Abstract

The thesis entitled "*Understanding Supramolecular Self-assembly of Bis-Urea Functional Low Molecular Weight Gel for Pharmaceutical Crystallization*" consists of six chapters; *viz*. introduction, four experimental working chapters followed by conclusion and future scope.

Low Molecular Weight Gels (LMWG) are dynamic class of materials that find its application in various domain of research [1,3]. Typically, the molecular weight of the gelators of LMWG are less than 3000 Da. LMWG by composition contain mostly liquid but exhibit viscoelastic 'solid-like' properties due to 3D network structure formed by the gelators. LMWG are held together by multiple non-covalent interactions and therefore easily switchable between gel to sol state. These versatile soft materials have applications across diverse fields, including crystallization matrices, catalysis, drug delivery, optoelectronics, art conservation, and environmental remediation [4].

Drug polymorphism of pharmaceutically active molecules is an important topic of study as various polymorphs of a single molecule are a patentable entity due to its difference in various physicochemical properties [5]. Concomitant polymorphism refers to the crystallization of different polymorphic forms in the same environmental condition [6]. Contrary to traditional mode of crystallization from solvent, gel phase crystallization offers significant advantages for selective nucleation of the substrate APIs (Active Pharmaceutical Ingredients). This advantage in nucleation is attributed to the inherent property of the gel matrix reducing the convection current of the media, reducing the energy barrier of nucleation, and providing nanoconfinement spaces for crystal growth [7].

Chapter 1 discusses on the strategic design, preparation methodology, characterization techniques, gel state and its application in crystallization matrix. The experimental work around these objectives is discussed in Chapter 2, 3, 4 and 5. In chapter 2, a *bis*-urea based LMWG **G1** is synthesized and subjected to polymorph screening in different solvents. Three distinct polymorphic phases were isolated and gel screening was done for each polymorph using four different stimuli viz. i) heat-cool, ii) sonication, iii) shaking, iv) grinding. Solubility of the polymorphs is found to be the decisive factor for its multi-stimuli responsiveness. In chapter 3, the solvent scope of gelation was extended to highly volatile solvents at ambient conditions. Chapter 4 establishes the gels of **G1** as a suitable

crystallization media for the selective nucleation of CBZ. Unlike the conventional methodology followed so far has been replaced by a novel *in-situ* gel phase crystallization strategy for crystallizing APIs is placed in Chapter 5. Chapter 6 is the concluding chapter of the findings incorporated in the thesis with future perspectives.

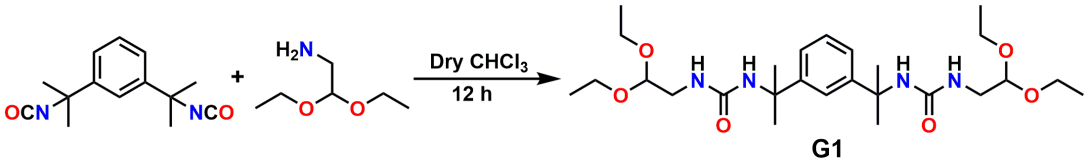
Chapter 1. Introduction

Gels are semi solid materials that largely consists of liquid with small portion solid in it. Depending on the solvent, entrapped gels can be classified into a hydrogel, organogel, and aerogel [1-3]. However, depending upon the interactions or mechanism of forming a gel, it can be classified either as macromolecular or polymeric and supramolecular gels. Unlike macromolecular gels, supramolecular gels are sustained solely by noncovalent interactions such as hydrogen bonding, π···π interactions, and van der Waals interactions forming the backbone of the growing fibers [2-4]. Supramolecular gelators with a molecular mass of less than 3000 Da are refereed as LMWG. In early developmental stage of LMWG, most of the gelators discovery were serendipitous but later with better understanding of these systems lead to design strategies that consider employing functionalities to favor 1D growth of gelator fibers and at the same time hampers growth towards 3D crystalline formation [8]. Gel state depends on many parameters like the nature of the solvent and conditions used during preparation. Role of the solvent is crucial as gelator's solubility must be balanced for the growth of gel fibres [9-10]. Amongst various applications gels are also used as crystallization matrix for growing crystals with different shape and size. Gel helps in reduction of the convection current, sedimentation, and allows better aggregation of the substrate [11-12]. Another advantage of using LMWG is the recovery of crystals from the gel. Moreover, gel fibers act as nucleating template and crystallization may be manipulated by introducing mimetic functionality of the substrate [13]. Thus gel matrix provides a potential tool for controlling nucleation and crystal growth of a substrate.

Chapter 2. Translating Solid-Phase Conformational Memory in the Prophecy of Multi-stimuli Responsive Low Molecular Weight Gels

This chapter discusses the strategic design and synthesis of *bis*-urea functionalized low molecular weight gelator (LMWG) **G1** (1,1'-(1,3-phenylenebis(propane-2,2-diyl))*bis*-(3-(2,2-diethoxyethyl)urea) from the condensation of aminoacetaldehyde diethyl acetal (ADA) and 1,3-*bis*(2-isocyanto-2-propyl)benzene in dry chloroform at room temperature (Scheme 2.1). Formation of **G1** was confirmed with various thermal (DSC, TGA),

microscopic (SEM, FESEM, TEM), mechanical (rheology), computational, and spectroscopic techniques (FT-IR, PXRD, SC-XRD). Presence of flexible end groups and possibility to alter H-bonding and other weak interactions results in three distinct polymorphic phases (**G1** Form I, II, and III).



Scheme 2.1 Schematic representation of the synthesis of LMWG **G1**

The solubility difference in all the three polymorphs of **G1** results in different gelling efficiency. **G1** Form I respond to four different stimuli i.e. heat-cool, sonication, shaking and grinding to exhibit gelation. The minimum gelator concentration (M.G.C.), T_{gel} (gel to sol transition) values, rheological property, gel fibre morphology, and solvent scope were different for each of the stimuli explored. Unlike **G1** Form I, **G1** Form II and III failed to respond to multiple stimuli except heat-cool with higher M.G.C. value due poor solubility in the gelling solvent.

Chapter 3. Stable Gel from Volatile Solvents at Ambient Condition

Generally volatile solvents are found not to gel at ambient temperature condition. In Chapter 2, gel screening of **G1** using heat-cool as stimuli revealed inefficiency of the process in gelling solvents having low boiling points. Chapter 3 addresses this concern and further extends the process of gelation for high volatile solvents viz. Diethyl ether (DEE) and di-isopropyl ether (IPE). **G1** was designed in such a manner that flexible end groups offer potential interaction sites for solvents along with balancing between crystallization and precipitation. **G1** Form I could gel DEE and IPE at room temperature (25ºC) with sonication and shaking as stimuli. Gels formed in DEE and IPE exhibited distinct properties, including difference in their M.G.C., rheological behavior, and gel morphologies, which make them distinct gels. As anticipated, **G1** Form II and III failed to show gelation in DEE and IPE due to poor solubility. Therefore, sonication and shaking stimuli offer potential alternatives to the heat-cool strategy for gelling relatively high-volatility solvents, expanding the range of solvents suitable for gelation by a given gelator.

Chapter 4. Control Drug Polymorph Nucleation in Gel Matrix

A series of gels were prepared using various combinations of stimuli and **G1** polymorphs to investigate the role of the gelator's polymorphism in the nucleation and crystal growth of Carbamazepine (CBZ) in gel phase crystallization. CBZ is an anticonvulsant medication used in the treatment of epilepsy and neuropathic pain. CBZ is highly polymorphic in nature and five polymorphs are reported till date. Solution crystallization in toluene CBZ crystallized concomitantly into polymorph II (CBZ Form II) and polymorph III (CBZ Form III). The CBZ Form II (metastable form) transforms into CBZ Form III (stable form) in solution over the time. In gel of **G1** Form I, heat-cool, sonication and grinding stimuli resulted in CBZ Form II without transforming to CBZ Form III as observed up to four weeks. However, upon application of mechanical stimuli (shaking) CBZ Form III could be selectively crystallized within 30 mins of gel formation. The gel of **G1** Form II also nucleated CBZ Form II whereas gel of **G1** Form III concomitantly nucleated both CBZ Form II and III. This results highlighted the role of gelator's polymorphism as well as stimuli used in gel preparation on the nucleation and crystal growth of a drug molecule.

Chapter 5. *In-Situ* Gelation as Selective Drug Crystallization Strategy

This chapter reports an alternative route of gel preparation for effective crystallization of APIs (Active Pharmaceutical Ingredients). The *in-situ* synthesis of **G1** in non-polar solvents like hexane, petroleum ether, cyclohexane *etc*. lead to instant gel formation. The advantage lies in skipping the need of a stimulus for gelation. Of the eight different APIs chosen for crystallization by this technique, five of them could form better quality crystals with selective polymorphic outcome. In this chapter, to tackle problems associated with conventional gel phase crystallization strategy; an alternate route for gel phase crystallization is introduced. In this new route, gelator is generated *in-situ* in the API solution which then form the gel matrix to facilitate the crystallization of API. However, for an example Niclosamide (NCA) the strategy was modified a little to avoid possible interaction of NCA with **G1**'s precursor molecules.

Chapter 6. Conclusion and Future Scopes

This chapter presents a summary of all the significant findings from the series of experiments carried out to meet the objectives of the thesis. Flexible end groups present in **G1**, hydrogen bonding affinities and weak intermolecular interactions increased the

potential of occurrence of multiple polymorphic phases of **G1**. The three polymorphic phases identified for **G1** has varied solubility and gelation behavior with respect to different stimuli. Importance of polymorph screening prior to its use as crystallization media is established. Use of other stimuli like sonication and shaking is shown as alternative of heat-cool in cases where raising temperature is not practical. **G1** gels were used as crystallization matrix for controlling polymorphic transition and crystallization of CBZ polymorphs. Importance of both stimuli and polymorph selection for the application of gel is highlighted. A new alternate strategy for gel phase crystallization is presented to overcome the difficulties associated with the conventional method of gel phase crystallization. Applicability of this new strategy is examined with APIs with varied functionalities. As a future scope, gelators with different strategic design and functional groups must be explored for generating highly selective media for crystallization and separation. The *in-situ* gelation process must further be tested with varying drug, solvent and reactant ratios towards enhanced output.