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Polymorph control: Success so far and future expectations

Renuka, Sachin Kumar Singh*, Ankit Kumar Yadav, Monica Gulati, Amit Mittal, Rakesh Narang, Varun Garg

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, 144401, Punjab, India

Abstract: The phenomenon of the appearance and disappearance of polymorphs has been an enigma for the chemists and formulators alike. The ability to successfully and consistently produce the specific stable polymorphs directly affects the efficiency and speed of drug development, the robustness of manufacturing process, and quality and stability of APIs. Though a number of diverse methods have been utilized and reported for polymorph control, reliable techniques for polymorph control still remain far from perfect. This article discusses different methods for polymorph control like supersaturation, antisolvent addition, temperature and pH control and addition of additives. It also deliberates on their successful applications over the last two decades.
Keywords: Polymorphs, Stability, Supersaturation, Antisolvent, Temperature, pH control, Additives.

Introduction

Polymorphism is a solid-state phenomenon involving different forms of the same chemical compound which have distinctive properties[1, 2]. Need to control polymorph formation has been viewed as a critical issue by the pharmaceutical industry since a long time. Polymorphism was perceived as major problem in the development of azo pigments and copper phthalocyanide for the dye industry a century back in history also[3]. More recently, polymorphism of drugs, due its newly found applications has evoked an intense interest in the pharmaceutical industry[4]. The properties most often affected by polymorphism which are of utmost relevance in the pharmaceutical industry include stability, solubility, bioavailability and density. A distinguishing feature of polymorphs is their structural difference which can be observed as a difference in the spatial arrangement of the atoms of the molecule or as a difference in packing arrangements of the molecules in the unit cell[2]. The structural differences in turn, may, or may not affect the physiochemical properties of the compound in the solid state. Polymorphs can be prepared by normal traditional methods as well as by high throughput technologies. However, one of the most challenging properties of polymorphs is the difficulty of consistently preparing the desired polymorph in a pure form. Preparation of polymorphs can be accomplished by traditional methods such as crystallization from solutions and crystallization from melts[4], as well as modern methods such as supercritical fluid crystallization[5, 6], capillary crystallization[7, 8, 9], non-photochemical laser-induced nucleation[10], crystallization with polymer heteronuclei[11, 12], and template-assisted crystallization[13]. A potentiometric method for the crystallization of polymorphic forms of active pharmaceutical ingredients (APIs) has also been described[14]. Polymorphism has been extended to include zwitterions of acids containing amide groups able to accept protons[3]. The problems associated with polymorphism and the possible methods for isolating the desired polymorphs have been reported by Kitamura, 2009 and Llinas and Goodman[4, 15]. It has been suggested that the production of polymorphs in their pure form may be possible by applying thermodynamic and kinetic principles to control polymorph formation[16]. A number of reports exist about the quest for suitable solvents, or mixtures of

solvents, in which the selected compound dissolves and leads to crystallization of only one of the polymorphs[17, 18]. The addition of other compounds to initialize, or enhance formation of one, and only one, polymorph have also been reported[19, 20].

Though a large amount of efforts have been made to identify all possible polymorphs of active pharmaceutical ingredients (API), appearance of a new polymorph can still spring a surprise[4]. Polymorphs can convert spontaneously from less stable to more stable forms, and it is well-known that the most stable polymorph is the least soluble one. Since solubility could be a major limiting factor in the efficacy of an API, the most pragmatic approach is to isolate and identify the most stable form at the earliest. Ideally this should be targeted while the drug candidate is still in the discovery phase, so that this form could be used for subsequent testing[4]. There is no such method that can provide absolute confidence that the most stable polymorph of a compound has been obtained, and mistakes can be costly[21]. New forms may appear as a result of a change in the manufacturing process, even if the change is just in the equipment used to dry the final drug substance. A change may even occur when materials are being stored, with no recorded change in the storage conditions[22]. The appearance of a new polymorphic form of an API is a major concern for pharmaceutical world. Over the last decade, many new methods of controlling polymorph formation have been developed, and a huge number of new polymorphic forms have been characterized, partly as a result of improvements in the methods for the characterization of polymorphs[23].

The growth of crystals from solution is often the method of choice for purification, particularly for pharmaceutical compounds. Whilst some materials form crystals readily, others can be extremely troublesome to crystallize[24]. Despite advances in solving crystal structures from powder diffraction in recent years, growth of single crystals remains important if the solid-state structure of a compound is required. Crystallization occurs in two steps: first, crystal nuclei are formed; second, some of these nuclei grow into larger single crystals. If a system obeys Ostwald's rule of stages, metastable forms will be obtained first[4, 25]. Single crystals will usually be produced readily from systems that can form a metastable solution over a wide range of conditions. Systems in which the metastable region is very restricted require careful control of the crystallization conditions to achieve single crystals rather than fine precipitates. In general, fast crystallization processes have a greater tendency to form metastable polymorphs than slow processes[4, 26].

Controlling Factors of Polymorphism in Crystallization Process

The crystallization process of polymorphs is composed of the competitive nucleation and crystal growth of the polymorphs, and the transformation from metastable forms to stable forms. Therefore, to control the polymorphism, the dependence of the crystallization behaviour of the polymorphs on the operational factors, and the crystallization mechanism in each elemental process should be understood clearly[27]. To know the key-controlling factors in the crystallization, the selective crystallization of the polymorphs is essential. Temperature and supersaturation are important controlling factors[28]. Also, the addition of polymorphous seed crystals influence on the crystallization behaviour[29]. Furthermore, the crystallization of the polymorphs is frequently influenced by additives[30-32], solvents[33-35] and interfaces[36,37]. The addition of antisolvents in pharmaceutical industries are frequently used as the crystallization process for polymorph control. While using antisolvents for selective crystallization, the influence of the solvent compositions and the mixing rate of the antisolvent are the important factors[38]. Polymorph control also depends on the type of crystallization method used. The best example of polymorph control by crystallization method is the reactive crystallization where, the mixing conditions of the reactant solutions are considered[39].

In Fig.1, supersaturation, temperature, seed crystal and stirring rate are included in the primary factor for polymorph control. The mixing rate of reactant solutions in the case of reactive crystallization is also included in the primary factors in crystallization of polymorphs. The factors due to the external substances such as solvents and additives are grouped in the secondary factor. The host and guest composition is also included in the secondary factor in Fig.1 for polymorph control[27]. Since, supersaturation of each polymorph is based on the solubility of the drug in the given solvent, solubility of drug is also considered as one of the factors for polymorph control. Furthermore, the relative thermodynamic stability and the direction of the transformation between the polymorphs can be known from the solubility of polymorphs[39].

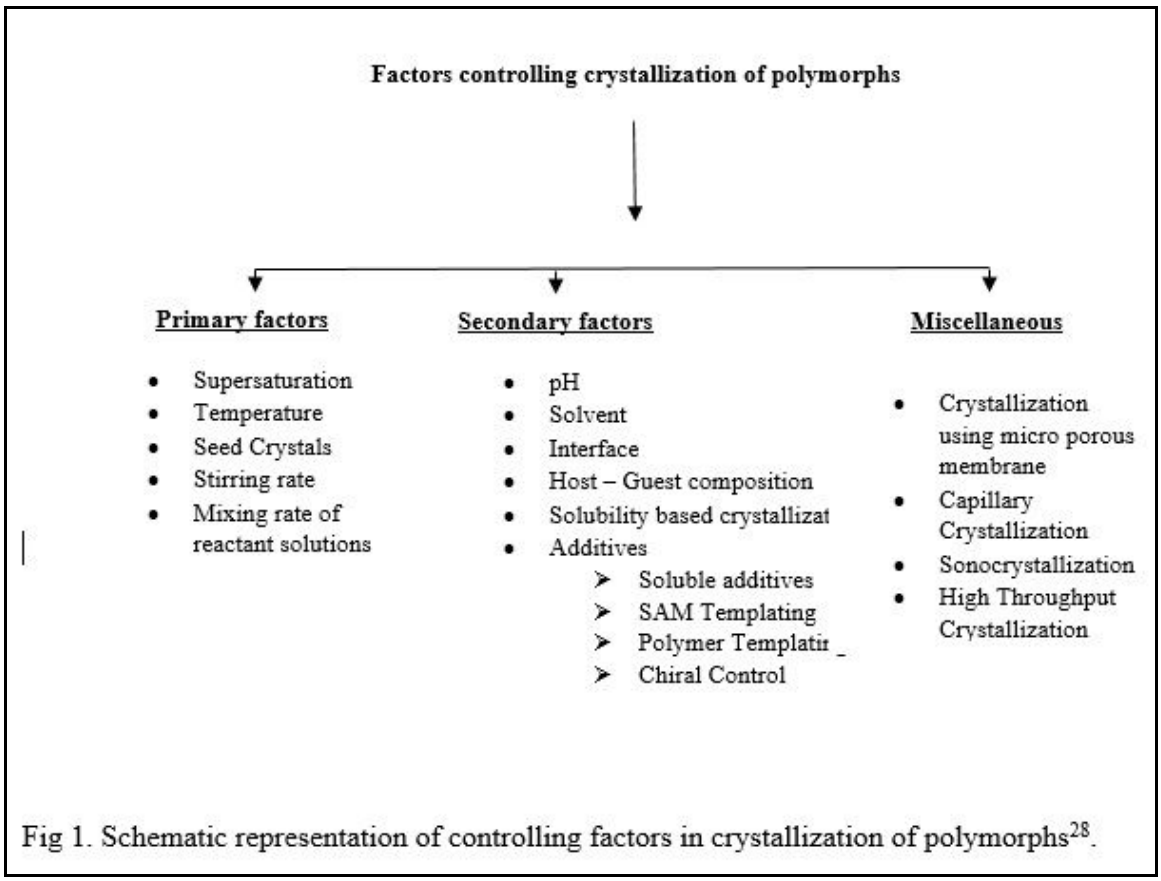

Fig 1. Schematic representation of controlling factors in crystallization of polymorphs[28].

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Primary factors in crystallization of polymorphs

Temperature and supersaturation

Temperature and supersaturation are considered as independent factors. However, the temperature and supersaturation changes simultaneously in the cooling crystallization. In order to examine the effect of supersaturation and temperature on the controlled growth of polymorphs, Kitamura, 1989, described the method of "Differential Crystallization", in which the small amount of crystals were precipitated by keeping the solution concentration (supersaturation) and temperature constant[39, 28].

The relative nucleation rate (R) of the two polymorph, e.g. A and B, was expressed by Eq. (1), where, the nucleation, J is expressed by the classical equation[23, 25].

$$R = J_A / (J_A + J_B) = 1 / [1+PB/PA) \exp (YB - YA)] \quad \text{Eq. (1)}$$

$$YB - YA = -16\pi / 3(kT)^3[\gamma^3_B \nu^2_B / (\text{In } S_B)^2 - \gamma^3_A \nu^2_A (\text{In } S_A)^2] \quad \text{Eq. (2)}$$

Where, "J" is nucleation rate; "P" is frequency factor; "γ" is interfacial free energy;"*ν*" is solid density; "S" is supersaturation ratio (C / C^e; C is solution concentration and C^e is solubility);"T" is absolute temperature, and "k" is Boltzmann constant. In Eq. (2) the supersaturation ratio (S) and interfacial energy (γ) are included as the key-factor for the relative nucleation rate of the polymorph at the constant temperature[39].

According to ''Ostwald's step rule''[40], at low supersaturation, the difference of the supersaturation ratio (S) between the polymorphs is influential on the crystallization and the stable form may preferentially precipitate. On the other hand, at high supersaturation, the difference of the interfacial energy (γ) between the polymorphs is supposed to be relatively dominated and the metastable form may tend to precipitate. However, practically such behaviour is rarely to be observed. This could be understood by the experiment carried out to evaluate the effect of supersaturation on the growth behaviour of α and β forms of L- Glutamic acid and L-Histidine[39].

Kitamura et al., 2002, reported the effect of supersaturation on the growth behaviour of α and β forms of L- Glutamic acid and L- Histidine[39]. In this process the unsaturated solution was rapidly cooled to set the temperature and at the set temperature a small amount of crystal was precipitated under the stirring condition. Then the supersaturation of L- Glutamic acid was carried out at each temperature from 280 to 320K. It appeared that the supersaturation ratio hardly effect on the crystallization ratio of L- Glutamic acid polymorph at each temperature. It could be seen from the fact that the supersaturation ratio range for β- crystals was found to be 1.7 and 4.8 and at 308K the supersaturation ratio was from 1.3 to 3.0. This showed almost no influence of the supersaturation ratio of L- Glutamic acid crystals and thus "Ostwald's Step Rule" cannot be observed in this system. However, same approach was tried by the author on L- Histidine which exists in two forms orthorhombic (α) and monoclinic (β). It was observed from the solubility measurements that when the temperature was increased from 293 to 330K, the formation of β crystals was increased whereas; the formation of α crystals was decreased. Slavin et al., reported the controlled growth of one of the two forms of indomethacin α (metastable) and γ (stable) by applying the principle of high and low supersaturation using different crystallization solvents[41]. When the high and low supersaturated solution of indomethacin was prepared in benzene, chloroform, dichloromethane, carbon tetrachloride, tetrahydrofuran and cyclohexanone, the fine short needle shaped solvate form of indomethacin was precipitated out. These fine short needle solvates or α form (metastable) of indomethacin were also obtained at high supersaturation conditions when the drug was dissolved in methanol, propane - 2- ol, propane -1- ol, butan -1-ol, isobutyl alcohol, pentan-1-ol, isoamyl alcohol, octan -2- ol and cyclohexanol respectively. When the drug was dissolved at low supersaturation in all aforementioned solvents only the rhombic plates of γ (stable) form were precipitated out. Thus "Ostwald's Step Rule" was not obeyed when indomethacin was dissolved and crystallized out either at high or low supersaturation in these solvents. But, in methanol, at high supersaturation only the fine needles of α form (metastable) were precipitated out and at low supersaturation columnar solvates were formed. The results were almost found same when forms of indomethacin were crystallized out from its supersaturated solution in acetonitrile i.e. the needle shaped metastable form α was purely obtained at high supersaturation and rhombic plates of stable form γ were purely obtained at low supersaturation of indomethacin in acetonitrile. This showed that when indomethacin was dissolved in methanol and acetonitrile the "Ostwald's Step Rule" was well obeyed and the metastable α form of indomethacin should form under rapid precipitation conditions. In another experiment, crystallization behaviour of taltirelin polymorphs was observed in a mixture of water and methanol[42]. The solvent effect on the crystallization behavior of the polymorphs was investigated in a mixture of water and methanol under agitated crystallization. At a low concentration of methanol (0 and 10 wt %), the α-form was precipitated at the initial stage of crystallization regardless of the seed form. Thereafter the α-form was transformed into the β-form. In 30% methanol, only the β-form was precipitated regardless of the seed form. In 30% methanol without agitation, the β-form grew on the surface of the α-seed crystal. The effect of methanol on the crystal growth rate was also examined at 10^0C and at a prescribed supersaturation ratio. As the methanol concentration increased, the crystal growth rate of the α-form decreased and that of the β-form inversely increased.

Effect of temperature, concentrations and addition rate of the reactant solutions

The reactive crystallization of calcium carbonate was carried out by Kitamura by adding 0.05 or 0.2mol/l concentrations of sodium carbonate solutions to the equal molar concentrations of calcium chloride solution in the crystallizer[43]. In this system it appeared that temperature influences on the crystallization behaviours of polymorphs. The nucleation of aragonite was observed in addition to that of calcite and vaterite when temperature was increased to 323 K. However, when the crystallization was carried out at 298K the aragonite crystals did not appear and only the fine particles of calcite and vaterite precipitated. This revealed that crystallization process is composed of three steps; (a). The formation of amorphous precursor, (b). The nucleation, and (c)growth of the calcite and vaterite with dissolving of the precursor, and the transformation from vaterite to calcite by the ''solution mediated'' mechanism[44].

The crystallization behavior and the morphology of calcite and vaterite crystals were observed to be very influenced by the concentrations of reactant solutions and the addition rate of sodium carbonatesolution. The experiment was carried out by mixing 0.05mol/l sodium carbonate solution and 0.2 mol/l calcium chloride solution at the addition rates of 5.0 ml/s. Two different types of crystals were obtained, the prismatic crystal was calcite and the spherulite crystal was vaterite. The portion of vaterite in the precipitates obtained at 0.2mol/l was larger than that at 0.05 mol/l. Furthermore, the crystal size decreased with the concentrations. The decrease of the crystal size may be due to the high nucleation rate with high supersaturation (0.2mol/l). This result also

indicated that at high supersaturation (0.2mol/l) the metastable vaterite tended to crystallize and the stable calcite precipitates preferentially at low supersaturation (0.05mol/l). This result seemed to obey to the ''Ostwald's step rule''. When the addition rate of sodium carbonate solution was compared, the amount of vaterite at the addition rate of 0.5 ml/ was higher than that at 5 ml/s. Since the local supersaturation degree produced in solutions by the addition of the sodium carbonate solution may be lower with the slower addition rate, the decrease of the crystallizing vaterite with the addition rate seemed to be contradictory to the effect of the solution concentrations.

Effect of supersaturation on the crystallization of phenylbutazone polymorphs was studied by Datta and Grant[45]. The article described the effect of degree of supersaturation (σ), on the crystallization of specific polymorphs of phenylbutazone from its methanolic solution at 20 °C. At low initial supersaturation ($\sigma \leq 2.0$, the fraction of the metastable α polymorph in the crystallized product exceeded that of the δ polymorph, while at $\sigma \geq 5.0$, the fraction of the stable δ polymorph increased in the crystallized product. The results were explained by the effect of supersaturation on the relative rates of nucleation and crystal growth of the polymorphs. Furthermore, the mechanism of nucleation and crystal growth also changed with supersaturation. Supersaturated methanolic solutions of phenylbutazone exhibited a critical temperature at which the nucleation rates of the polymorphs decreased drastically. This effect was partly explained by the decreased mobility of phenylbutazone molecules at lower temperatures. Nucleation was most rapid when the crystallization temperature was close to the transition temperature, T_t ($\alpha \leftrightarrow \delta$), between the polymorphs, α and δ. The nucleation rate decreased as the temperature difference between T_t ($\alpha \leftrightarrow \delta$) and the crystallization temperature increased. In another study effect of supersaturation on polymorphs of clopidogrel hydrogen sulfate in drowning-out crystallization was studied. To crystallize selectively forms I and II of clopidogrel hydrogen sulfate (CHS), nucleation behavior and supersaturation level were studied in mixed solvents such as formic acid/isopropanol, *N*, *N*-dimethyl formamide/isopropanol, and *N*-methyl pyrrolidone/isopropanol[46]. The effect of supersaturation on induction time and nucleation rate was evaluated by comparison between nucleation mechanisms of seeded and unseeded crystallizations. Experimental results indicated that the polymorph obtained by crystallization depends on the type of seed crystals, amount of seed crystals, and seeding point. Homogeneous nucleation was desirable for the formation of form I. Form II corresponds to primary nucleation, i.e., homogeneous and heterogeneous nucleations[46].

Supersaturation dependent nucleation control and separation of mono, ortho and unstable polymorphs of paracetamol by swift cooling crystallization technique was studied by Sudha and Srinivasan[47]. In this study a novel method for the separation and crystallization of all the three polymorphic forms of paracetamol from aqueous solution was reported. The polymorphic nucleation behaviour of the paracetamol has been investigated under different concentrations of the solute from pure aqueous solution by adopting swift cooling technique. With the variation in the concentration of the mother solution, the resulting effect of supersaturation on the nucleation rate of the three different polymorphic forms of paracetamol was studied. The variation in the induction period of nucleation at different supersaturation ranges was determined. The nucleation regions of three different polymorphs were separated in terms of supersaturation ranges at the end of the crystallization process. The main advantage of this technique is the achievement of the nucleation control without incorporating any nucleation selecting additives into the mother solution.

Recently the effects of the rate of supersaturation on generation of polymorphic crystallization have been investigated through evaporation and cooling crystallization of m-hydroxy benzoic acid (m-HBA) in methanol, acetone and ethyl acetate, and o-amino benzoic acid (o-ABA) in ethanol. The results revealed that the rate of supersaturation generation and the tendency of growing less stable polymorph were positively correlated. The results revealed that kinetic effects were dominant when the rate of supersaturation generation was high, thereby produced the metastable polymorphs (orthorhombic m-HBA; Form II of o-ABA); on the contrary, more stable polymorphs (monoclinic m-HBA; Forms III and I of o-ABA) were formed when the rate of supersaturation generation was low and the thermodynamic effects were prevailing[48]. Additionally, it was observed that the effects of the rate of supersaturation generation on polymorphic crystallization of m- HBA were not uniform for all solvents. Authors observed that the rate of supersaturation generation was influential to the polymorphic outcome of m-HBA in methanol; however, orthorhombic m-HBA has been constantly produced in acetone and ethyl acetate despite the changing rate of supersaturation generation, suggested that solvent was the determining factor in these two systems[49]. Hu and Deng reported supersaturation control in aragonite synthesis using sparingly soluble calcium sulphate as reactants[50]. Sparingly soluble calcium salts were studied as reactants in the synthesis of needle-like precipitated calcium carbonate (PCC). The morphology and

aspect ratio of the PCC particles were characterized with SEM. The counterions of the sparingly soluble salts influenced the growth kinetics of PCC as well as the polymorphism and morphology of product particles. The authors reported that either chrysanthemum-like or needle-like aragonite could be synthesized from calcium sulphate and sodium carbonate depending on the supersaturation and synthesis conditions. Low concentration and slow addition rate of sodium carbonate solution were favourable to the formation of aragonite. Addition of sodium sulphate to the reaction system (calcium chloride and sodium carbonate) promoted the formation of aragonite and decreased the crystal size of aragonite due to the decrease of supersaturation and adsorption of sulphate ion. The excess added sodium sulphate, however, did not further increase the aragonite fraction. The authors also reported that slow dissolution kinetics of sparingly dissoluble salt was also very important for controlling PCC polymorphism and morphology[50].

Secondary factors in crystallization of polymorphs

Antisolvent Crystallization

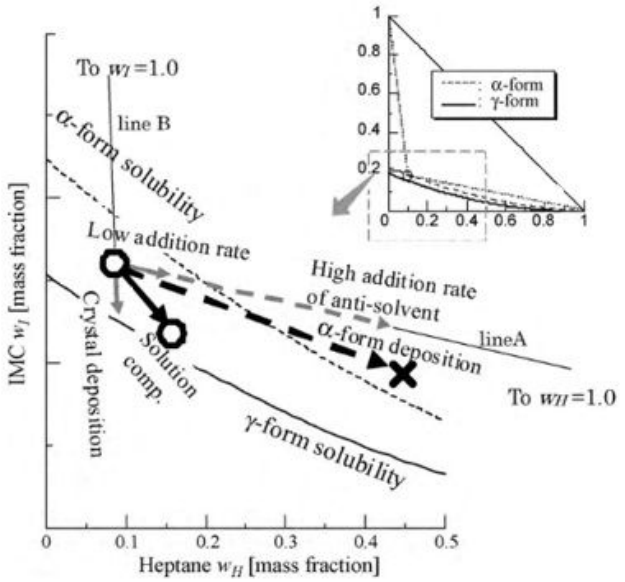

Fig 2. Schematic diagram for controlling polymorphism based on ternary phase diagram[54]

(Reproduced from Takiyama et al. 2010, with prior permission)

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In the manufacture of pharmaceuticals, anti-solvent or drowning-out crystallization is widely used from the viewpoint of the ordinary temperature operating condition and high yield production[50, 51]. However, in anti-solvent crystallization to select the suitable operating conditions for controlling polymorph formation are difficult because a particular polymorph may precipitate at limited temperatures and solvent compositions. Kitamura and Sugimoto reported that the crystallization behaviour of polymorphous crystals of thiazole-derivative depends on the water-addition rate and the initial concentration of the solution in the anti-solvent crystallization[52]. These phenomena were explained with crystallization map in which the stability regions of each polymorph were described. Therefore it becomes necessary to determine the operating conditions for controlling polymorph formation. If several kinds of polymorphic crystals precipitate and the target polymorph crystal is stable form, the solvent-mediated transformation of metastable polymorph crystals must be completely suppressed in order to avoid contamination. In order to obtain only desired stable polymorph, it is required not to be precipitated metastable polymorph crystals. In the anti-solvent crystallization solubility profiles are essential data for crystallization operation design to selectively isolate the target polymorph. Takiyama et al. established a production method of the target polymorph in the anti-solvent crystallization

(Indomethacin–acetone–heptane system)[53]. In this anti-solvent crystallization for indomethacin (IMC), supersaturation was generated by adding heptane (anti-solvent) and the crystals were precipitated. Operation strategy for controlling polymorph formation based on ternary phase diagram is shown in Fig. 2 as a rectangular triangle diagram. The horizontal axis describes heptane composition and vertical axis describes IMC composition, respectively. In order to perform anti-solvent crystallization in the operation area where only a certain polymorphism (γ-form was a target polymorph in this study) deposits, it is necessary to control the feed rate of heptane according to the deposition rate of γ-form. If α-form crystals deposit in the solution, it is difficult to agitate the slurry because agglomerated α-form crystals have cotton-like shape. By the consideration on a ternary phase diagram[54], an operating point left from a solubility curve by addition of heptane. According to rectangular triangle ternary phase diagram, when the anti-solvent is fed to the solution, an operating point moves to W_H= 1.0 by using lever rule along the line A. When the crystals are deposited, an operating point closes to solubility curve along the line B by using lever rule. Finally an operating point moves toward resultant vector of anti-solvent addition rate and crystal deposition rate. An operating point becomes higher supersaturation by antisolvent addition and then an operating point approaches a solubility curve by precipitation of IMC. Hence, the operating point can pass through a specific solution concentration range which does not exceed the solubility of α-form (undesired polymorph) by choosing the optimal anti-solvent feed rate suitably.

In order to determine suitable anti-solvent feed rate, Takiyama et al. (2010), proposedthe antisolvent crystallization model[53]. The assumptions of this semi-batch operation model for seeding type antisolvent crystallization were as follows:

1. The shape of crystal (γ-form) does not change.
2. A nucleation does not occur, and the supersaturation of a solution is consumed with growth of γ-form seed crystals.

The growth rate expressed the difference of solution concentration as a driving force (Eqs. (3) and (4)):

$$\frac{dW}{dt} = K\phi_s\left(\frac{W}{\phi_v\rho_c}\right)^{2/3}\rho_L(w - w^*)^m \qquad \text{Eq. (3)}$$

$$= K_g'(W)^{2/3}(w - w^*)^m \qquad \text{Eq. (4)}$$

Growth rate constant K'g and the growth order *m* were computed by optimization calculation from the solution concentration change of preliminary γ-form crystal precipitation experiments.

The model for anti-solvent crystallization operation was proposed using the growth rate constant in each solvent composition. And the IMC concentration change of the solution was predicted from the simulation result. The operation model is as follows:

$$\frac{dW}{dt} + \frac{dM}{dt} = P_H \qquad \text{Eq. (5)}$$

$$\frac{dW}{dt} + M\frac{dw}{dt} + w\frac{dM}{dt} = 0 \qquad \text{Eq. (6)}$$

$$w_H(t) = \frac{\int_0^t P_H\, dt}{Mw + M_0 - M_0w_0 + \int_0^t P_H\, dt} \qquad \text{Eq. (7)}$$

Eq. (5) is total mass balance of semi-batch operation for antisolvent crystallization. Eq. (6) is IMC component mass balance and Eq. (7) is heptane composition in the solution at time "*t*".

It was proposed that (1) The stability of the polymorph of IMC crystal in the solution changed not only with temperature but also with composition of the mixed solvent. (2) The modelling of the crystallization

operation for determining the optimal anti-solvent feed rate was carried out by using the ternary phase diagram, and the operation strategy for considering control of polymorph formation was proposed.

In another experiment, Takiyama and Minamisono reported control of polymorphism in the anti-solvent crystallization by using four different methods A, B, C and D respectively to get desired polymorphic form of Indomethacin[55]. The drug was dissolved in acetone and heptane was used as anti-solvent for this method. The anti-solvent addition rates in each experiment were determined by the simulation. Method A was the method that an anti-solvent was added at the constant flow rate. Method B was the method that the addition rate of an anti-solvent increased in three stages. Method C was the method that an anti-solvent was added intermittently at the constant rate. Method D was anti-solvent crystallization with a particular temperature profile.

For method A, three runs were carried out at anti-solvent addition rates of 0.726, 2.46 and 3.68 g/min for 120 minutes respectively. In Run1, precipitation of α-form was not observed during the experiment. It became clear that γ-form can be selectively obtained from this result using an anti-solvent addition rate with which solution composition does not approach the solubility of α-form. So, an anti- solvent addition rate was adequately low. In Run 2 and Run 3, α-form deposited during the experiment. In order to obtain γ-form in stability, there was an anti- solvent addition rate, which did not exceed the solubility curve of α- form. It was confirmed that it was important to control the solution composition in the operation area where only γ-form deposits using the ternary phase diagram and the simulation. However, under the conditions of a constant addition rate, the batch operation time became long.

In method B i.e. gradual change of addition rate (Run 4), it was understood that a crystal growth rate constant became large with heptane composition. Using the nature of this crystallization phenomenon, if an anti-solvent addition rate increases gradually, the batch operation time will be shortened. Then, the end point of Method A and Method B (Run 4) were compared by the simulation. Under the same batch time condition, the end point of Method A (Run 1) is $W_H = 0.29$ (yield 29%) and Method B (Run 4) is $W_H = 0.52$ (yield 58%), respectively. In this way, when Method B was used, it is expected that the yield can increase even in the same batch operation time. From the experimental result of Run 4, γ-form was selectively obtained in 2h after the experiment start-up[55].

For method C, two runs were carried out at an anti – solvent addition rate of 3.60 for 100 min with 20 min intermission (Run 5) and 2.46 g/min for 110 min with 10 min intermission (Run 6), respectively. It was observed that the existence of local supersaturation near the anti-solvent addition position is a problem under this operating condition. If the crystallization is carried out using the lower addition rate than the critical rate at which the accumulation of α-form occurs by local supersaturation, and in the operation region in which solution composition does not exceed the solubility of α-form, it is considered that γ – form can be obtained selectively. In the early stage of Run 5, the plate-like crystal (γ -form) deposited. However, in the middle stage of Run 5, the cotton- like crystal deposited in large quantities, and stirring operation became difficult. In Run 6, although the cotton-like crystal deposited in the middle of the experiment, the crystals, which suspended at the end of batch operation time became only γ-form[55].

In method D (anti-solvent crystallization with a particular temperature profile), it was observed that if the solution is heated from 313 to 333 K at anti-solvent addition rate of 2.70 g/min for 2h then the pure γ form gets precipitated with an yield of 27 %. However, the yield of pure γ form could be increased upto 65 % when the solution is heated from 313 to 333 and from 323 to 313 at anti-solvent addition rate of 2.70 g/min for 2 h[55].

The aforesaid research suggested that it is important to select the suitable operating conditions for controlling polymorph formation in anti-solvent crystallization because a particular polymorph may precipitate at limited temperatures and in limited solvent compositions.

Controlled growth of polymorphs by pH titration technique

The pH titration method is also known for selective growth of polymorphs in their pure form. However, its use in pharmaceutical industries has not been properly explored as compared to antisolvent addition and super saturation processes. Potentiometric cycling for polymorph creation $(PC)^2$controls the level of supersaturation by altering the pH of the solution. This approach, which requires the solute to have a pKa in an appropriate range for the solvent and available buffers, was originally designed to measure the intrinsic solubility of ionisable compounds, and is described in detail elsewhere[4, 56-58]. The $(PC)^2$ method explores the

metastable zone, starting from the kinetically driven highest-energy polymorph which precipitates at high supersaturation, through to more stable forms which precipitate at lower supersaturation. This is achieved by cycling the system between supersaturation and subsaturation by pH variation. Metastable polymorphs encountered during this process are not, in general, stable enough to isolate, but from time to time a metastable polymorph arises which is stable enough to characterize. Continued cycling between supersaturated solution and subsaturated solution will push this metastable form towards morestable ones.

The anti-depressant pharmaceutical tianeptine has been investigated to determine the dynamics of polymorph formation under various pH conditions. By varying the pH two crystalline polymorphs were isolated. One polymorph is an amino carboxylic acid and the other polymorph is a zwitterion[2].

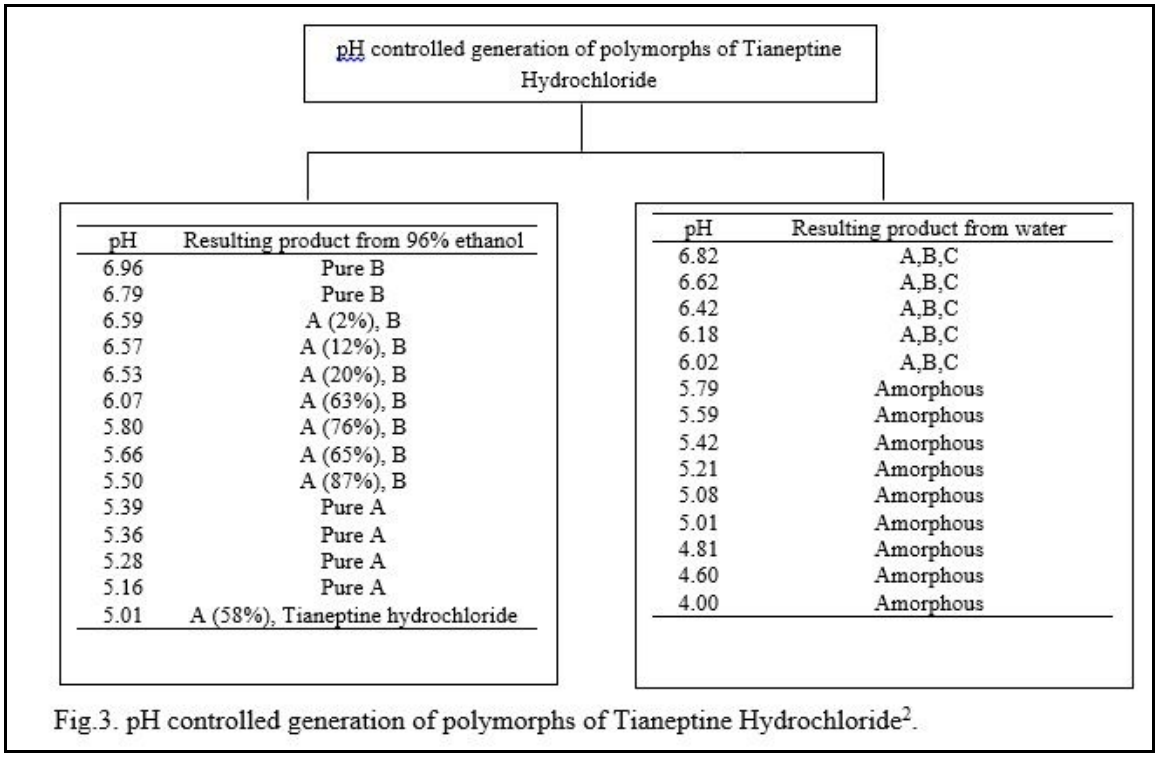

Fig.3. pH controlled generation of polymorphs of Tianeptine Hydrochloride[2].

Fig.3. pH controlled generation of polymorphs of Tianeptine Hydrochloride[2].

Orola et. al., [2] have titrated fourteen samples of the sodium salt of tianeptine (0.40 g) by dissolving in 20 mL of ethanol (96%). The tianeptine solutions were titrated with 0.547 M hydrochloric acid to different pH values of 6.96, 6.79, 6.59, 6.57, 6.53, 6.07, 5.80, 5.66, 5.50, 5.39, 5.36, 5.28, 5.16 and 5.01. These fourteen pH-adjusted solutions were allowed to crystallize at ambient temperature. Another series of fourteen samples of the sodium salt of tianeptine (0.20 g) were each dissolved in 50 mL of water. Titration with hydrochloric acid (0.5470 M) to the following pH values: 4.00, 4.60, 4.81, 5.01, 5.08, 5.21, 5.42, 5.59, 5.79, 6.02, 6.18, 6.42, 6.62 and 6.82 was performed. The pH adjusted samples of the sodium salt of tianeptine in ethanol yielded pure "A", pure "B", a mixture of "A" and "B", and also a mixture of "A" and tianeptine hydrochloride as shown in Fig 3. The initial pH of sodium salt of tianeptine in ethanol solution was about 9.1. At pH 6.96 and above pH 6.79 the metastable polymorph "B" crystallized from the solution of the sodium salt of tianeptine. Between pH 6.59 and 5.50 the crystallization product was a mixture of both stable polymorph "A" and metastable polymorph "B". From pH 5.39 to 5.16 the stable polymorph "A" crystallized. The mixture of "A" and the hydrochloride of tianeptine formed at a pH less than 5.16. The respective polymorphs and their mixtures were determined by PXRD analysis of the crystal samples harvested at indicated pH values. The results show that with a decrease of pH the metastable polymorph B changes to the stable polymorph "A". The crystallization results of the pH-adjusted ethanol solutions of tianeptine sodium salt show that there was a region between the pH value of 5.50 and 6.59, where "A" and "B" forms coexisted in a state of equilibrium between the two polymorphs. This equilibrium was pH dependent and as the hydrogen ion concentration increased, the equilibrium shifted to the left and the stable acid form "A" of tianeptine predominated. The equilibrium shifted to the right as the hydrogen ion concentration decreased and form "B" predominated. Crystallization of the pH-adjusted water

solution of the tianeptine sodium salt yielded a mixture a crystalline product when the pH of the solution was above 6.02 (Fig 3.). Utilizing PXRD, the crystals were determined to be an equilibrium mixture the stable "A" polymorph as well as the zwitterion "B", and "C", with form "A" predominating. An amorphous precipitate was observed in water solutions after addition of hydrochloric acid when the pH was below 5.79, as shown in Fig 3.

Fioritto et al, reported solubility measurement of eight polymorphic compounds via pH - metric titration technique[59]. Eight ionisable compounds, Acetaminophen, Acetazolamide, Chlorpropamide, Sulfamethoxazole, Sulfathiazole, Furosemide, Premafloxacin and Proprietary compound (Pfizer compound X), that existed at least in two polymorphic form were subjected for the pH metric titration technique. The results of this study showed that the pH metric titration technique for solubility measurements serves as a valuable tool to produce and measure the solubility of stable form of ionisable polymorphic compounds. The authors reported that, when using the pH metric titration technique, if the intrinsic solubility was found to decrease over the course of titration experiment (% RSD < 2.5%), it was predicted that the compounds were converting from metastable to more stable forms. Conversely, when using the pH metric titration method, if the intrinsic solubility was found to remain constant over the course of titration experiment (% RSD < 2.5%), it was predicted that the compounds were not changing the form. The intrinsic solubility values of the metastable forms of Furosemide, Compound X and Sulfamethoxazole remained constant over the course of three titrations (% RSD < 2.5%). In the case of Furosemide, the metastable form converted to stable form within 30 min of during the experiment. Therefore, during the pH metric titration, it is believed that the metastable form reprecipitated as the stable form prior to the start of titration. In the case of compound X, the metastable form did not convert to the stable during the experiment. In the case of Sulfamethoxazole, the metastable form converted to hydrate during the pH metric experiment. In case of Premafloxacin, the stable form converted to amorphous material during the experiment[59].

Additive effects as a secondary factor in crystallization polymorphs

Two points must be considered for controlling growth of polymorphs by the help of additives. First one is the approach with the concept of tailored-made additive[33, 37, 38] and the second one is kinetic effect[20, 32, 60, 61]. It must be noted that the additives will effect on both stable and metastable polymorphs. Therefore, to know the relative effect of additives on each polymorph is important for the control.

The influence of structurally related additives, namely N4-acetylsulfamerazine (NSMZ), sulfadiazine (SD) or, sulfamethazine (SMZ), on the rate of the solvent-mediated polymorphic transformation (I-II) of sulfamerazine in acetonitrile (ACN) at 241ºC was studied[62]. It was observed that structurally related additives significantly inhibit thetransformation of Polymorph I ofSMZ to Polymorph II in suspension in ACN,by inhibiting both thenucleation and thecrystalgrowth of themorestablePolymorph II.

Kitamura et al., reported that L- phenylalanine as an additive suppresses the nucleation and growth of both polymorphs of L- Glutamic acid[32]. In another study, Orola et al., crystallized tianeptine polymorphs in the presence of glutaric acid, suberic acid, nicotinamide, 4,4-bipyridine. Mixtures of equimolar amounts (0.17 mM) of tianeptine and additives were dissolved in hot ethanol. The solutions were allowed to crystallize at ambient temperature[2]. A mixture of equimolar amounts of tianeptine and mildronate dihydrate (3-(2, 2, 2-trimethylhydrazinium) propionate dihydrate), zwitterion, was dissolved in hot 1:1 water/ethanol solution and left to crystallize at ambient temperature. The authors reported that, the use of additives to block or enhance the formation of a single polymorph indicated that, an organic acid has enhanced the formation of the zwitterion polymorph/acid polymorph mixture, but the presence of an organic base promoted the formation of the acid polymorph. Addition of a zwitterion did however resulted in crystals of the zwitterion polymorph. In solution, mixing "A" and "B" in equimolar ratios the metastable "B" transforms to the stable "A" polymorph. Although melting points of zwitterions were usually higher than those of specific amino acid, in this instance a lower melting point was for the zwitterion notwithstanding the fact that there were hydrogen bonds in this moiety. This suggested that the hydrogen bonds in "B" were relatively weak because each nitrogen atom has formed multiple hydrogen bonds to adjoining oxygen atoms.

Song and Helmut, reported that crystallization reactions are controlled by soluble additives and insoluble additives[63, 64]. There are two principal types of additives, which are used for the control of crystallization events. The first one, associated with the so-called insoluble or structural matrix, is composed of

water insoluble molecules like chitin or collagen. Crystallization reactions are then controlled by soluble additives — the so-called soluble or functional matrix. Combination of these two additive types in a synergistic way, leads to the exquisite control, which is generally found in bio mineralization events. An overview of the roles of soluble and insoluble additives in crystallization control is shown in Fig. 4. Crystallization control by insoluble additives is a templating approach by which the insoluble additive serves as a template to control either the nucleation or polymorphs of a nucleated crystal. In addition, they can promote crystallization by heterogeneous nucleation which has, lower activation energy barriers than homogeneous nucleation. A number of different templating possibilities were reported including Langmuir monolayers[65-69], self-assembled monolayers[70-74], latexes[75,76] colloidal crystals[77,78] and other insoluble scaffolds like sea urchins spine replicas[79] and viruses[80]. These insoluble templates have advantages and disadvantages with various characteristics. A detailed study on control on crystallization by the help of additives has been carried out by Song and Helmut[64]. Few of them are discussed below.

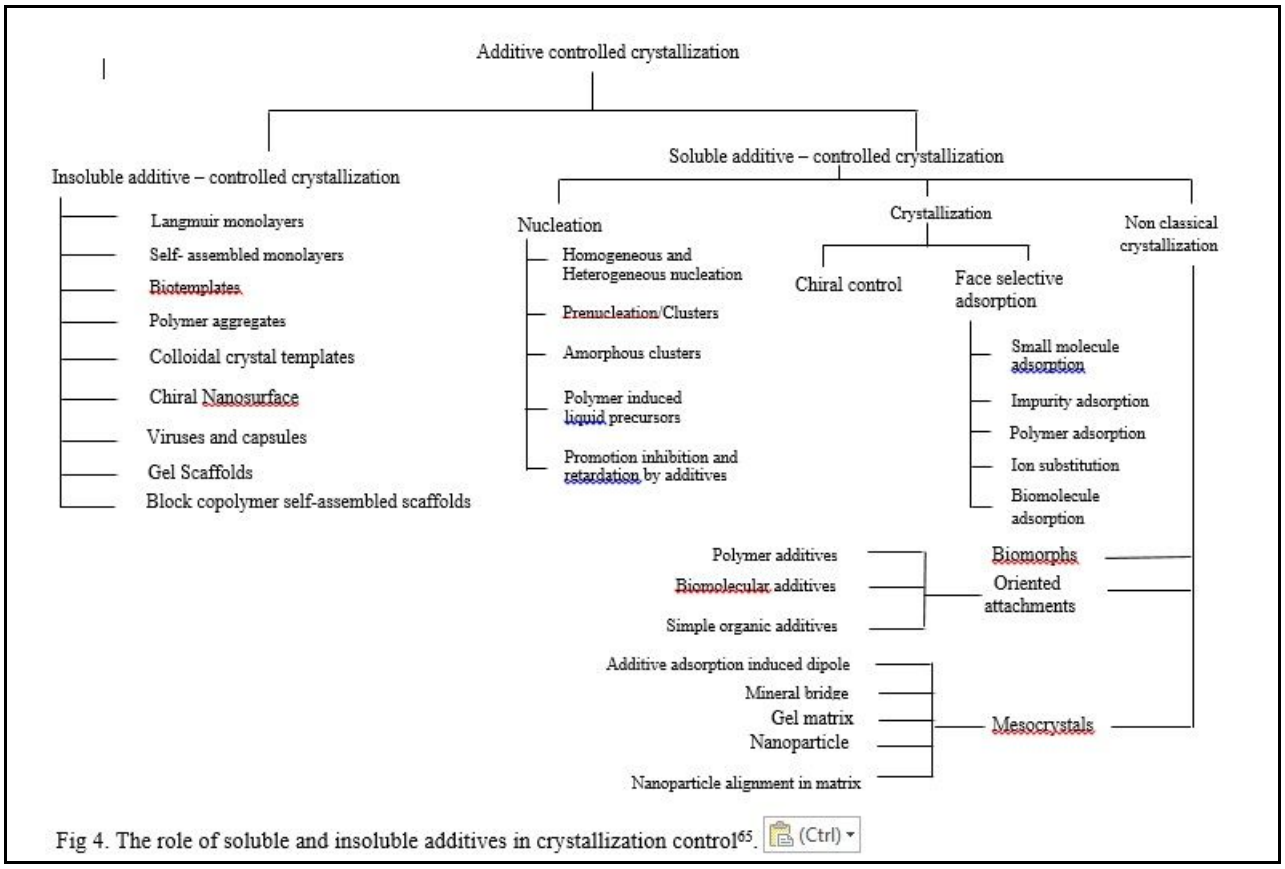

Fig 4. The role of soluble and insoluble additives in crystallization control[65].

Fig.4. The role of soluble and insoluble additives in crystallization control[65].

Polymorph control by insoluble additives

Langmuir monolayers

Langmuir monolayers (LM) can be used to control the polymorph and the nucleation face of a crystal. The basic advantage of LM is that they can be compressed and therefore, the distance and packing between the functional surfactant groups can be varied[81-83]. Mann and co-workers proposed that the lattice match between polar head groups of fatty acids and crystal planes of $CaCO_3$ is a critical factor in controlling the crystal orientation[84]. They also found that the degree of compression of a stearic acid monolayer influences the homogeneity of vaterite nucleation[85].

Self – assembled monolayers (SAMs)

Self-assembled monolayers (SAMs) do not compress since the surfactant molecules are fixed on a surface. For SAMs, the functional group of the surfactant is of importance as well as the substrate onwhich the

surfactants are attached. A number of SAMs were obtained from alkanethiols on gold and silver surfacesimmobilized on silicon substrates[74]. By functionalization of the thiols with different terminal groups, -- COO, -- OH, -- SO_3^-, and -- PO_3^{2-} for example, SAMs can be used for a precise control over the oriented nucleation of a series of specific crystal faces of calcite[70-73].

Rigid solid body templates (Latexes)

Rigid bodies were used as templates to shape the final crystal. A number of crystalline inverse opals have been synthesized via a templating approach with a colloidal crystal. For example, polystyrene colloidal crystals were infiltrated with amorphous calcium phosphate (ACP) [77] or amorphous calcium carbonate (ACC) [78] that subsequently crystallized in the interstices of the colloidal crystals and thus formed a macroporous crystalline replica of the colloidal crystal. The latexes can be used as templates to create size adjustable porosity in single crystals like ZnO [86] or $CaCO_3$[81, 87].

Block copolymer self – organized templates

Deformation of an organic self-organized template upon mineralization can lead to complex structures if a synergetic structuration of crystallizing and organic mesophase can be reached, which can lead to a feedback loop. Delicate neuron like structures formed by adsorption of the polymethacrylic acid block onto all hydroxyapatite (HAP) faces parallel to the *c*-axis. This blocking effect inhibits these surfaces from further growth and only allows for *c*-axis growth of the HAP filaments. On the other hand, the growth of HAP filaments deforms the polymeric aggregate, which in turn influences the growth of HAP crystals in a feedback loop. This synergetic structure formation process shows the advantage of feedback loops in the synthesis of complex non-equilibrium structures[88].

Gel scaffold grown single crystals

The porous network structure of gels places a highly complex restriction on the crystallization reaction environment, including material diffusion suppression, nucleation retardation, and stress alleviation[89]. These benefits motivated a substantial research in the crystallization community to realize the formation of single crystals. Carcamo and coworkers grew calcite and KH_2PO_4 single crystals in industrial sodium silicate[90]. They found the morphology of calcite was defined by a rhombohedron. The agarose gel-grown calcite single crystals reported more recently by Estroff and coworkers were also rhombohedral in shape[91].

Enantioselective crystallization on nanostructured chiral surfaces

Dressler and Mastai studied the enantioselective crystallization of racemic and also conglomerate crystals of amino acids on chiral self-assembled nanofilms of cysteine[92, 93]. The authors used nanosize chiral surfaces of cysteine for the chiral recognition and crystal morphology modification of glutamic acid. The nano chiral surface was fabricated by the SAM assembly technique. X-Ray diffraction (XRD) demonstrated that enantiomers of glutamic acid with identical chirality to that of the cysteine surface grow in an unchanged manner on the surfaces. For example, while a preferential growth of the D-enantiomer along the [020] direction, L-glutamic acid did not show preferential orientation when crystallizing on the L-cysteine surfaces. Thus, enantiomers with opposite chirality to that of the chiral surface grew in a particular direction on the surface.

Control by soluble additives before crystallization

In addition to insoluble additives which act as templates, soluble additives can influence crystallization reactions to a large extent in terms of morphology, size, and polymorph of the crystal. Additives usually perform multiple roles in a crystallization process, which start with the complexation of ions, generate the local ion enrichment, and decrease the supersaturation of solutions [64, 94].

Classical homogenous nucleation

Zhang and Liu reported the first experimental observation of the structural transition of nucleating clusters at the initial stage. The precondition of their observation was based on the assumption that the phase behavior of colloidal suspensions and that of atomic and molecular systems is similar[95]. They built a setup with polystyrene (PS) colloidal particle suspension sealed between two indium tin oxide-coated conducting glass plates separated by insulating spacers. The results of their experiments suggested that the initial structure of the

crystal nuclei is supersaturation-dependent. At high degrees of supersaturation, classical nucleation theory was plausible in describing the dynamic behavior of nucleation. At low degrees of supersaturation, the crystal nuclei tended to nucleate with a metastable liquid-like structure. Subsequently the liquid-like structure evolves to the stable and crystalline-ordered structure. Such a gradual route significantly facilitates the nucleation dynamics with a lower nucleation barrier.

Heterogeneous nucleation

A nucleus undergoes further growth towards the formation of a crystal above its critical size. During this process, the presence of a substrate or template can exert influence on nucleation[96]. Since the surface energy of a nucleus on a surface in most of the cases is lower than that in solution due to the lower nucleus-- liquid interfacial free energy, heterogeneous nucleation is usually energetically favored. The interaction between these three phases lead to a stabilized polymorph or a specific crystal plane parallel to the template surface[97].

Polymer induced liquid precursor (PILP) formation (Polymer Templating)

In a PILP process, the negatively charged polymeric additive, like poly (aspartic acid) or poly (acrylic acid), induces a highly hydrated amorphous phase separated in the crystallization solution of mineral systems like $CaCO_3$, while simultaneously delaying crystal nucleation. The metastable precursor phase usually coalesces into amorphous films settling on the substrate. A pure liquid phase can only be observed when large quantities of the phase accumulate at the interface of an air bubble. The observation of partially coalesced particles at the micrometer size scale in the systems suggests that the polymer and associated hydration water impart some fluidic character to the amorphous precursor[98-100]. This was explained as the consequence of a kinetically dominated process, where both the excess water and polymer become excluded with time as the carbonate species compete with the polymer for its bound calcium.

Control by soluble additives after crystallization

Face selective adsorption

A crystal may form ionic faces with charges, coordinatively binding faces, electrically neutral but dipolar faces, or highly polarizable faces as well as hydrophobic faces. Hydrophilic or hydrophobic faces may also form in one and the same chemical crystal system[101]. Additives can recognize the surface bonds of some faces of a crystal and the adsorption process results in a partial saturation of the surface bonds. Thus, the surface energy of crystal faces can be reduced by the adsorption of additives. As a result, crystals with defined shape can be formed in a predictable and selective way, if the additive adsorption is face selective.

Chiral Control

Asymmetric growth of non-chiral crystals

De Yoreo et al., reported the chiral morphogenesis of calcite through the interaction with chiral amino acid molecules[102].

Controlled crystallization of chiral molecules

When a chiral molecule crystallizes from solution, it can form either racemic crystals, conglomerates of separate left- or right-handed crystals of the pure enantiomers, or a racemic solid solution in which the two enantiomers coexist in a disordered manner. Addadi and coworkers realized the kinetic resolution of racemic conglomerates by the addition of enantiospecific chiral inhibitors that prevent ordelay the growth of one of the enantiomorphs[103].

Nonclassical crystallization

An Oswald ripening process occurs when crystals coarsen from a precipitate [104-106]. It is a thermodynamically driven spontaneous process. Small particles, with a higher collision frequency, a greater mobility and a higher surface to volume ratio, have a higher surface energy than large particles. The classical model assumes that the initial formation of many small crystals is followed by the growth of a few larger ones via monomer attachment, at the expense of the smaller particles[106-111]. In contrast to the classical model,

oriented attachment provides an energetically favored pathway to the production of defect-free single crystals by the crystallographic fusion of adjacent nanoparticles. Penn and Banfield coarsened the aggregates of titania nanocrystallites under hydrothermal conditions[106, 107]. They found that adjoining nanoparticles can spontaneously join with each other by sharing a common crystallographic orientation[106].

Miscellaneous Approaches for Polymorph Control

Mechanical grinding

Mechanical grinding has been brought as mechano-chemical alternative to solution-based crystallization. It can be used to obtain crystalline complexes such as salts, charge-transfer complexes and co-crystals. The kinetics of present technique can be enhanced by the addition of a few drops of solvent,that is popularly referred as "solvent drop grinding"[4]. Using the solvent drop grinding technique, Rafilovich and Bernstein[112] reported the crystal structures of four polymorphs of benzidine. Maleic acid polymorphs have also been prepared by this technique[113].

Supercritical Fluidization

The reduction of particle size to micron or submicron level increases the surface area and dissolution rate of the drug and thereby increases its bioavailability[114]. During this process the developed electrostatic charges may lead to aggregation and agglomeration (Ozone ripening), that can decrease the API's performance. Moreover, the classical techniques used for production of micro particles or nanoparticles can lead to thermal and mechanical stress on the particles that may changes the crystallinity of drug and further may increase its tendency to aggregate. In order to avoid these problems and obtain particles with desirable characteristics, Supercritical fluid technology was developed as an alternative method for particle size reduction[4]. Crystallization of a solid using supercritical fluids utilizes two processes - Rapid expansion of a supercritical solution [RESS] and supercritical antisolvent solution (SAS)[115]. Both, RESS and SAS techniques have been applied to manufacture pure polymorphs. Arecent modification of the SAS technique called SEDS (solution enhanced dispersion by supercritical solution) is widely used for polymorph control in pharmaceutical industries. By using this technique, forms I, III and IV of sulfathiazole (using methanol as solvent)[116, 117], different polymorphs of carbamazepine[118], Salmeterol xinafoate (SX)[119], Hydrocortisone[120], flunisolide[121], budesonide[121], terbutaline sulphate[122], natural carotene[123], and many other pharmaceutical drugs[124]have been successfully produced and characterized.Three of the four polymorphs of tolbutamide (Forms I, II and IV), and one of the three polymorphs of barbital (Form II), α-, β-and γ-glycine[125], poly (L-lactide) [126], felodipine[127], and phenylbutazone[128], the metastable polymorph of chlorpropamide (CPD) [129]were generated by RESS.

Crystallization using micro porous membranes

Microporous membranes have recently utilised as a new method of crystallisation. The membrane acts as a physical support separating two isothermal solutions, and allows solvent to move between them [130]. The ability to control the rate of solvent transfer by micro porous membranes accurately affects the morphology and the crystallinity of the product obtained[131], in both inorganic[132] and organic materials[133, 134]. The kinetics of nucleation is related to the width of the metastable zone of micro porous membranes, which can be increased by adjusting the solvent transfer rate. By controlling these parameters thermodynamic or kinetic control can be achieved. At low solvent transfer rates the more stable polymorph has time to grow at the expense of the less stable form; high solvent transfer rates induce nucleation at higher values of supersaturation, favouring the appearance and growth of metastable polymorphs[4].

Polymorph control by confinement

Three techniques widely used for polymorph control are capillary crystallization, Crystal nucleation in nanoscopic confinement, and, contact line crystallization, respectively.In capillary crystallization technique large supersaturation factors can be achieved whilst making heterogeneous nucleation difficult. The volume of the tubes is so small that each rarely contains more than one nucleation site. This means that less stable polymorphs can grow without competing with more stable polymorphs nucleated in the same vessel[135]. This method offers the advantage of being able to generate the high-energy forms of the system studied using a near-isothermal approach and requiring only a very small amount of material.

Using nanoporous polymers and glass matrices, the influence of pore confinement on polymorph selection has been studied[136]. Crystallization experiments carried on anthranilic acid in controlled conditions showed that in the presence of nonporous glass beads or commercially available 55 nm controlled pore glass

(CPG), only Form III of anthranilic acid was observed[136]. It was also observed that when a 23 nm CPG was used, the presence of the metastable Form II was also observed. When the crystallization was carried out in the presence of 7.5 nm CPG, only the metastable polymorph Form II was detected[4].

Crystallization around the edge of a drop (contact line crystallization) [137], is a well-known phenomenon, and in the recent years it has been applied to the selective crystallization of metastable polymorphs. The metastable form of paracetamol (Form II) at the edge of a meniscus have been developed[138]. The novelty of this method can be understood from the fact that Form II has not converted to the more stable Form I via the solvent mediated phase transformation that normally occurs if the metastable crystals are not harvested from the solution fast enough[4].

Polymorph control by Sonocrystallization

The rate of crystallization of metals, inorganic salts [139], and, co-crysatls can be enhanced using Sonocrystallization[140]. Sonocrystallization is commonly used during the nucleation phase of the crystallization process that allows the nucleation to take place at lower supersaturation levels. The factors that contribute to sonocrystallization process are - a). Enhancement of nucleation by the shear forces that are produced when the bubbles produced by cavitation collapse[141], b). Enhancement in rate of crystallization by the fragmentation of seed crystals[142,143], and, c). Uniformity in crystal size distribution[144]. By using sonocrystallization, metastable form of p-amino benzoic acid has been achieved[145]. The major advantage of this technique is the generation of smaller crystals with uniform shape and crystal morphology, lesser agglomeration and generation of polymorphs closer to the ground state[4].

High Throughput Crystallization (HTC)

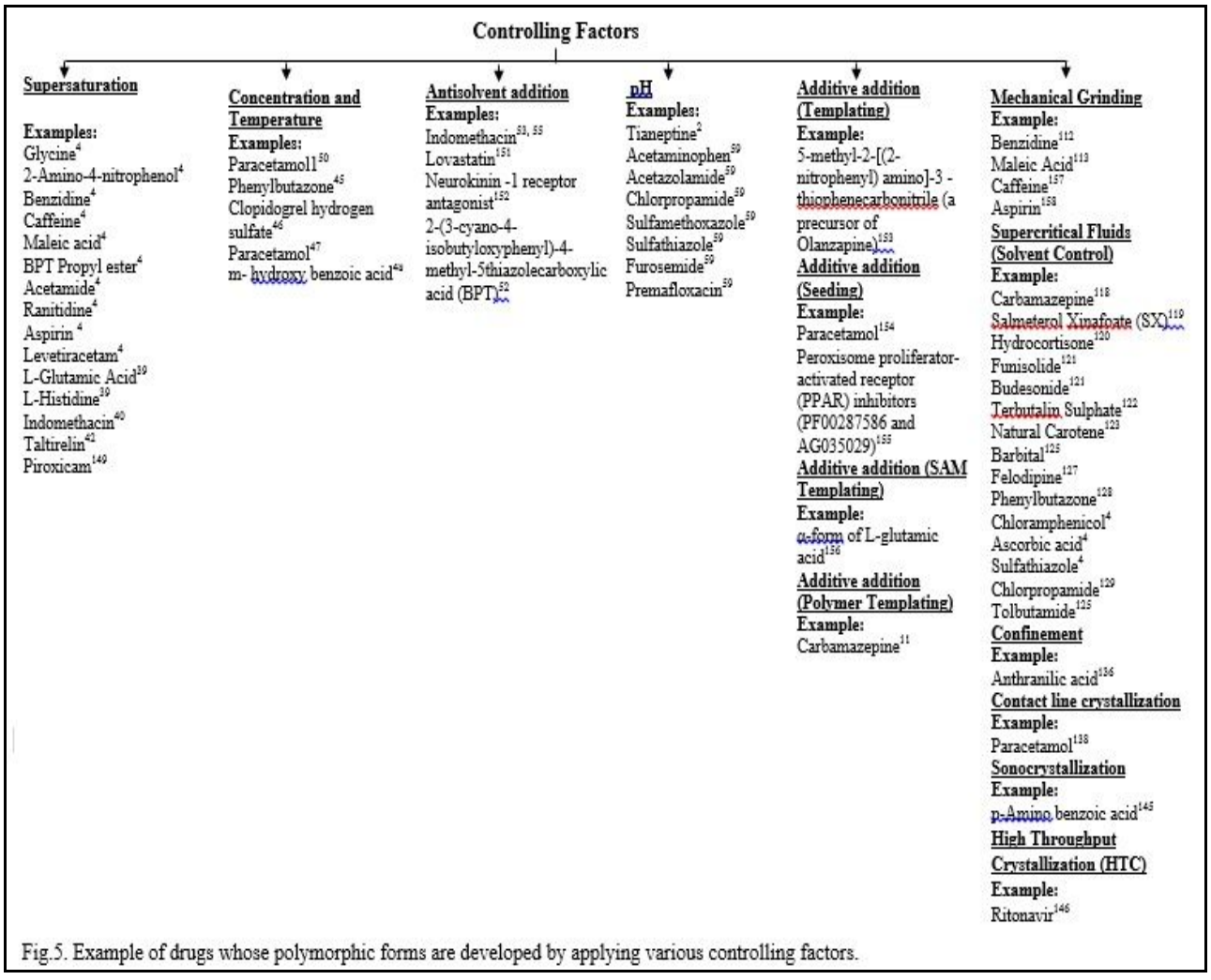

Fig.5. Example of drugs whose polymorphic forms are developed by applying various controlling factors.

Fig.5. Example of drugs whose polymorphic forms are developed by applying various controlling factors.

HTCpermits rapid and more comprehensive exploration of solidfrom diversity with only small amount of drug. Moreover, the HTC could provide a solution to the complex problems like a condition where a desired polymorph is tough to be obtained either through pH control, temperature gradient, combination of solvents in different concentrations and at different rates, addition of additives, radiation or, mechanical or chemical confinements [4]. By using HTC, about two thousand experiments have been carried out by Morissette et al., to find all possible polymorph of ritonavir using only 2 g of drug [146].

The list of drugs whose polymorphic forms are developed by applying various controlling factors discussed in the above sections are summarized in Fig.5.

Conclusions and Future Perspectives

The choice of the most suitable form of the crystalline drug in the initial stages of drug development can save time and cost in the initial stages of drug development. Recently, a good deal of research has been directed towards achieving this goal. The systematic isolation and early characterization of the largest number of possible forms of a drug reduces the chances of surprises at the late production stage due to identification of a new crystalline form or phase change. In future, with the development of more sophisticated computational tools, the main focus of many investigators should to be able to predict all the possible forms of a drug from its molecular structure. This will make the process more selective as well as sensitive. Moreover, a high throughput tool is expected to get selective production of desired polymorph with desirable stability.

The origins of the multiple solid forms of a drug molecule, either due to differences in packing arrangement or conformation of the molecules should be understood properly and should be the first step in prediction of type of polymorph. Improved experimental methods leading to more accurate and detailed phase diagrams are also finding increased use in determining the stability of various polymorphs. It is important to make every effort to prepare and to identify the most stable polymorph in order to guide the selection of the optimal form for development. An increased understanding of the phenomenon of polymorphism should enable pharmaceutical scientists to gain control over the crystallization process in order to selectively obtain the desired polymorph or, suppress the growth of an undesired one. Phase changes during processing and scale-up are a problem, which may be avoided by carefully designed initial small-scale studies. The availability of detailed structural data, combined with strategic design of substrates and additives, has led to significant advances in the control over the polymorphs obtained in a particular crystallization. With all the information available from these initial studies, it should be possible to design and to select processing conditions which would give a desired polymorph and maintain the desired form throughout the various stages of drug processing and manufacture. In view of this several parameters for controlled crystallization and stabilization of desired crystal form like temperature, supersaturation, addition of polymorphous seed crystals, antisolvent addition, antisolvent addition rate at different temperature as well as at particular temperature, pH controlled crystallization and addition of additives has been discussed.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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