Chapter 4

Control Drug Polymorph Nucleation in Gel Matrix

4.1 INTRODUCTION

Chapters 2 and 3 delve into the comprehensive development of the bis-urea LMWG **G1**. This led to a series of gel prepared from **G1**, employing various stimuli and polymorphic phases of the gelator. The one of the major goal in developing **G1** is its application as a versatile media for pharmaceutical crystallization. Crystallization is the most widely used purification technique in both laboratories and industries [1]. Crystallization processes are done through several methodologies including cooling, evaporative, reactive, solvent diffusion, vapor diffusion, sublimation, and melt crystallization [2]. Over the centuries, this technique evolved, adapting to overcome the diverse challenges it faced. Many other challenges like controlling crystal size distribution, polymorphic form, morphology, purity, flowability, compactibility, solubility, and dissolution rates in crystallization continues to motivate researchers worldwide [3].

Various theories have been proposed to explain the crystallization process, with the two-step model being the most widely accepted which consist of nucleation as first step and second step is the crystal growth from the nucleus [4]. Nucleation step is crucial as molecules arrange themselves into an ordered cluster in solution which act as nuclei for the subsequent growth into a crystals. Molecules may have different possible arrangements in the nuclei based on their intermolecular interactions, packing, conformations etc. Therefore different types of nuclei may formed in the solution which ultimately led to different crystalline phases of the same molecules. This phenomenon is known as polymorphism and different crystalline phases are known as polymorphs [5]. Polymorphs show different physical and chemical properties such as color, stability, morphology, melting point etc [6]. Polymorphism constitutes one of the most significant challenges encountered in the field of crystallization.

Polymorphism in drugs can significantly influence their physicochemical properties, including solubility and dissolution rate. These variations directly impact the bioavailability and stability of the drug substance [7]. Pharmaceutical industries recognize the profound impact of polymorphism on both their operational performance and financial success of their drug development programmes [8,9]. Different techniques have been used for polymorph screening and preferential crystallization of desired polymorphs which also include gel phase crystallization [10-17]. Gel matrices employed for crystallization can be either polymeric or supramolecular (mainly LMWG) in nature.

Fibrillar networks formed by low-molecular-weight gelators (LMWGs) can serve as nucleation templates, guiding crystal growth. By incorporating functional groups into the gelator structure that mimic the substrate, the crystallization process can be effectively modulated [18-20].

Sometimes, polymorphic systems crystallize simultaneously into multiple forms. This phenomenon is known as concomitant crystallization and the polymorphs are called concomitant polymorphs [21]. This may be advantageous as multiple forms of a compound can be obtained from a single crystallization experiment. But in pharmaceutical industry, purity of the drug polymorph is utmost important. As it may alter the efficicacy of the drug and unnessarily increase the drug dose amout. Therefore it is important to control the concomitant crystallization of polymorphs to selectively crystallize the desired polymorph. Few examples of drugs that give concomitant polymorphs: Disopyramide crystallized into two forms (modifications I and II) [21]; three polymorphs of Tolbutamide from ethanol solution [22]; four polymorphs of Barbital from ethanol solution [18]. Carbamazepine (CBZ) is concomitantly crystallized in selected solvents and the crystallization outcomes depend on nature of the solvent and degree of supersaturation [23]. CBZ also show polymorphic transition from metastable form to thermodynamically stable form.

CBZ (shown in Figure 4.1) is an anticonvulsant used to treat epilepsy and trigeminal neuralgia. CBZ exhibits significant polymorphism, with its polymorphs primarily categorized as packing polymorphs. Form II of CBZ (here as CBZ Form II) is solvate and other three are anhydrous; all of them exhibit dimeric molecular arrangements [24-26]. Recently, fifth polymorph of CBZ is reported which is catemeric in nature. The fifth form (CBZ Form V) of CBZ was selectively formed by templating the growth of carbamazepine from the vapour phase onto the surface of a crystal of dihydrocarbamazepine Form II [27]. The polymorphic behaviour of carbamazepine makes it a widely used model system for studying and controlling polymorphic behaviour during crystallization processes.

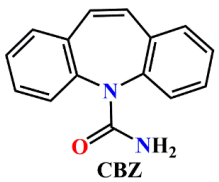

Figure 4.1 Structure of Carbamazepine (CBZ)

Table 4.1 Preparation techniques for different polymorphs of CBZ

Sl. No.	CBZ Polymorph	Procedure	Reference
01	CBZ Form I	From melt crystallization	[23, 26]
02	CBZ Form II	Solution phase crystallization from ethanol solution at 5 °C	
03	CBZ Form III	Solution phase crystallization from slow evaporation ethanol solution	
04	CBZ Form IV	Solution phase crystallization from methanol solution containing small amount of hydroxypropylcellulose	[24]
05	CBZ Form V	Vapour phase crystallization onto the surface of a crystal of dihydrocarbamazepine form II.	[27]

Gel-phase crystallization also uses CBZ functioned as a model system for various crystallization studies. For example, Steed and his co-workers reported the application LMWG as crystallization matrix for drug molecules including CBZ. By adjusting the concentration of CBZ, both CBZ Form II and III could selectively crystallized. Higher concentrations of CBZ result in CBZ Form II (needles) and lower concentrations give CBZ Form III (blocks) in the gel as former is the kinetic form and the later one is the thermodynamic form [28]. Aparicio et. al used a pair of a chiral and achiral gelator to prepare gels and their influence on the crystallization outcomes of different drug molecules including CBZ. The CBZ crystals obtained from the gel of achiral gelator corresponds to CBZ Form III. Whereas the crystals obtained inside organogel of corresponding to chiral gelator and organogel formed upon both chiral and achiral gelator in a 9/1 ratio showed peaks corresponding to a mixture of CBZ Form II and III respectively [29]. Dawn et. al investigated the effect of crystallizing substrate (CBZ) on the properties of gel matrix used for the purpose. The concentration of the gelator and its relative proportion to CBZ are crucial factors in controlling the competitive nucleation events involving gelation and crystallization [30]. Therefore it is important to design a robust gel matrix that control the nucleation of CBZ. Also to identify the gelator: drug ratio where drug will have least impact on gel's properties.

In this chapter, how the polymorphic phases of a gelator affect the crystallization outcomes of pharmaceutical crystallization in gel matrix considering CBZ as model system.

4.2 RESULTS AND DISCUSSION

Crystallization of CBZ from toluene resulted needle shape crystals (CBZ Form II) at first which then slowly transform to block shaped crystals (CBZ Form III). Microscopic image of CBZ crystals obtained from toluene showing the presence of both forms is showin in Figure 4.2. Both polymorphs are characterized by PXRD and DSC to confirm the identification the polymorphs.

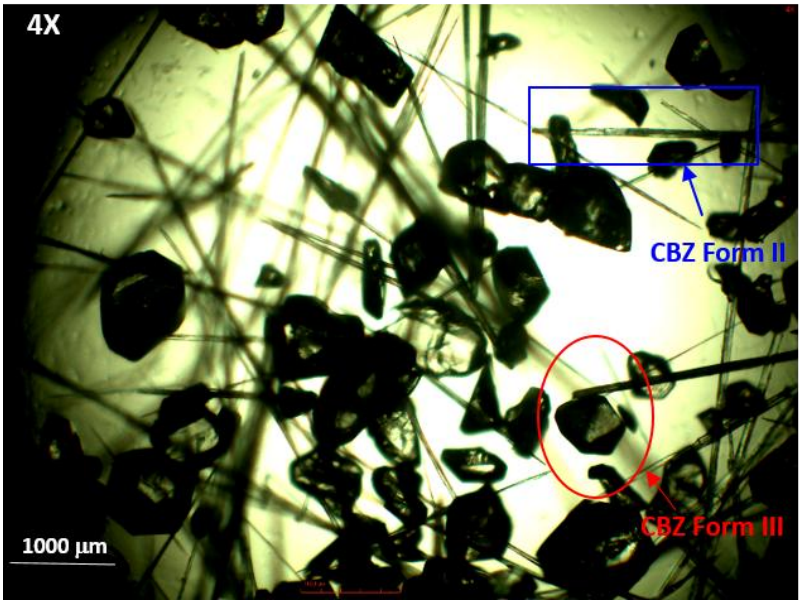

Figure 4.2 Microscopic image of CBZ Form II (needle shape) and CBZ Form III (block shape) obtained from crystallization in toluene

By comparing characteristic peaks in the PXRD patterns of CBZ polymorphs with the that of crystals obtained form toluene, polymorphs can be easily identified. As shown in Figure 4.3a, peak positions in 8.7, 13.4, 18.7, and 24.5 (2θ values) confirm formation of CBZ Form II whereas peaks at around 15.4, 19.6, 25.2, and 27.4 (2θ values) identified as CBZ Form III. Similaryl, by matching temperature for phase change DSC endotherms CBZ polymorphs can be identified without any confusion. Figure 4.3b is the DSC endotherms of CBZ polymorphs. Endotherm (blue colored) showed two endothermic peaks at onset values at 161.1 °C and 187.9 °C represent the polymorphic transition of CBZ Form II to Form I and melting of CBZ Form I respectively. The other endotherm (red colored) showed two endothermic peaks and one exothermic peak. First endothermic peak at 170.2 °C corresponds to melting of CBZ Form III, which immediatel recrystallized into CBZ Form I (corresponds to the exothermic peak) and the second endothermic peak corresponds melting of CBZ Form I at onset value 188.1 °C.

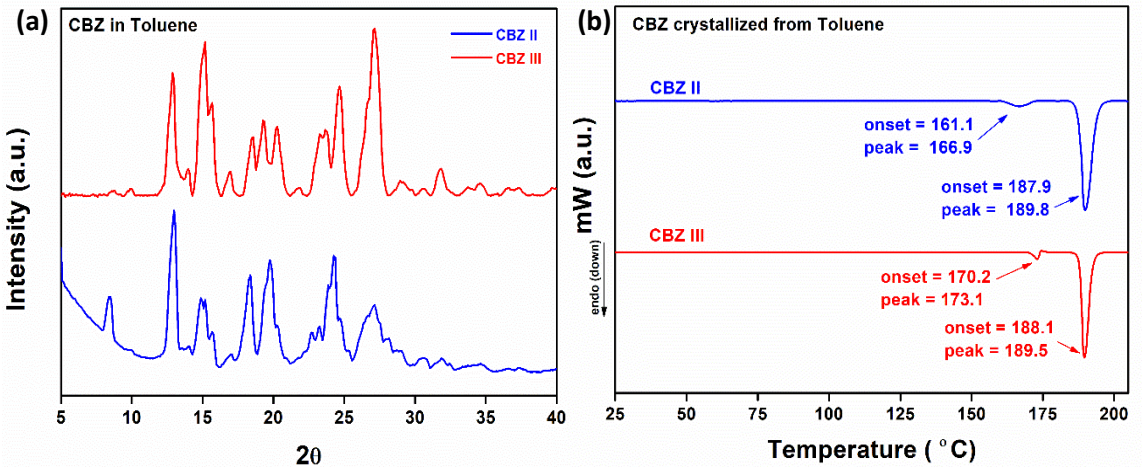

Figure 4.3 (a) PXRD patterns and (b) DSC endotherms of CBZ polymorphs obtained using toluene

For the gel-phase crystallization of CBZ, **G1** was synthesized (ref. to section 2.4.3) and then all the three **G1** polymorphs were isolated from solution recrystallization using the procedure described in Chapter 2 (ref. to section 2.4.5). The crystallization of CBZ in **G1** gel involves two steps. In the first step, CBZ solution in toluene (20 mg/ml) was prepared at elevated temperature. In the second step, 2 % (w/v) **G1** was added followed by application of different stimuli to form the gel (ref. to section 4.4.3). The ratio of CBZ:**G1** was optimized and found that CBZ in 20 mg/ml was optimum concentration where **G1** retain its gel state. Therefore, the crystallization of CBZ was performed in all the three polymorphs of **G1** by employing different stimuli. Four stimuli heat-cool, sonication, shaking, and grinding were used to prepare gels from **G1** Form I. In the crystallization experiments, gel formed first followed by crystallization of CBZ inside the gel matrix. From 'vial inversion' test (Figure 4.4), it is evident that **G1** gels were stable even in the presence of CBZ. The microscopic images of CBZ crystals grown inside the gels of **G1** Form I is shown in Figure 4.5.

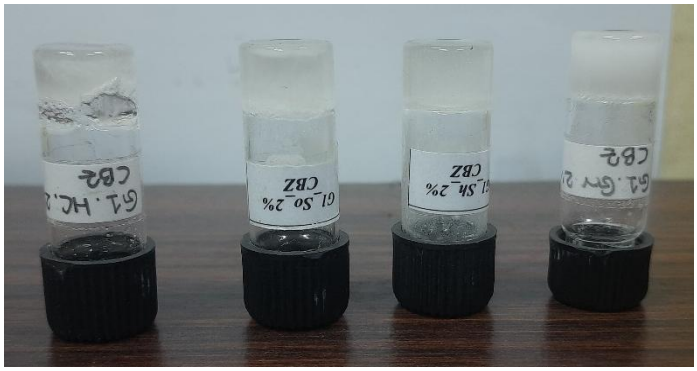

Figure 4.4 'vial inversion' test of **G1** Form I gel prepared by different stimuli containing CBZ crystals

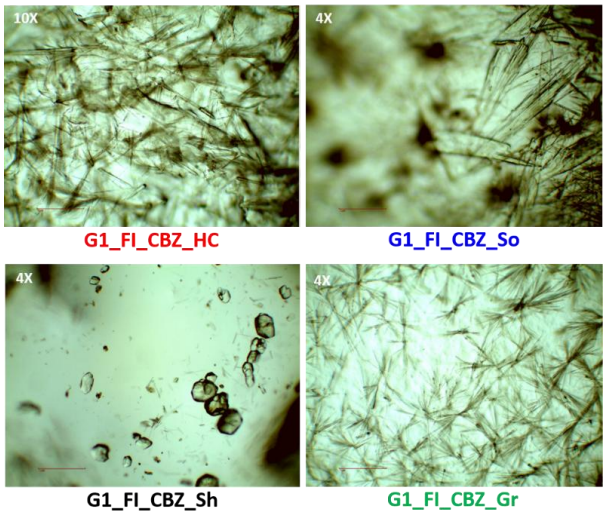

Figure 4.5 Microscopic images of CBZ crystals in gels of **G1** Form I prepared by different stimuli

CBZ crystals were recovered from the gels by adding 2-3 drops of acetic acid followed by slight warming the gel to convert it into the sol phase. Then immediately crystals were recovered by simple filtration. For analysis of CBZ crystal outputs, multiple crystallization batches were carried out under identical condition and crystals were collected. At first, three crystals randomly selected from each type of gel were used to check unit cell parameters. Unit cell parameters of the crystals suggested that CBZ Form II is obtained in **G1** Form I gels prepared by heat-cool, sonication and grinding as stimuli. Moreover gel phase prevented the polymorphic transition from CBZ Form II to III. Whereas unit cell parameters of crystals obtained from gel formed by shaking found to be CBZ Form III exclusively. Further phase purity of the crystals obtained from these gels were characterized and confirmed by comparing PXRD and DSC results with individual CBZ polymorphs (PXRD pattern and DSC endotherms are shown Figure 4.6).

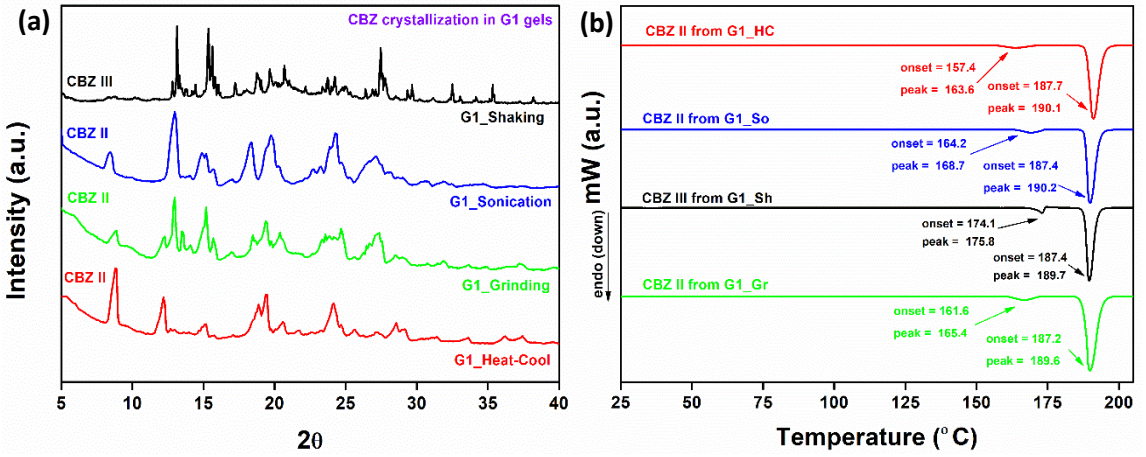

Figure 4.6 (a) PXRD patterns and (b) DSC endotherms of CBZ crystals obtained from **G1** Form I gels prepared by different stimuli

The presence of CBZ crystals in the gel matrix intend to influence the rheological properties of the gel. Therefore rheological properties of the gels used for crystallization were examined using amplitude and frequency sweep rheology experiments. Figure 4.7 shows two different amplitude sweep rheology graphs of **G1** Form I gels one with CBZ crystals and other is without crystals. Gap between G′ and G″ is decreased for gels containing CBZ crystals compared to gels no CBZ crystals.

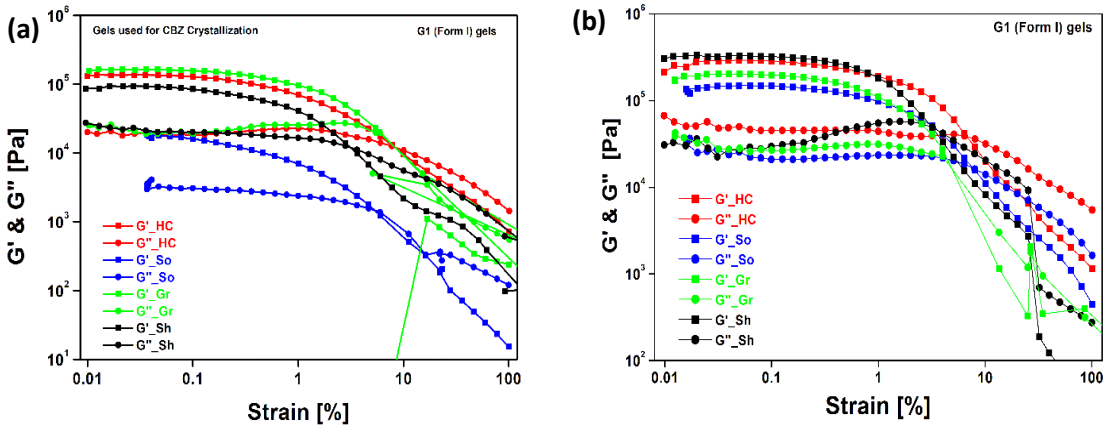

Figure 4.7 Amplitude sweep rheology of **G1** Form I gel prepared by different stimuli (a) with CBZ and (b) without CBZ under constant frequency of 10 Hz. G′ and G″ denote storage and loss modulus. Heat-cool (HC), sonication (So), shaking (sh), and grinding (Gr)

Similarly, the incorporation of CBZ in gels drop highest values of the G′ and G″ which mean that viscoelasticity of gels reduced. The viscoelastic property of **G1** Form I gels formed by sonication decreased drastically in presence of CBZ. This is because of incorporation of CBZ crystals in the gel fibers during the evolution of the gel state from sol phase. Frequency sweep experiments (as shown in Figure 4.8) demonstrated the stability of these gels across the frequency range from 0.1 to 100 rad/s. Both rheological experiments collectively demonstrate that the presence of CBZ within the gels reduces their viscoelastic properties while maintaining their overall structural stability.

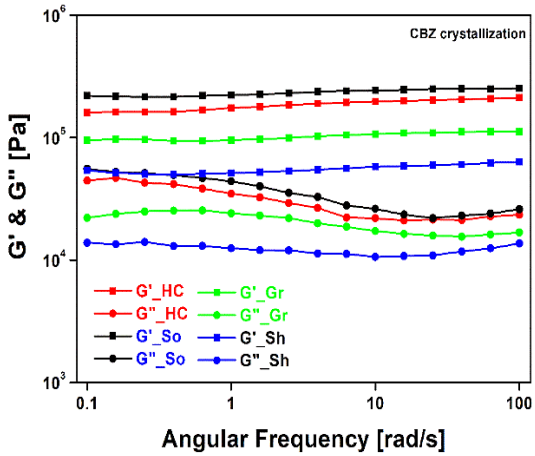

Figure 4.8 Frequency sweep rheology of **G1** Form I gels prepared by different stimuli containing CBZ crystals. G′ and G″ denote storage and loss modulus. Heat-cool (HC), sonication (So), shaking (sh), and grinding (Gr)

To investigate the influence of CBZ crystals in gel fibre morphology, xerogels of these gels were prepared. FESEM images of the xerogels were recorded for morphological analysis reveal changes occure in gel fibre morphology as shown in Figure 4.9.

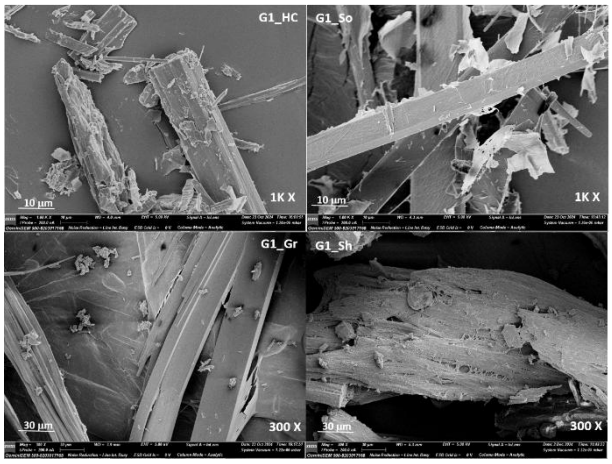

Figure 4.9 FESEM images of xerogels of **G1** Form I gels prepared by different stimuli used for CBZ crystallization. Heat-cool (HC), sonication (So), shaking (sh), and grinding (Gr)

In heat-cool, sonication, and grinding gels, entrapment of CBZ crystals within the gel fiber network were observed. In contrast, shaking gels exhibited nucleation of CBZ crystals on the gel fiber network. The presence of CBZ crystals significantly altered the morphologies of the gel fibers. Thus **G1** gels prepared by different stimuli controlled the CBZ crystallization event. All these gels formed by **G1** Form I. Again, remaining two polymorphic phases of **G1** responded to heat-cool stimuli only to form stable gels. Therefore, gels formed by the **G1** polymorphs can be utilized to investigate the influence of gelator's polymorphic phases on the outcomes of CBZ from gel phase crystallization. As M.G.C. value of **G1** Form II is higher than the other two forms (M.G.C. is 3.8 % w/v for **G1** Form II) and concentration of **G1** Form II for gel preparation is 4 % w/v (other two gels prepared at 3 % w/v). All the three gels were found stable in presence of CBZ as evident from 'vial inversion' test (shown in Figure 4.10).

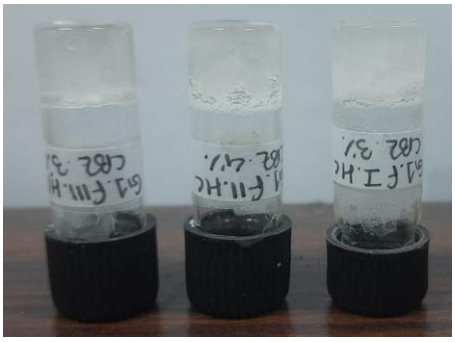

Figure 4.10 'vial inversion' test of gels prepared from three polymorphs of **G1** containing CBZ

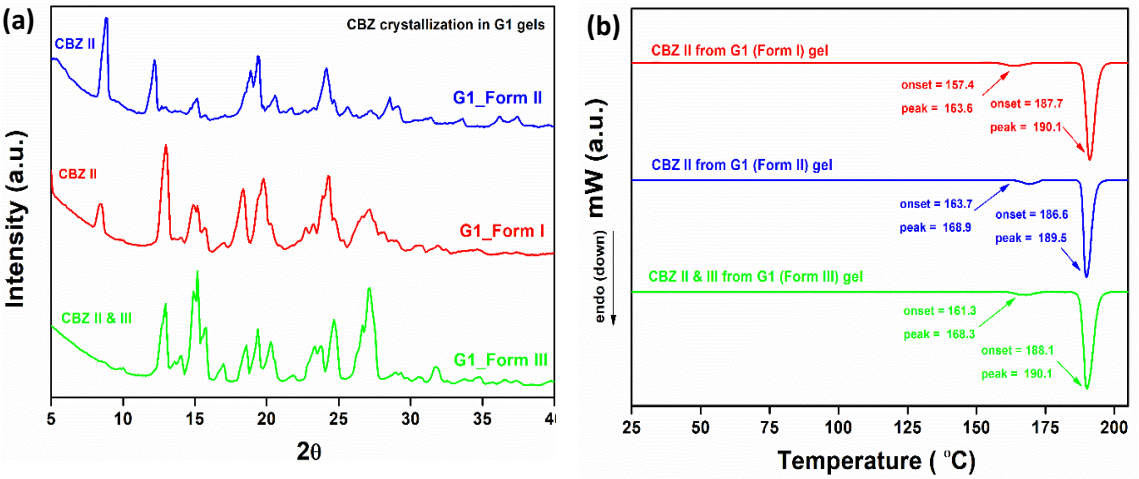

Figure 4.11 PXRD patterns (a) and DSC endotherms (b) of CBZ crystals obtained from gel of **G1** polymorphs

CBZ crystals were isolated and characterized following the procedure outlined above. Unit cell parameters of CBZ crystals grown in gels of **G1** Form I and II match with reported CBZ Form II. Whereas in **G1** Form III gels both CBZ Form II and III were present. Further phase purity of the crystals obtained from these gels were characterized by PXRD and DSC analysis (shown above in Figure 4.11). Apperance of characteristics peak of CBZ Form II at around 8.7 (2θ value) in the PXRD pattern of crystals obtained from G1 Form II gels and two endothermic peaks at 163.7°C and 186.6°C confirmed the polymorphic form of CBZ as CBZ Form II. Similarly presence of characteristic peaks of at around 2θ = 13.4, 18.7, 24.5 (for CBZ Form III), 15.4, 19.6, 25.2 (for CBZ Form II) in the PXRD pattern confirms the presence of both CBZ Form II and III in **G1** Form III gel. In DSC endotherm of CBZ crystals obtained from **G1** Form III gel, endothermic peak corresponding to polymorphic transition of CBZ Form II to I is present however the exothermic peak of recrystallization of CBZ Form I is not observed. This may be due to presence of CBZ Form I (due to conversion of CBZ Form II to I) in the system CBZ Form III converted along with CBZ Form II to I.

Changes in the rheological properties of the gels were examined using amplitude and frequency sweep rheological experiments (shown in Figure 4.12). Results from these experiments indicate that the presence of CBZ within the gels reduce the viscoelastic nature of the gels along with decrease in the gap between G′ and G″ values. However even in the presence of CBZ gel maintained its gel state.

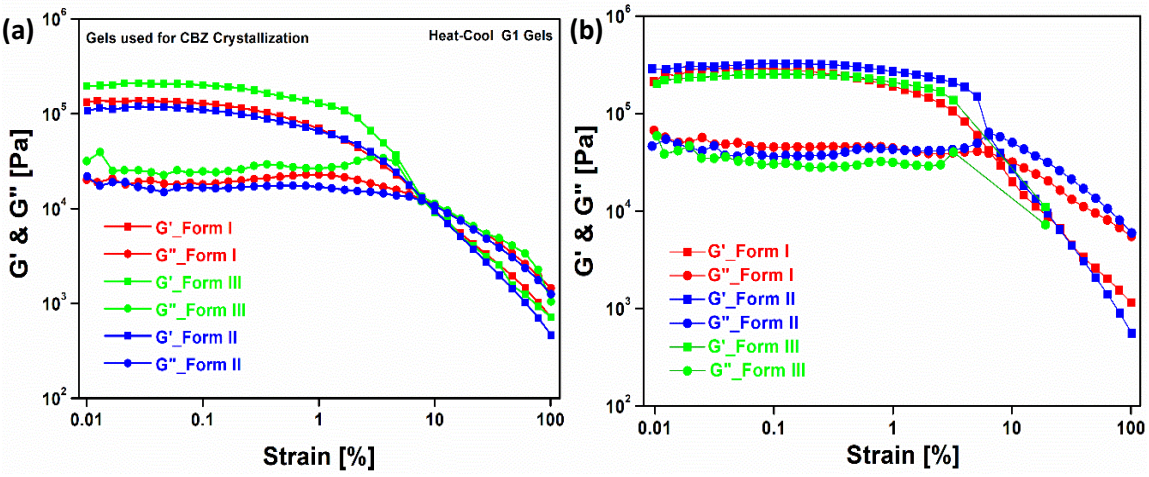

Figure 4.12 Amplitude sweep rheology of gel prepared by three **G1** polymorphs (a) with CBZ and (b) without CBZ under constant frequency of 10 Hz. G′ and G″ denote storage and loss modulus. Form I, II, and III represent three polymorphs of **G1**

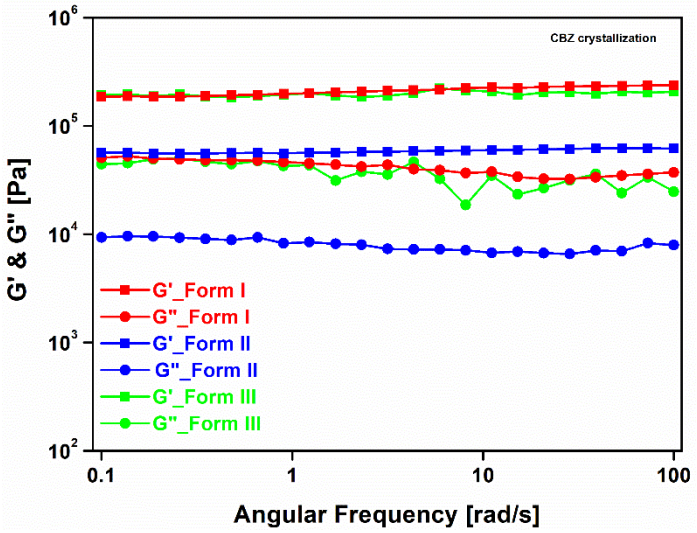

Figure 4.13 Frequency sweep rheology of gels prepared by **G1** polymorphs containing CBZ crystals. G′ and G″ denote storage and loss modulus.

4.3 SUMMARY

In this chapter, a new approach of gel phase crystallization of Carbamazepine (CBZ) is discussed. Solution phase crystallization of CBZ from toluene resulted concomitant crystallization of CBZ Form II and III. Although CBZ Form II appeared first which then transformed slowly into CBZ Form III within 6-12 hour depending on

CBZ concentration. In gel phase crystallization of CBZ, gelator's polymorphic forms influenced the outcome. **G1** Form II gel selectively crystallized CBZ Form II and also prevented the polymorphic transition to CBZ Form III. However, **G1** Form III gel unable to crystallized selectively but slowed down the transition rate. Among all three polymorphs of **G1, G1** Form I gel found to most effective as gel matrix for crystallization. Heat-cool, sonication and grinding crystallizes CBZ Form II exclusively and at the same shaking resulted CBZ Form III directly without encountering with CBZ Form II.

Although exact mechanism of selective crystallization is not clear but it is evident that gelator's polymorphic state and gel preparation conditions are deciding factors in selective drug crystallization. Moreover, CBZ crystals can easily recoverable from the gel phase. Therefore, utilization of various combinations of stimuli and gelator polymorphs to prepare the gel matrix for crystallization applications holds significant potential.

4.4 EXPERIMENTAL SECTION

4.4.1 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. Carbamazepine was purchased form Merck India. All solvents used in experiments are of laboratory grade and purchased from SRL.

4.4.2 Instrumental Details:

The instruments used for characterization including PXRD, DSC, and rheology tests as mentioned in section 2.4.2 of Chapter 2.

Gel samples were air dired to transform into xero gels, which were then used to get electron microscopy images for FESEM technique. FESEM images were recorded in Gemini 500 FE-SEM. Samples were coated with 2 nm of Pt before recording in both instruments. Microscopic images are recorded in Motic Microscope 3.O+ and analysed with Motic software.

4.4.3 Gel phase crystallization

(a) CBZ crystallization in stimuli induced gels:

Initially, required amount of CBZ (20mg/ml) was mixed with toluene in a glass vial (size= 5ml) and heated until a clear solution was obtained. The CBZ toluene solution

was cooled down to room temperature and required amount of **G1** Form I added immediately followed by appropriate application of stimuli to prepare the gel. After application of stimuli, the glass vials were kept undisturbed for crystallization of CBZ.

(b) CBZ crystallization in gels of G1 polymorphs:

All three polymorphs of **G1** responded to heat-cool stimuli only. Gels were prepared following procedure described above for all three polymorphs of **G1**.

4.4.4 Recovery of CBZ crystals from the gel matrix:

Crystals of CBZ were recovered from the gel by converting the gel into sol phase, and then crystals were filtered out easily. To convert the gel to sol, 2-3 drops of acetic acid was added followed by slight warming the vial to break the gel networks to sol phase. Microscopic images were captured by placing a small amount of gel containing CBZ crystals smeared on a glass slide to observe under microscope.

4.5 REFERENCE

[1] Myerson, A. S. (2002). *Handbook of industrial crystallization*. Butterworth-Heinemann, Oxford, United Kingdom, 2nd Edition.

[2] Metherall, J. P., Carroll, R. C., Coles, S. J., Hall, M. J. and Probert, M. R. Advanced crystallisation methods for small organic molecules. *Chemical Society Reviews*, 52(6):1995-2010, 2023.

[3] Cote, A., Erdemir, D., Girard, K. P., Green, D. A., Lovette, M. A., Sirota, E. and Nere, N. K. Perspectives on the current state, challenges, and opportunities in pharmaceutical crystallization process development. *Crystal Growth & Design*, 20(12):7568-7581, 2020.

[4] Vekilov, P. G. The two-step mechanism of nucleation of crystals in solution. *Nanoscale*, 2(11):2346-2357, 2010.

[5] McCrone, W. C. Polymorphism in Physics and Chemistry of the Organic Solid State, Vol II (Eds.: D. Fox, M. M. Labes and A. Weissenberg), Interscience, New York, 1965.

[6] Saha, B. K., Nath, N. K. and Thakuria, R. Polymorphs with remarkably distinct physical and/or chemical properties. *The Chemical Record*, 23(1):e202200173, 2023.

[7] Chemburkar, S. R., Bauer, J., Deming, K., Spiwek, H., Patel, K., Morris, J., Henry, R., Spanton, S., Dziki, W., Porter, W. and Quick, J. Dealing with the

impact of ritonavir polymorphs on the late stages of bulk drug process development. *Organic Process Research & Development*, 4(5):413-417, 2000.

[8] Cabri, W., Ghetti, P., Pozzi, G. and Alpegiani, M. Polymorphisms and patent, market, and legal battles: cefdinir case study. *Organic process research & development*, 11(1):64-72, 2007.

[9] Bučar, D. K., Lancaster, R. W. and Bernstein, J. Disappearing polymorphs revisited. *Angewandte Chemie International Edition*, 54(24):6972-6993, 2015.

[10] Parambil, J. V., Poornachary, S. K., Heng, J. Y. and Tan, R. B. Template-induced nucleation for controlling crystal polymorphism: from molecular mechanisms to applications in pharmaceutical processing. *CrystEngComm*, 21(28):4122-4135, 2019.

[11] Gómez-Morales, J., Hernández-Hernández, Á., Sazaki, G. and García-Ruiz, J. M. Nucleation and polymorphism of calcium carbonate by a vapor diffusion sitting drop crystallization technique. *Crystal Growth & Design*, 10(2):963-969, 2010.

[12] Sarma, B., Roy, S. and Nangia, A. Polymorphs of 1, 1-bis (4-hydroxyphenyl) cyclohexane and multiple Z′ crystal structures by melt and sublimation crystallization. *Chemical communications*, (47):4918-4920, 2006.

[13] Diao, Y., Whaley, K. E., Helgeson, M. E., Woldeyes, M. A., Doyle, P. S., Myerson, A. S., Hatton, T. A. and Trout, B. L. Gel-induced selective crystallization of polymorphs. *Journal of the American Chemical Society*, 134(1):673-684, 2012.

[14] Yang, X., Sarma, B. and Myerson, A. S. Polymorph control of micro/nano-sized mefenamic acid crystals on patterned self-assembled monolayer islands. *Crystal Growth & Design*, 12(11):5521-5528, 2012.

[15] Bora, P., Saikia, B. and Sarma, B. Oriented crystallization on organic monolayers to control concomitant polymorphism. *Chemistry–A European Journal*, 26(3):699-710, 2020.

[16] Parmar, M. M., Khan, O., Seton, L. and Ford, J. L. Polymorph selection with morphology control using solvents. *Crystal Growth & Design*, 7(9):1635-1642, 2007.

[17] 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.

[18] Saikia, B., Mulvee, M. T., Torres-Moya, I., Sarma, B. and Steed, J. W. Drug mimetic organogelators for the control of concomitant crystallization of barbital and thalidomide. *Crystal Growth & Design*, 20(12):7989-7996, 2020.

[19] Jayabhavan, S. S., Steed, J. W. and Damodaran, K. K. Crystal Habit Modification of Metronidazole by Supramolecular Gels with Complementary Functionality. *Crystal Growth & Design*, 21(9):5383-5393, 2021.

[20] Andrews, J. L., Kennedy, S. R., Yufit, D. S., McCabe, J. F. and Steed, J. W. Designer gelators for the crystallization of a salt active pharmaceutical ingredient─ Mexiletine hydrochloride. *Crystal Growth & Design*, 22(11):6775-6785, 2022.

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

[22] Zhang, J., Liu, A., Han, Y., Ren, Y., Gong, J., Li, W. and Wang, J. Effects of self-assembled monolayers on selective crystallization of tolbutamide. *Crystal Growth & Design*, 11(12):5498-5506, 2011.

[23] Grzesiak, A. L., Lang, M., Kim, K. and Matzger, A. J. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. *Journal of Pharmaceutical Sciences*, 92(11):2260-2271, 2003.

[24] Kelly, R. C. and Rodríguez-Hornedo, N. Solvent effects on the crystallization and preferential nucleation of carbamazepine anhydrous polymorphs: a molecular recognition perspective. *Organic Process Research & Development*, 13(6):1291-1300, 2009.

[25] Lang, M., Kampf, J. W. and Matzger, A. J. Form IV of carbamazepine. *Journal of Pharmaceutical Sciences*, 91(4):1186-1190, 2002.

[26] Cabeza, A. J. C., Day, G. M., Motherwell, W. S. and Jones, W. Solvent inclusion in form II carbamazepine. *Chemical Communications*, (16):1600-1602, 2007.

[27] Arlin, J. B., Price, L. S., Price, S. L. and Florence, A. J. A strategy for producing predicted polymorphs: catemeric carbamazepine form V. *Chemical Communications*, 47(25):7074-7076, 2011.

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

[29] Aparicio, F., Matesanz, E. and Sánchez, L. Cooperative self-assembly of linear organogelators. Amplification of chirality and crystal growth of pharmaceutical ingredients. *Chemical Communications*, 48(46):5757-5759, 2012.

[30] Dawn, A., Mirzamani, M., Jones, C. D., Yufit, D. S., Qian, S., Steed, J. W. and Kumari, H. Investigating the effect of supramolecular gel phase crystallization on gel nucleation. *Soft Matter*, 14(46):9489-9497, 2018.