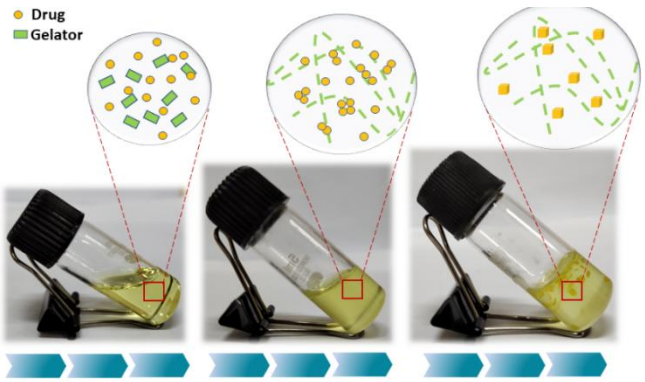
Chapter 6

Conclusion and Future Scopes

6.1 CONCLUSION

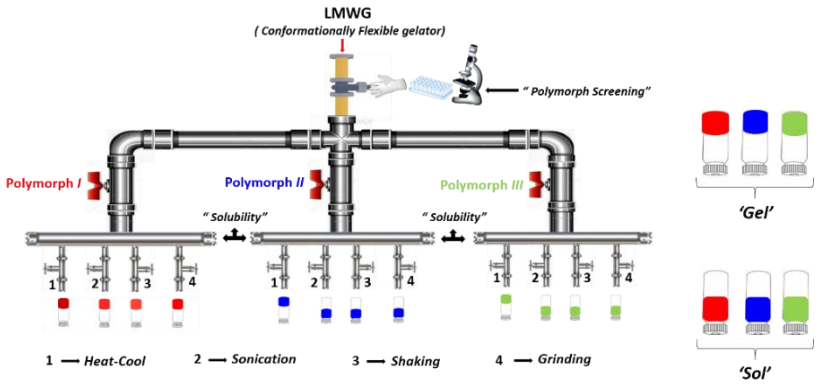
This thesis delves into the innovative field of gel-based pharmaceutical crystallization. It comprehensively explores this technique, structured across six distinct chapters. The inaugural chapter lays the groundwork by introducing the fundamental principles of gel phase crystallization. The subsequent four chapters constitute the core research component, meticulously detailing the development of a novel gel matrix. This matrix is ingeniously crafted from a specific type of *bis*-urea gelator, demonstrating its remarkable potential in facilitating the controlled crystallization of pharmaceutical compounds (APIs).

Chapter 1 introduces the subject domain of different aspects of gel phase crystallization of pharmaceuticals with special emphasis on LMWG systems. The basic idea of gel and its applications are highlighted. The transformation from serendipitous discoveries to the strategic design of LMWG using crystal engineering principles is discussed. Factors like the nature of the solvent, gelator concentration, stimuli, or rate of heating/cooling play a crucial role in the process. Since these systems are dynamic it requires different characterization techniques to understand their structure, self-assembly, and mechanical properties. Some of the aspects of these techniques are also discussed. LMWGs serve as a useful crystallization matrix for polymorph screening, control over the concomitant nature, and preferential crystallization of desired polymorphic form. Scheme 6.1 shows the different stages in the gel phase crystallization process. The addition of functionality into the gelator's structure that mimics or compliments the drug's functionality or structure is found to be useful in gel phase crystallization.



Scheme 6.1 Pictorial representation of different stages in gel phase crystallization process

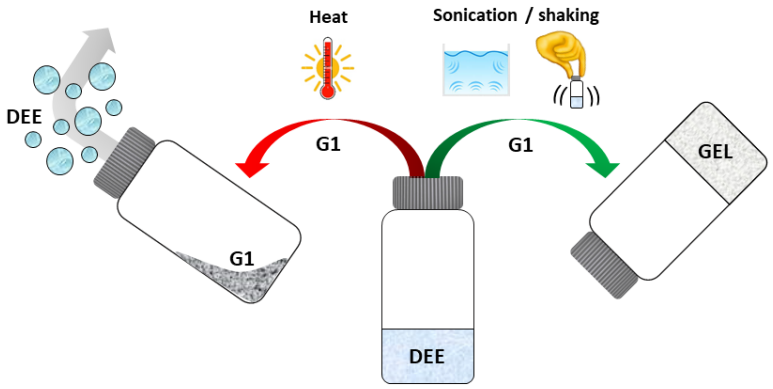
Chapter 2 discusses the development of a *bis*-urea gelator **G1** for its application as a gel phase matrix for pharmaceutical crystallization. Synthesis, characterization, and polymorph screening resulted in the isolation of three distinct polymorphs **G1** Form I, II, and III. Gel screening results showed that **G1** Form I responds to multiple stimuli heat-cool, sonication, shaking, and grinding in at least 7 solvents. However, **G1** Form II and III responded to heat-cool stimulus only. Stimuli responsiveness of **G1** polymorphs is controlled by their solubility parameter. The gel state of different gels prepared from **G1** was characterized by measuring their M.G.C., T_{gel}, and rheological properties. **G1** Form I required different M.G.C. for gel formation; sonication and shaking required the least amount (i.e. 0.2 % w/v) whereas heat-cool required 0.8% w/v. T_{gel} results suggest that heat-cool gels are the most stable among others. The viscoelastic nature of the gels is supported by the rheological analysis. Gel fibre morphology is in good agreement with other results to support that gels prepared from each stimulus are unique and have different gel properties. Similarly, the gel prepared from all three polymorphs of **G1** is also different based on their M.G.C and rheology. The findings of this chapter highlight the importance of polymorph screening in LMWG systems. Designing a gelator that forms gels in a wide range of solvents is a challenging and unpredictable process. The discovery of new polymorphs of an existing gelator may lead to a series of gelators with potentially superior gelation properties. Furthermore, it will help in lowering the risk of reproducibility that is often observed in many low molecular weight gelator (LMWG) systems. Scheme 6.2 demonstrates the benefit of polymorph screening before starting with gel screening of **G1**.



Scheme 6.2 Important key stage in the gel-making process for **G1** gels

Chapter 3 emphasizes finding alternative strategies to deal with problems associated with heat-cool as stimuli used for gel preparation. In Chapter 2, it was observed that heat-cool stimuli failed to form gel in polar solvents due to the high

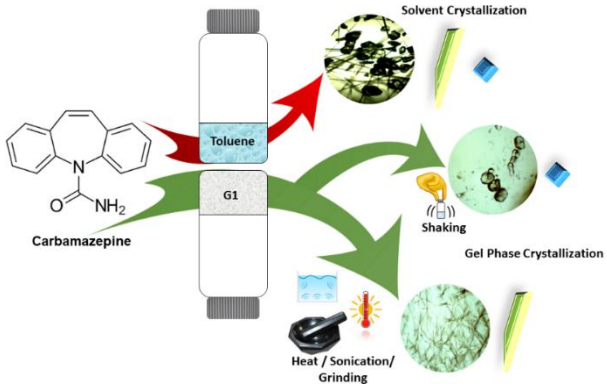
solubility of **G1**. However, when using low-boiling solvents, heating the **G1**-solvent mixture at elevated temperatures led to solvent evaporation from the glass vial. Also, gel screening with other stimuli was performed with only the solvents that form gel in the heat-cool process. In this chapter, gel screening was done with sonication, shaking, and grinding as stimuli to those solvents that failed to form gel in heat-cool stimuli. Diethyl ether (DEE) and di-isopropyl ether (IPE) responded to both sonication and shaking to form a gel (shown in Scheme 6.3). Characterization of the gel state for both DEE and IPE gels demonstrated that both sonication and shaking stimuli produced gels with distinct properties. Gels formed by shaking as stimuli are found to be better than the sonication gels as reflected on their M.G.C., T_{gel}, and rheological properties. Morphology of the xerogels of DEE gel reveals the formation of a fibrillar network structure. However, in the case of IPE gels long rod-shaped crystalline morphology were observed. Subsequent investigations of suspecting phase change of **G1** were confirmed by PXRD and DSC analysis of the xerogels. Comparison of PXRD patterns and DSC endotherms of xerogels with respective **G1** polymorphs reveals polymorphic transformation from **G1** Form I to III in the case of IPE gel. Gel screening for the other two forms of **G1** resulted in no gel formation due to poor solubility in the gelling solvents. Phase transformation of **G1** in IPE occurred during the xerogel preparation. Gel structure breaks down and dissolves in IPE which subsequently recrystallizes into **G1** Form III after evaporation.



Scheme 6.3 Gel preparation strategy for low boiling solvents at ambient conditions

Chapter 4 employed **G1** gels as a crystallization matrix for Carbamazepine (CBZ). CBZ is a highly polymorphic drug used to treat epilepsy and trigeminal neuralgia. In toluene, at first, CBZ crystallized out from the solution as CBZ Form II which then slowly transformed into CBZ Form III and appeared concomitantly in the solution. Since **G1** forms different gels by using various combinations of stimuli (to prepare gel) and polymorphs (of **G1**), these gels were used as a crystallization matrix for

CBZ crystallization. Heat-cool, sonication, and grinding gels of **G1** Form I crystallized CBZ as polymorph CBZ Form II and also prevented the polymorphic transition of CBZ Form II to III. Shaking gel (**G1** Form I) crystallized CBZ as polymorph CBZ Form III. Gels of **G1** Form I and II also prevented the polymorphic transition of CBZ Form II to III. However, in the gel of **G1** Form III, both CBZ Form II and III crystallized concomitantly. The selective crystallization of CBZ in the gel phase is connected to the gel preparation condition and polymorphic form of **G1**. Scheme 6.4 shows the pictorial representation of the summary of this chapter.



Scheme 6.4 Carbamazepine (CBZ) crystallization outputs from solution and gel matrix

Chapter 5 introduced a new strategy for gel phase crystallization of pharmaceutical compounds (APIs). Conventional gel phase crystallization involves the dissolution of **G1** and the drug in a gelling solvent at elevated temperature followed by a resting phase. In this procedure, both the gelator and drug are in solution before gel formation. This sometimes trigger the interaction of the gelator with drug molecules which disrupts gel formation and the drug is not suitable for crystallization in the gel media. The new strategy introduces the gelator (here **G1**) directly into the drug solution via *in-situ* generation from the precursors to prepare the gel phase. This strategy eliminates the requirement of stimuli for **G1** gel preparation. Eight drug molecules were tested using this new strategy and the *in-situ* gel phase crystallized them selectively in a single phase. The limitations and potentials of this new technique were discussed. *In-situ* gel phase crystallization technique essentially reduces the multi-step procedure into a single step and also expands the overall solvent scope for **G1**.

Scheme 6.5 Pictorial representation of differences between conventional and *in-situ* gel phase crystallization. A and B represent reactants for the synthesis of **G1**

6.2 Future Scope of the Work:

While computational studies suggested the existence of multiple numbers of conformations for **G1** with small differences in their energy parameter. Thus, the adjustment of conformation continuously occurs in the closely related conformations to minimize the lattice energy during crystallization events, leaving the possibility of finding different crystalline phases. However, only three polymorphs were isolated experimentally. The identification of new polymorphs of **G1** could be enhanced by expanding polymorph screening to include techniques like vapor diffusion, sublimation, and melt crystallization. Apart from its application as a crystallization matrix, **G1** can be used for the removal of organic solvents, and dyes from polluted water due to its multi-stimuli responsive character. The *in-situ* strategy of crystallization can be improvised to overcome the challenges of use as an alternative to conventional gel phase crystallization. Moreover, as the *in-situ* gelation process does not require stimuli for gel making; this process hold potential to be integrated into continuous manufacturing process of pharmaceuticals as crystallization chamber. Apart from the use as crystallization matrix, *in-situ* gel preparation technique can be used for 3D moulding conveniently its easy and instant gel formation.

The strategic design of LMWG is a key component of gel phase crystallization. In the last few decades, researchers achieved significant advancements in understanding LMWG systems and established practical thumb rules for designing new gelators. However, developing a gelator that can form a gel in specific solvents with desired properties is always challenging. To reduce somewhat these challenges, a library of gelators can be designed by changing different combinations of linkages and end groups.

This library of gelators can be used for different applications depending on their gel properties. In my view, a promising future direction lies in discovering new polymorphs of existing gelators, those with desirable gel properties, as new polymorphs may show improved gel properties.