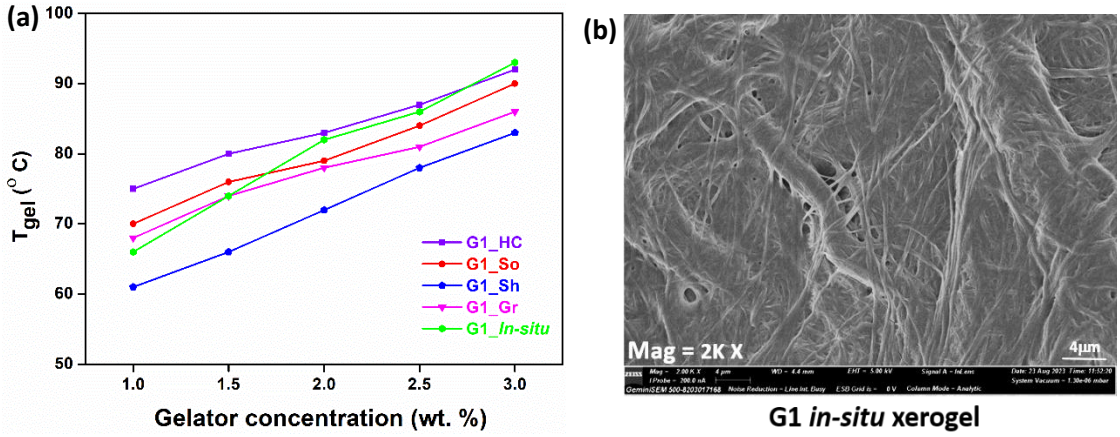


Figure 5.3 (a) T_{gel} vs. gelator concentration (wt. %), (b) FESEM image of **G1** in-situ xerogel

Rheology experiments were performed to investigate viscoelastic nature and stability of the gel. Amplitude sweep results suggest that the *in-situ* **G1** gel is viscoelastic in nature and contain more solid-like property (G′) compared to liquid (G″). Similarly, stability of the gel state is found satisfactory in a wide range of frequencies supported by the frequency sweep results. (Figure 5.4). LVE region for the gel is 0.02% and gel-sol transition occurred at 16% strain value (γ).

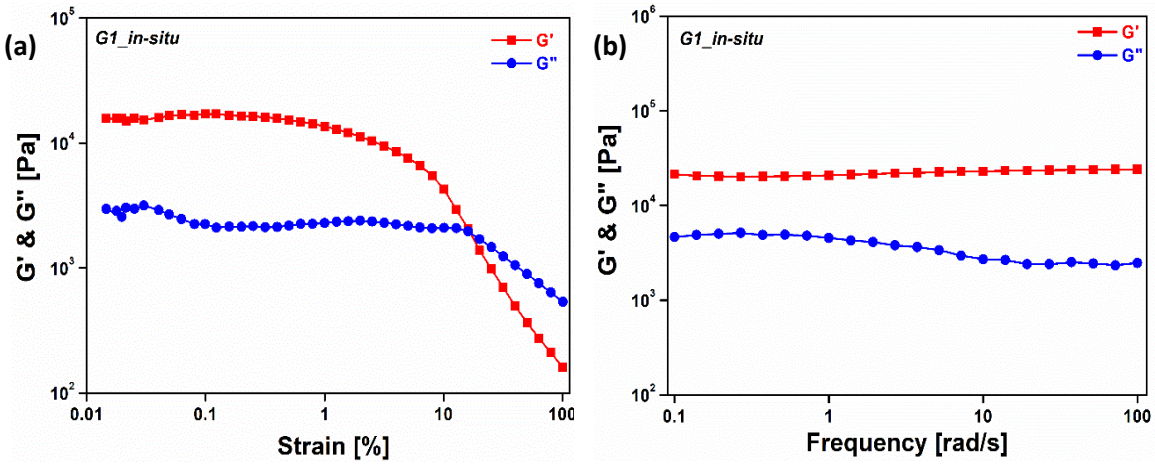


Figure 5.4 Rheology graphs of different oscillatory sweep experiments of **G1** *in-situ* gel (3 wt. %); amplitude sweep (a), and frequency sweep (b). G′ and G″ represent storage modulus and loss modulus

Thus, the *in-situ* gel preparation approach improvised the gel making strategy by skipping multi-steps procedure of gelator synthesis and subsequenct preparation of gel from the gelator. Conventional gel preparation strategy , **G1** requires at least one trigger (stimuli) for making a gel without which no gelation observed. Surprisingly, *in-situ* gel preparation process doesn't require any external trigger, and gelation was instantaneous in most of the gelling solvents . Thus, the *in-situ* approach improvised the gel making

strategy by skipping multi-steps procedure, and eliminating the dependency of the stimuli on gel synthesis. Comparing the benefits between the conventional and *in-situ* gel preparation is shown below in the Figure 5.5.

Figure 5.5 Pictorial representation of comparing the benefits between conventional and *in-situ* gel preparation process

Chapter 4 demonstrated the influence of gelator's polymorphism and stimuli employed for gel preparation on selective nucleation of CBZ. However, few attempts were tried to crystallize APIs such as Flufenamic acid (FLU) in **G1** gel matrix failed as gel was not formed at all. FLU present in gelator solution might interact with gelator molecules which eventually hamper the gelation process. One of the most significant hurdles in gel-phase crystallization is the interference of the gelator with the crystallization process. A common strategy to address this issue involves substituting the original gelator with an alternative that exhibits weaker interactions with the crystallizing substrate. In the *in-situ* gelation process, gelator is generated directly in gelling solvent and gel is formed instantly. This might reduce the interaction time between the gelator and crystallizing substrate. With this idea, an alternate route for gel phase crystallization is designed. Gel phase is prepared by *in-situ* synthesis of **G1** in the drug solution and subsequently drug would crystallized out from the gel phase.

There are many questions for this strategy. Reactants (precursors of the gelator) may react with drug molecule present in the solution. But the idea behind the strategy was that **G1** precursors would react faster to form **G1** than with the drug molecules. Moreover during the *in-situ* gel screening experiments, it was observed that the gel formed instantly in many case. This suggested a significant time lag between the gelation and crystallization events. Four possibilities can be speculated for this strategy, as follows

a) **G1** precursors will react with drug molecules to give side products.

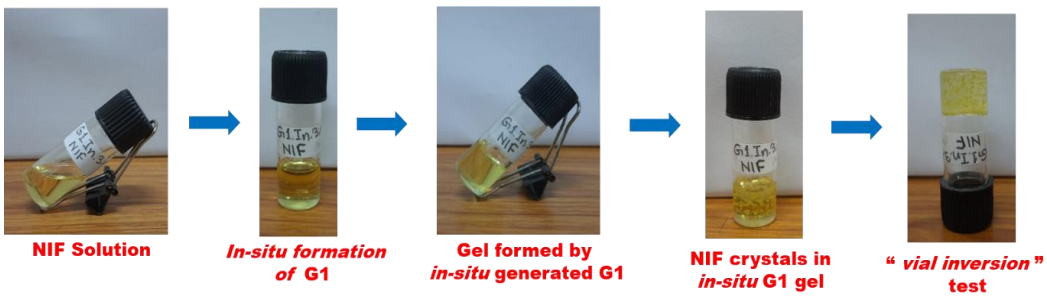
b) *In-situ* gel will form first, followed by crystallization of the API within the gel matrix.

c) *In-situ* generated **G1** will interact with API molecules, disrupting gel formation process.

d) *In-situ* generated **G1** will co-crystallize with the API in the solution.

To proceed with the strategy of *in-situ* gel phase crystallization, Nifedipine (NIF) was chosen based on functional groups present (shown in Scheme 5.2) in the molecular structure and crystallization behaviour in toluene (moderate saturation point). NIF is a calcium channel blocker used to treat high blood pressure and to treat angina [23]. NIF is highly polymorphic in nature due to its conformational flexibility. Six polymorphs NIF is reported till date and α Form is the thermodynamically most stable one [24].

For *in-situ* gel phase crystallization, precursors of **G1** were added to the NIF solution (in toluene) prepare the gel matrix (for detailed procedure refer to experimental Section 5.4). Gel formation process was formed within few minutes and NIF crystals grown in the gel within 12 h. The complete strategy of NIF crystalli in an in-situ **G1** gel was shown below Scheme 5.2. Initial observation revealed that **G1** precursors don't react with the drug molecules and **G1** formed transformed into gel instantly. The rapid *in-situ* formation of the **G1** gel prevents potential reactions between the gel precursors and drug molecules present in the gelling solvent. Consequently, NIF crystallize inside the gel matrix formed. NIF crystals were recovered from the gel by adding 2-3 drops of acetic acid and followed by heating at 40 °C until gel breaks completely to sol. Then, the sol was immediately filtered out to get the NIF crystals. PXRD pattern and unit cell parameters of NIF crystals confirmed the formation of α Form in the gel. Identical solution phase crystallization of NIF yielded α Form.



Scheme 5.2 Pictorial representation of steps in crystallization of drug (here Nifedipine) in *in-situ* **G1** gel

Table 5.2 Unit cell parameters of NIF crystals obtained from gel and solution crystallization

Sl. No.	Crystallization Condition	Unit cell parameter	Remarks [25-26]
01	*In-situ* **G1** gel	a = 10.92(4) Å; α = 90° b= 10.32(3) Å; β = 92° c = 14.84(7) Å; γ = 90° volume = 1683 Å^3	α Form
		a = 10.81(4) Å; α = 90° b= 10.38(3) Å; β = 92° c = 14.81(4) Å; γ = 90° volume = 1622 Å^3	
02	Solution phase	a = 10.98(1); α = 90° b= 10.34(4); β = 92° c = 14.83(1); γ = 90° volume = 1656 Å^3	α Form
		a = 10.72(6); α = 90° b= 10.12(2); β = 92° c = 14.74(1); γ = 90° volume = 1672 Å^3	

Further inspect for the applicability of the *in-situ* strategy, seven other drug molecules (APIs) with varied functionalities (limited to the drugs that soluble in toluene at room temperature or at elevated temperature) shown in Figure 5.6 were investigated for gel phase crystallization. Out of these seven drugs, Tolfenamic acid (TFA), Mefenamic acid (MFA), Carbamazepine (CBZ) and Ethenzamide (ETZ) were successfully crystallized in the **G1** *in-situ* gel (Figure 5.7).

Problems encountered in conventional gel-phase crystallization can be overcome by this alternative approach of *in-situ* gel-phase crystallization. Even in the presence of drugs that potentially interact with the gelator, disruption of the gelation process is not observed in this novel approach. However, this is not a general statement, and careful consideration must be given for each new drug prior to crystallizaiton in *in-situ* gels.

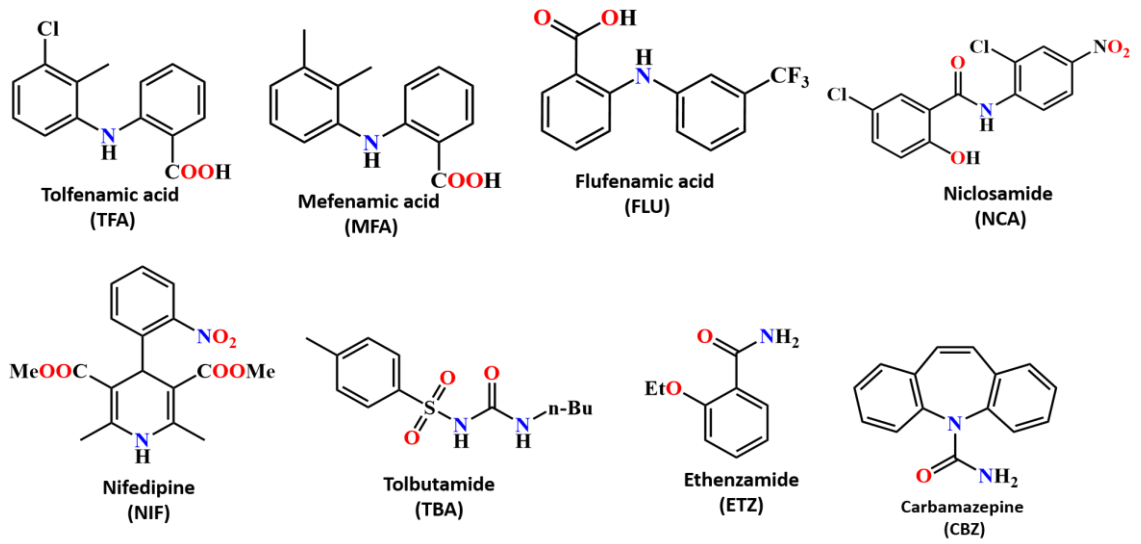


Figure 5.6 Chemical structures of different drugs used in the crystallization experiment

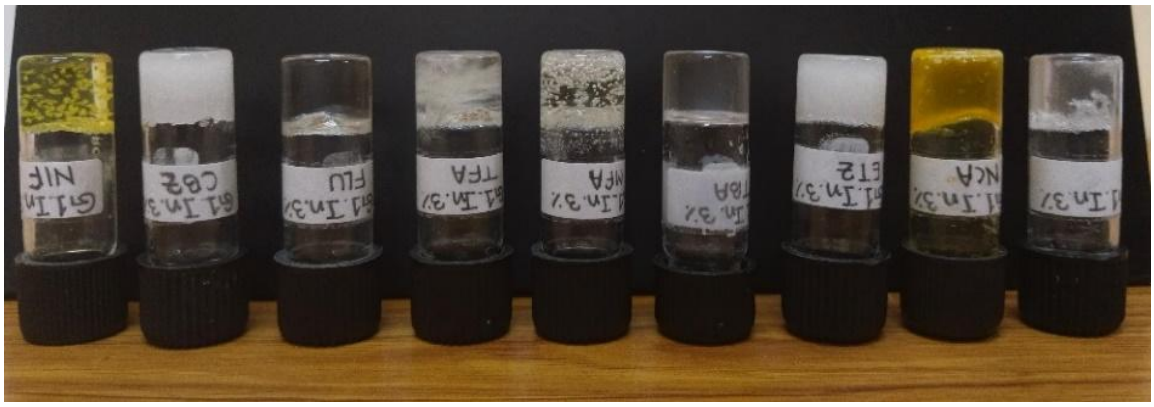


Figure 5.7 Picture of "inverted-vial" test for drugs crystallized in **G1** *in-situ* gel showing stability of the gel phase

For an example Niclosamide (NCA) crystallization in *in-situ* gel, it was observed that niclosamide (NCA) reacted with the amine (precursor of **G1**) immediately after addition to form a reddish-brown coloured compound which may because of salt formation [27]. When isocyanate (other precursor of **G1**) was subsequently added to complete the process, a partial gelation formed. But the resulting gel was compromised by the presence of the impurity (NCA-amine product). The reddish-brown impurity was further analysed with PXRD and DSC (Figure 5.8). Results suggested that it contained impurity along with NCA. To prevent this side reaction, sequence of precursor addition was reversed and isocyanate was added first followed by the amine. This prevented the side reaction and NCA was crystallized in the gel (Figures 5.9).

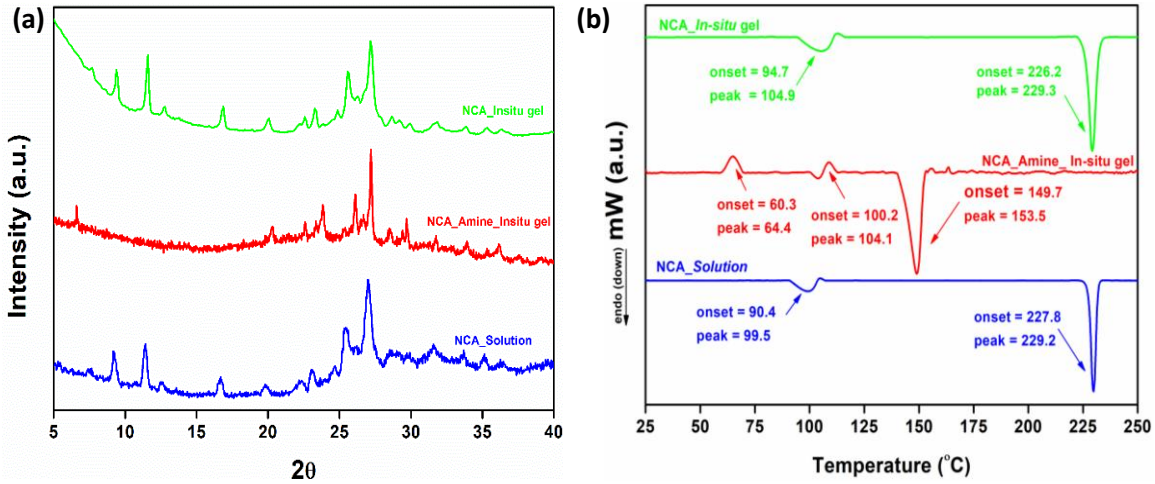


Figure 5.8 PXRD pattern (a) and DSC (b) of NCA obtained from solution, in-situ gel (amine added first), and in-situ gel (isocyanate added first)

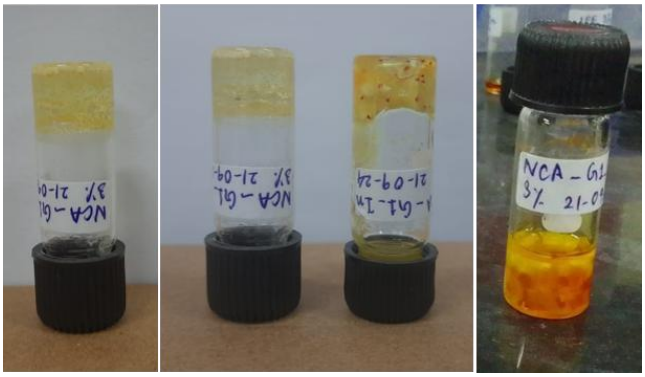


Figure 5.9 Niclosamide (NCA) crystallization in G1 in-situ gels following two different processes. From left to right: 'vial inversion' of NCA crystallized in **G1** in-situ gel made by addition isocyanate first followed by amine; 'vial inversion' test of both gels made by both process and in-situ gel of **G1** made by addition of amine first followed by isocyanate

In case of Tolbutamide (TBA), and Flufenamic acid (FLU), gel formed only at low drug concentration (up to 20-30 mg/mL). However, crystallization was not achieved due to their high saturation point. By increasing the drug concentration to attain the saturation point hindered gel formation, likely due to interactions between **G1** and the drug molecules (Figure 5.10).

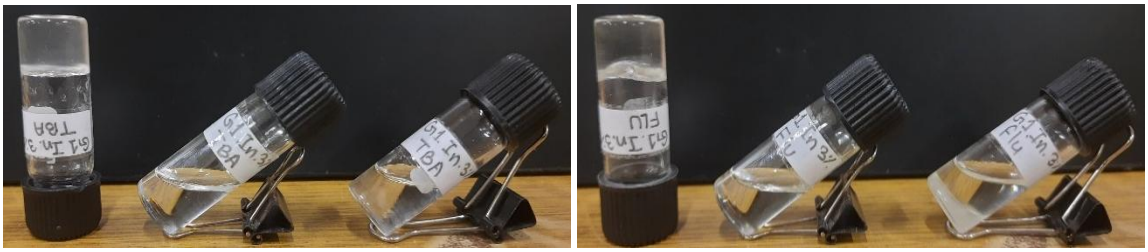


Figure 5.10 Picture of "vial-inversion" test of in-situ gel containing TBA (a) and FLU (b)

To compare with the *in-situ* strategy for crystallization, conventional gel phase crystallization were carried out by preparing **G1** using heat-cool as stimuli under similar conditions. Although conventional gel phase crystallization resulted drug crystallized in the gel matrix for CBZ, NIF, and ETZ; but interfer with the gelation process in the case of TFA, MFA, FLU, and NCA (Figures 5.10). For TBA, gel formation occurred, but crystal growth was not observed, likely due to an inability to reach the saturation point.

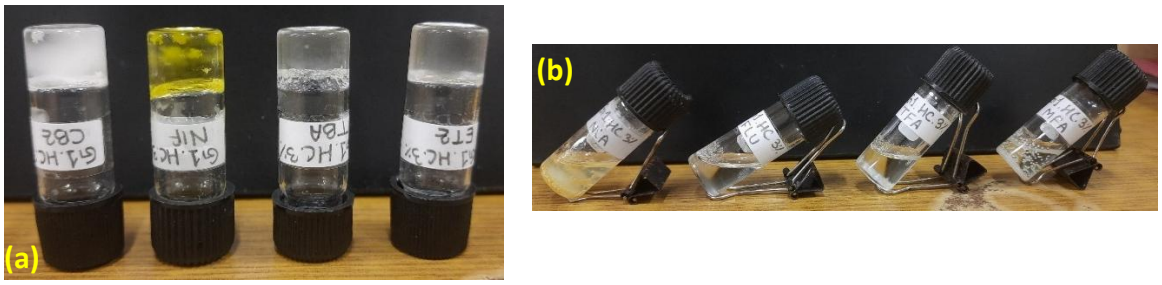
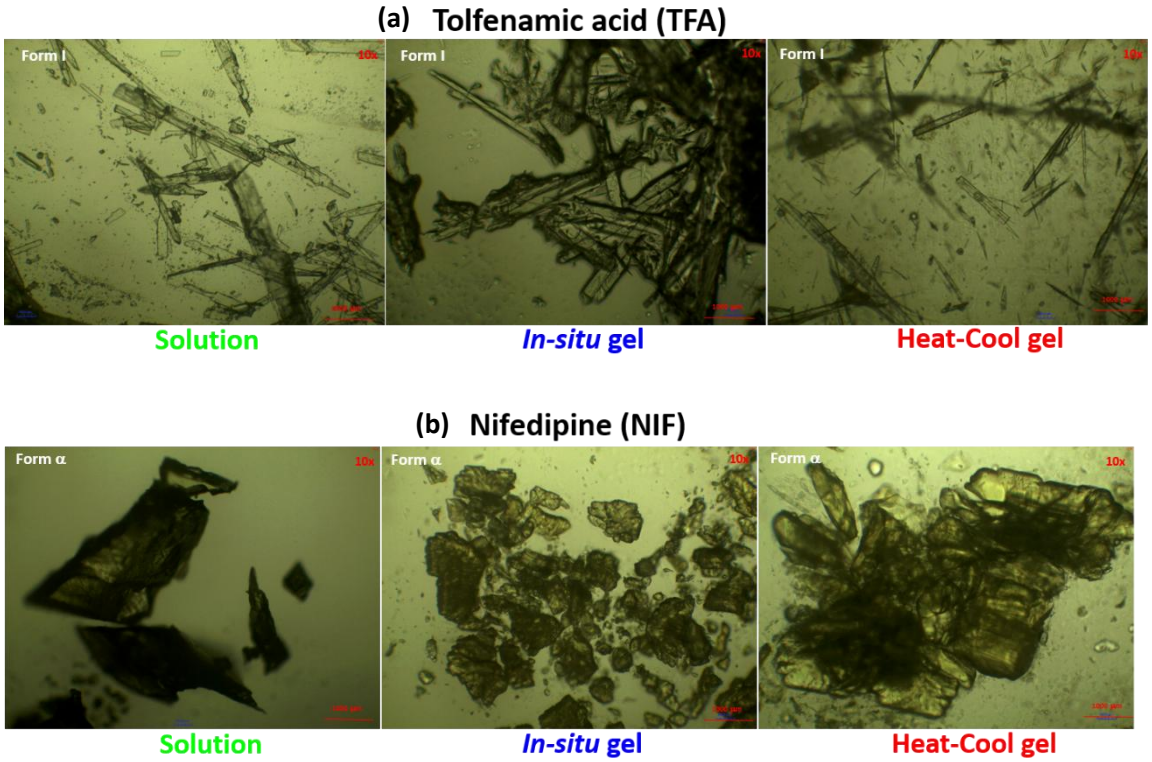


Figure 5.11 Picture of "vial-inversion" test for convention gel phase crystallization (heat-cool) containing drugs (a)CBZ, NIF, TBA, ETZ and (b) NCA, FLU, TFA, MFA

Crystals were recovered by following the procedure discuss in the above section and were observed under microscope for visual inspection and microscopic images were caputred and shown in Figure 5.11.



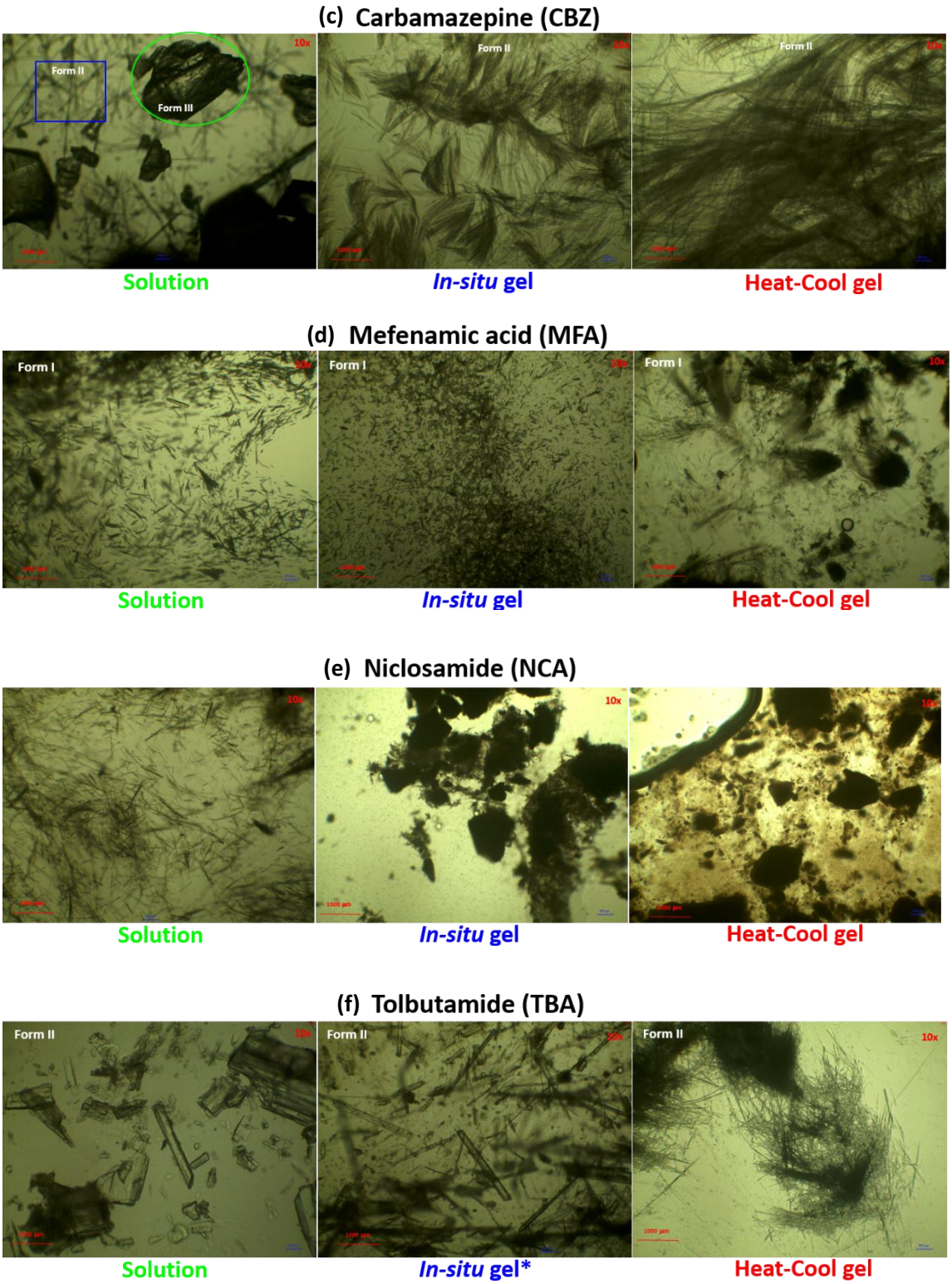


Figure 5.12 Microscopic images of crystals extracted from solution, in-situ gel, and heat-cool gel phase crystallizations. *denote gel was not formed and crystals growth from the solution containing gelator

As shown in Figure 5.13, SEM images of xerogels containing drug crystallized in the gel matrix. These images suggest that crystals were grown on the surfaces of the gel fibres.

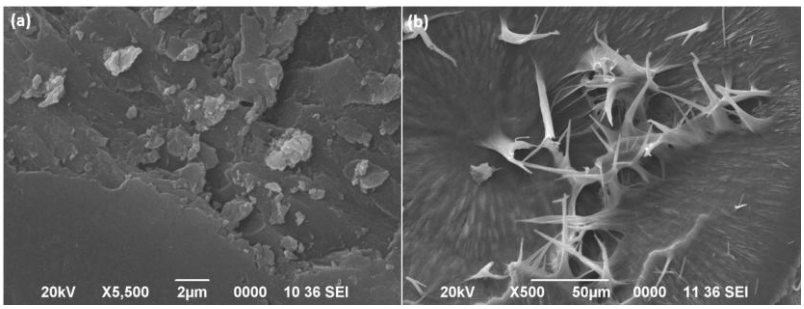


Figure 5.13 SEM images of xerogels of **G1** *in-situ* gel containing: (a) MFA and (b) NCA

PXRD patterns of the crystal recovered from the both gel phase crystallization and solution phase reveals that both solution and in-situ gel phase crystallization resulted the same polymorphic form except CBZ. CBZ in solution crystallized out as a mixture of polymorphs (CBZ Form II and III, where CBZ Form II transformed into CBZ Form III with time). Whereas in *in-situ* gel phase resulted CBZ Form II and also stabilized the polymorph to prevent the polymorphic transition to CBZ Form III. No change in polymorphic state in the gel phase crystallization can be inferred from the fact that they don't showed concomitant crystallizations in the gelling solvent (toluene) except CBZ.

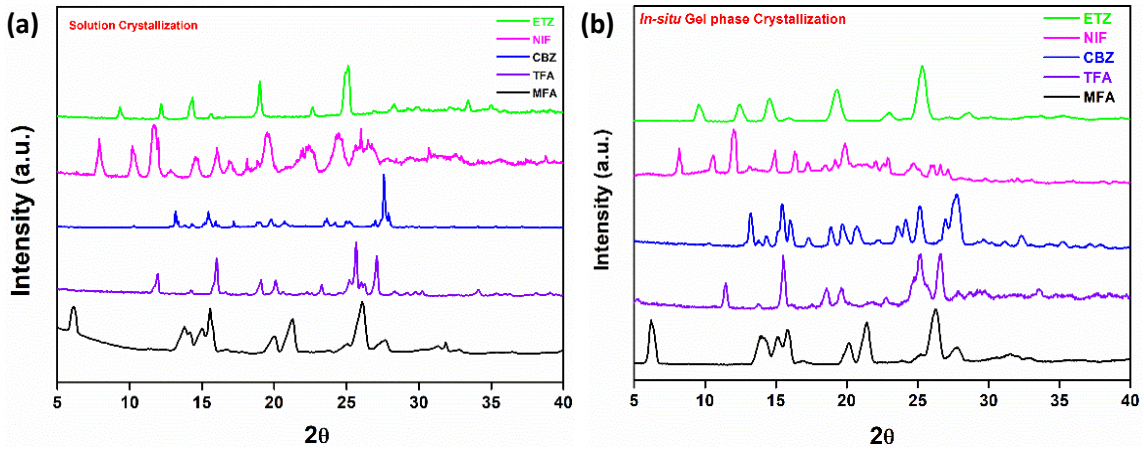


Figure 5.14 PXRD patterns of crystals of drug molecules obtained from (a) solution, and (b) *in-situ gel*

5.3 SUMMARY

A novel *in-situ* gel phase crystallization strategy was successfully developed and the utility of the strategy was examined for crystallizing different API. Eight drug molecules with varied functionalities were tested and results are discussed. Although no change in the polymorphic phase were observed in gel phase compared to solution except for CBZ. In case of CBZ, polymorphic transition from CBZ Form II to III was stopped in the gel phase crystallization. Interactions of **G1** precursors and **G1** itself with

the drug molecules were discussed, and measures to avoid such interactions were also stated. To effectively employ this *in-situ* approach, two crucial aspects must be carefully considered: (a) the reaction leading to gelator formation should occur rapidly at room temperature or at the elevated temperature that used for dissolve the drug molecule in the gelling solvent and the gelator precursors should not interact with the drug molecules; (b) crystallization event interfer with the gelation process, a time lag between the two is essential. Gel formation must occur more rapidly than crystallization, otherwise crystal growth will hinder gelation process, leading to a weaker gel. Gel phase crystallization offers significant advantages, and this strategy will further streamline the process by reducing steps and time consumption.

5.4 EXPERIMENTAL SECTION

5.4.1 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.

5.4.2 Instrumental Details: Refer to experimental section 2.4.2 in chapter 2.

5.4.3 Gel preparation method:

I. *In-situ* gel preparation:

For *in-situ* **G1** gel preparation, mix stoichiometric amount of the **G1** precursors aminoacetaldehyde diethyl acetal (ADA) and 1, 3-bis (2-isocyanto-2-propyl) benzene (ISB) in the gelling solvent (for example toluene) to form the gel instantly without any application of external stimuli. To prepare 3% (w/v) *in-situ* **G1** gel in 1.5 mL toluene, 21 μL of ISB and 27 μL of ADA added to 1.5mL toluene taken in a glass vial (size: 5 mL) and gel formed instantly.

II. Heat-Cool gel preparation:

Required amount of **G1** (polymorph **G1** Form I) and solvent (e.g. toluene) were mixed in a glass vial and close the cap tightly. The glass vial was then heated on a hot plate till a clear solution was observed. The clear solution containing **G1** was kept

undisturbed and allowed to cool down to room temperature. During the cooling process gel formation started.

5.4.4 Gel screening:

Gel screening was done by following the *in-situ* gel preparation procedure in different solvents. Initial screening was done at 2% w/v of **G1** in the gelling solvents and for other solvents, screening were done at 1% w/v of **G1**.

5.4.5 Procedures for crystallization of API:

I. Solution phase crystallization:

Required amount of API was added to a glass vial containing toluene and heated until a clear solution obtained. Then the vials were kept undisturbed to allow crystal growth.

II. Conventional gel phase crystallization of API:

Required amount of API and gelator (i.e. **G1**) were added to a glass vial containing toluene and heated until a clear solution obtained. Then the vials were kept undisturbed to allow the gel and crystal growth.

III. In-situ gel phase crystallization of API:

Required amount of API was added to a glass vial containing toluene and heated until a clear solution obtained. To this clear solution, **G1** precursors aminoacetaldehyde diethyl acetal (ADA) and 1, 3-bis (2-isocyanto-2-propyl) benzene (ISB) were added and kept undisturbed to allow the gel and crystal growth.

5.4.6 Measurement of Tgel of gels: Refer to experimental section 2.4.8 in chapter 2.

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