Article

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Cryst. Growth Des., **Just Accepted Manuscript** • Publication Date (Web): 19 Jun 2014

Interesting Morphological Behavior of Organic Salt Choline Fenofibrate: Effect of Supersaturation and Polymeric Impurity

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Abstract

Crystal habit of drug molecules can have significant influence on the processing and performance of pharmaceutical products. During the development of Trilipix®, a pharmaceutical product used for the treatment of mixed dyslipidemia, several crystal habits were observed for the active ingredient Choline Fenofibrate. The dissolution and performance of the drug product were not impacted by changes in crystal habit of the active ingredient due to high solubility of the drug. However, the formulation process was impacted by variations in crystal habit of the active ingredient, requiring robust control of the crystal habit. The crystal habit was greatly influenced by supersaturation during crystallization from a mixed solvent system comprising of methanol and isopropanol. In addition to supersaturation, trace levels of a polymeric impurity in the starting material Fenofibrate had a detrimental effect on the crystal habit. This article discusses the effects of these factors on the crystal habit of Choline Fenofibrate and the design of a crystallization process to deliver the target crystal habit, most suited to the formulation process. The article also provides preliminary mechanistic insights into the crystal habit of this organic salt using an extension of the spiral growth model for morphology prediction of organic molecular crystals. An attempt is made to explain the effect of supersaturation and impurity on crystal habit of Choline Fenofibrate using the concepts of stability of surfaces, building units, periodic bond chain theory and the spiral growth model.

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1. Introduction

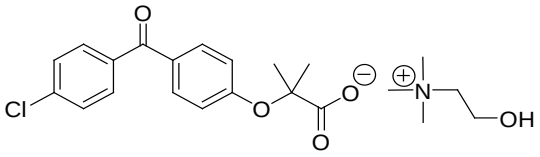
Crystallization is one of the most important unit operations in the manufacture of active pharmaceutical ingredients (APIs). The majority of solid dosage forms of pharmaceutical products contain crystalline APIs [1]. The physical and chemical properties of APIs dictate the processing and performance of drug products. While chemical purity of an API primarily impacts safety of the drug product, physical properties have the potential to impact downstream processing, as well as bioavailability of the drug product. API manufacturing processes rely heavily on the crystallization operation to achieve desired chemical purity and physical attributes of the drug substance. One of the key physical attributes of an API is its crystal habit. API crystal habit can play a pivotal role in defining many properties of the bulk drug such as surface area, surface charge, powder flow, bulk density, wettability, etc. One or more of these properties has the potential to influence the behavior of the drug product formulation process. The ability to tailor crystal habit continues to be a problem of great interest in the API process development community. Most pharmaceutical industry practitioners depend heavily on empirical approaches to obtain desirable crystal habits. These approaches typically involve variations in crystallization solvent and supersaturation, ripening via heat-cool cycles, application of sonication, etc. [2] Recent advances in mechanistic models have provided fundamental insights into crystal shape prediction. It is always beneficial to have sound theoretical understanding to support experiments. Theoretical understanding of the crystal growth process also allows us to configure and design possibilities of morphology control and engineering; thus meeting the current need of introducing the new material or product into the market in the minimum time. Various modifications to the classical Burton, Cabrera and Frank model [3] including the spiral growth model for non-centrosymmetric molecules by Kuvadia and Doherty [4] allow for the prediction of crystal morphology of realistic API molecules and also lay the foundation to design schemes to control and tailor the crystal morphology in accordance with the application requirements.

In this article, we discuss the crystallization process development for Choline Fenofibrate, with a particular emphasis on the crystal habit of this API. Choline Fenofibrate refers to the Choline salt of Fenofibric acid. Choline Fenofibrate is the API in Trilipix®, a prescription medication used along with diet to lower triglycerides and raise HDL (good) cholesterol in people at high risk of heart disease who have abnormal cholesterol levels and are taking a statin medicine to manage

LDL (bad) cholesterol. Trilipix® is available as delayed release capsules for oral administration. Each delayed release capsule contains enteric coated mini-tablets which are manufactured via a wet granulation process. During the early phases of development of this product, multiple crystal habits of the API were observed. The API crystal habit played a critical role in the performance of the wet granulation process. This will be briefly discussed in the paper, followed by a description of the crystallization process. We will then discuss the experimental findings relating API crystal habit to crystallization process parameters in two different solvent systems. We will also describe the impact of trace levels of a polymeric impurity, encountered in the starting material on the crystal habit of the API. Finally, we will attempt to build on the existing knowledge in the crystal growth community about crystal morphology prediction and provide a fundamental approach for prediction of crystal habit of this organic salt, together with mechanistic insights into the experimental observations. It is worthwhile to note that organic salts are a very challenging class of crystals as far as morphology prediction is concerned and in this article we will make a first pass attempt to gain some understanding in that direction.

2. Choline Fenofibrate crystal habits and impact on wet granulation process

The chemical structure of Choline Fenofibrate is shown in Figure 1. Choline Fenofibrate is manufactured from Fenofibrate, which is an API used in Tricor®. The process used to manufacture Choline Fenofibrate during early stages of development of the product is also shown in Figure 1.



Choline Fenofibrate

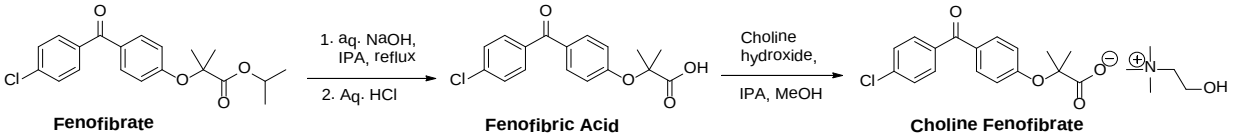


Figure 1. *Chemical structure and manufacturing process for Choline Fenofibrate*

The first step of the process is the saponification of Fenofibrate using aqueous sodium hydroxide. The reaction is carried out in isopropanol (IPA) at reflux (82 ºC) for approximately 2 hours to yield >99.5 % conversion of Fenofibrate. Fenofibric acid is isolated directly from the reaction mixture by acidification with hydrochloric acid. The Fenofibric acid is treated with a methanol solution of Choline hydroxide to form the Choline salt of Fenofibric acid (Choline Fenofibrate). The Choline Fenofibrate solution in methanol is distilled under vacuum. During distillation, IPA is periodically charged to maintain a volume of approximately 12 L/kg of initial Fenofibrate charge. The distillation replaces methanol (MeOH) with IPA, thereby reducing the solubility of Choline Fenofibrate and induces crystallization of the API. The solid product is isolated by filtration. The wet cake is washed with IPA to displace crystallization liquors and dried under heat and vacuum. The early development lots of Choline Fenofibrate manufactured by this process showed differences in crystal habit as depicted in Figure 2. It is worth noting that all of the observed habits belong to the same crystal structure. This was confirmed via independent measurements of their powder X-ray diffraction patterns and melting points.

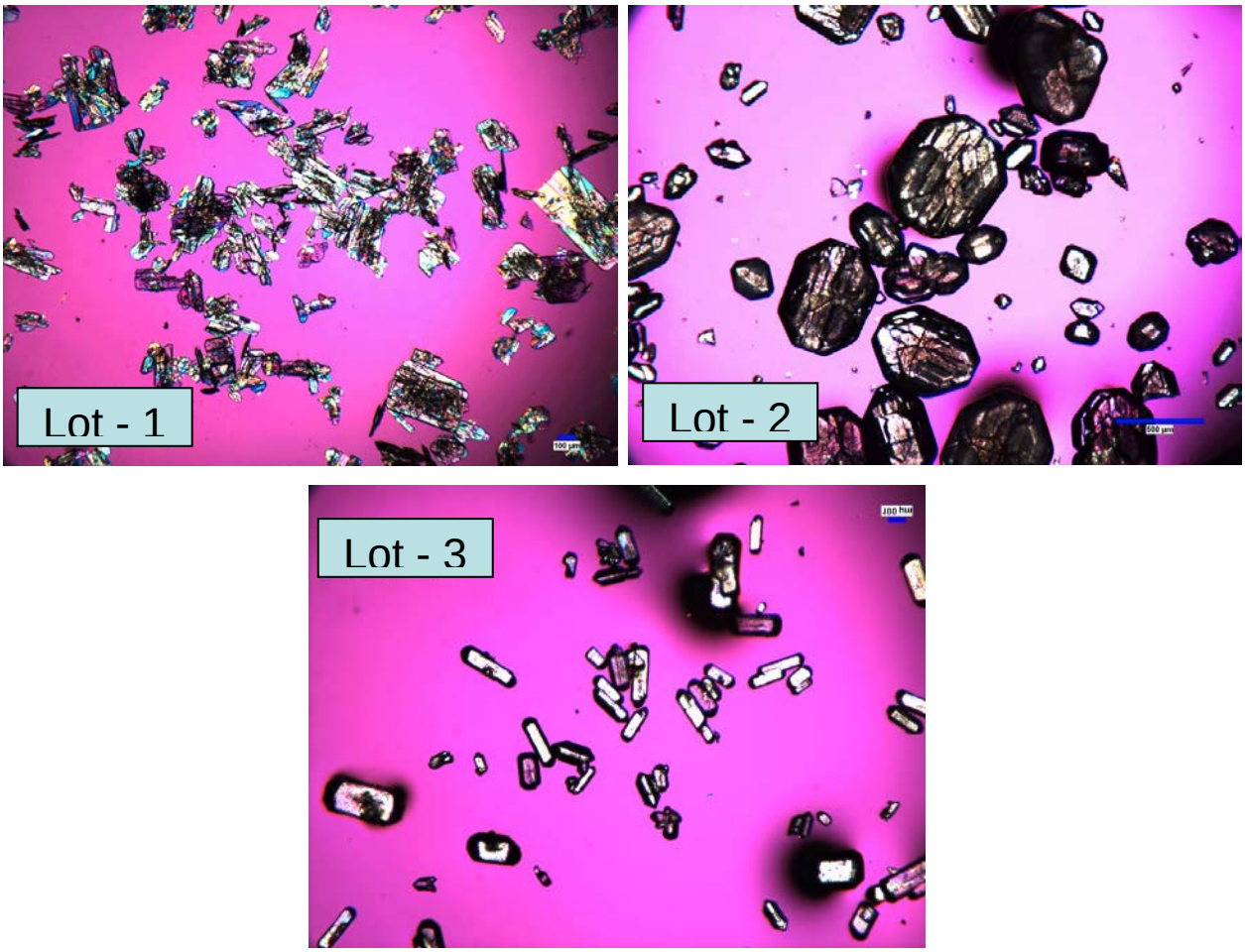


Figure 2. *Crystal habits of Choline Fenofibrate obtained during early development*

The optical microscope images in Figure 2 suggest that Lot-1 crystals exhibit a plate-like morphology with very small thickness. We will refer to this habit as “Thin Plates”. The crystals in Lot-2 appear thicker than those in Lot-1. We will refer to the crystal habit of Lot-2 as “Thick Plates”. The crystals in Lot-3 also exhibit significant thickness like those in Lot-2. However, they appear more elongated compared to Lot-2 crystals. We will refer to the Lot-3 habit as “Prisms”. Our initial hypothesis was that the variations in the crystal habit may be caused by evaporative crystallization. During the evaporation process, crystallization could occur at varying degrees of supersaturation across the different API lots. We will further discuss the validation of this hypothesis in the next section.

It was important to understand the impact of these crystal habits on the wet granulation process. Thus, we evaluated nine different lots of API in the wet granulation. These nine lots covered the

three crystal habits described above, each in three different particle size ranges. The different particle sizes for each habit were obtained by milling large particle size API lots under different milling conditions. The resultant particle sizes ranged from D(v, 0.9) of about 200 microns at the large end, D(v, 0.9) of about 70 microns in the mid range, to D(v, 0.9) of about 15 microns at the small end, as measured by laser light scattering using a Malvern Mastersizer instrument. D(v, 0.9) represents the particle diameter at which 90% of the volume distribution has a lower particle size than this value. The studies conducted using these API lots illustrated clear differences in their performance in the wet granulation process. The API constitutes greater than 50% of the granulation blend and thereby dominates performance of the process. The large particle size prisms and thick plates exhibited very good API flow. However, they produced weak and fluffy granules that did not produce mini-tablets of acceptable hardness. The very small particle size lots for all crystal habits produced granules with acceptable hardness. However, these lots suffered from very poor flow. The medium sized lots of prisms and thick plates showed good flow and they produced granules with acceptable hardness resulting in mini-tablets with optimal properties. However, the medium sized thin plates showed suboptimal flow. This lot of thin plates also required a larger amount of water and longer mixing time in the high shear granulator to reach the granulation end point. Despite this, the granules resulting from this lot were weak and fluffy, resulting in poor quality mini-tablets. Based on these results, the thin plate habit was not desirable for the formulation process. Prisms and thick plates in the medium particle size range were identified as the API property targets for the formulation process. Experience had shown that fairly large crystals of each habit could be obtained from the API crystallization and the desired particle size range could be easily accomplished through a milling operation. Thus, the API development objective was to design a robust crystallization process to consistently deliver large particle size prisms or thick plates which could then be milled to the desired particle size.

3. Crystallization of prisms and thick plates

Since the earlier API process involved evaporative crystallization from a mixed solvent system comprising of MeOH and IPA, further efforts to control the crystal habit were initiated using the same solvent system. To test the hypothesis about the role of supersaturation on crystal habit,

controlled crystallization studies were conducted. A prerequisite to controlled crystallization experiments is determining the solubility of the API under conditions relevant to the process. Solubility studies were conducted at varying ratios of methanol and IPA at different temperatures. The solubility data are presented in Figure 3.

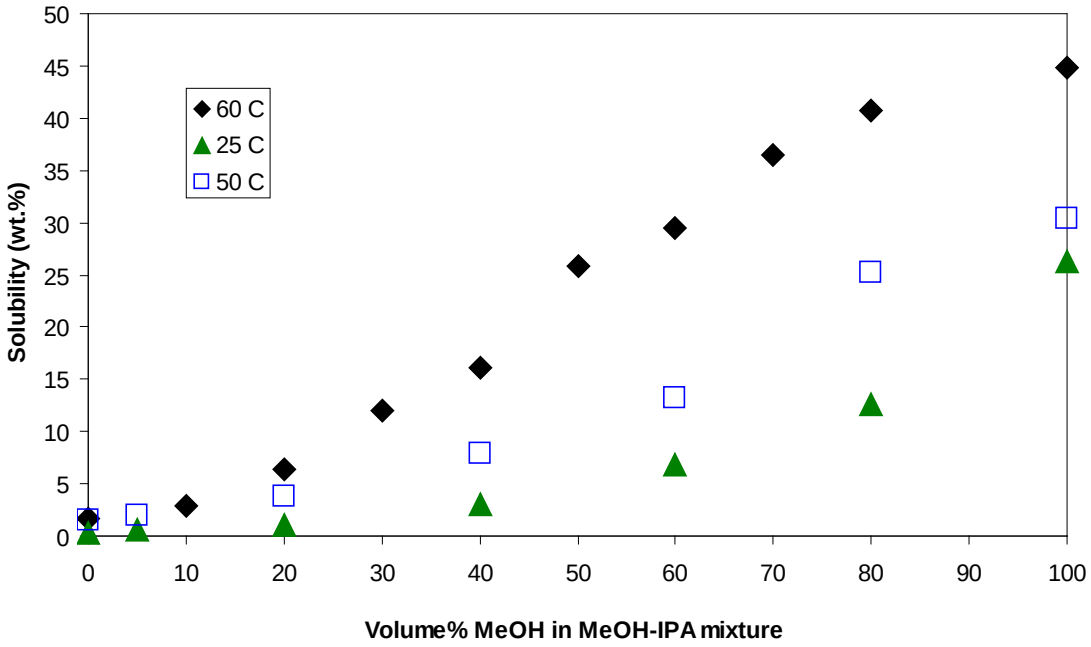


Figure 3. *Solubility of Choline Fenofibrate in MeOH-IPA as a function of temperature*

It is evident from Figure 3 that MeOH offers good solubility for the API and IPA is well suited as an antisolvent. Additional solubility values at intermediate temperatures were calculated using the van't Hoff equation [5]. Solubility at intermediate solvent compositions not experimentally measured, was estimated via interpolation of the above data. Using these data, a crystallization protocol was developed as follows. The Choline Fenofibrate isolated from the evaporative crystallization was dissolved in a certain ratio of MeOH/IPA by heating to a defined temperature. Additional IPA was charged to the solution to generate a supersaturated solution. The supersaturated solution was seeded with 1-5 wt.% (relative to the total amount of API in solution) of milled Choline Fenofibrate seed (Thin plates, D(v, 0.9) of 66 microns). Additional IPA was added at the seeding temperature at a controlled rate to crystallize more product,

following which the slurry was cooled to 20 ºC. The API was isolated by filtration and dried under vacuum at 50 ºC.

The solution supersaturation at seeding is a function of the API concentration, MeOH/IPA ratio and temperature. Table 1 lists some of the key experiments that demonstrate the impact of supersaturation on crystal habit. The supersaturation ratio (C/C*) is defined as the ratio of API concentration in solution (C) to the API solubility at those conditions (C*). Different supersaturation ratios at the seeding point were obtained through various combinations of API concentration, MeOH/IPA ratio and temperature. In each of these experiments (except 10 and 11), addition of seeds was followed by IPA addition over 30 min at the seeding temperature to reduce the MeOH/IPA ratio to 1/4. Since the API solubility decreases as the MeOH/IPA ratio decreases, addition of IPA post seeding was necessary for yield recovery. Following the IPA addition, the slurry was cooled to 20 °C at 10 °C/hr in order to recover more product. The crystal habit of isolated API is also reported in Table 1. This habit matched the habit seen after seeding and prior to IPA addition.

Table 1. *Crystallization Experiments using MeOH-IPA*

Experiment #	API Concentration[1] (wt.%)	MeOH/IPA Ratio[1]	Seeding Temperature (°C)	Supersaturation Ratio[1] (C/C*)	Product Morphology
1	20.1	57/43	50	1.7	Thick Plates
2	9.5	58/42	25	1.5	Thick Plates
3	20.7	59/41	50	1.6	Thick Plates
4	19.5	57/43	50	1.6	Thick Plates
5	17.2	50/50	50	1.7	Thick Plates
6	38	80/20	50	1.50	Thick Plates
7	36	80/20	50	1.42	Thick Plates
8	34	80/20	50	1.35	Thick Plates
9	7.2	40/60	22	2.5	Prisms
10	12.6	75/25	22	1.16	Thin Plates
11	12.3	75/25	25	1.1	Thin Plates

[1]Value at Seeding Conditions.

The experiments in Table 1 indicate that crystals with predominantly thick plate habit are obtained at a supersaturation ratio in the range of 1.3-1.7. Various combinations of the seeding temperature, MeOH/IPA ratio and API concentration were used to generate supersaturation in this range and all of those experiments produced thick plates. Higher levels of supersaturation (C/C* > 2) produced crystals with predominantly prism-like morphology and lower levels of

supersaturation (C/C* ~ 1.1) resulted in predominantly thin-plate morphology. Representative scanning electron micrographs (SEM) and optical microscope images of the three habits are shown in Figure 4.

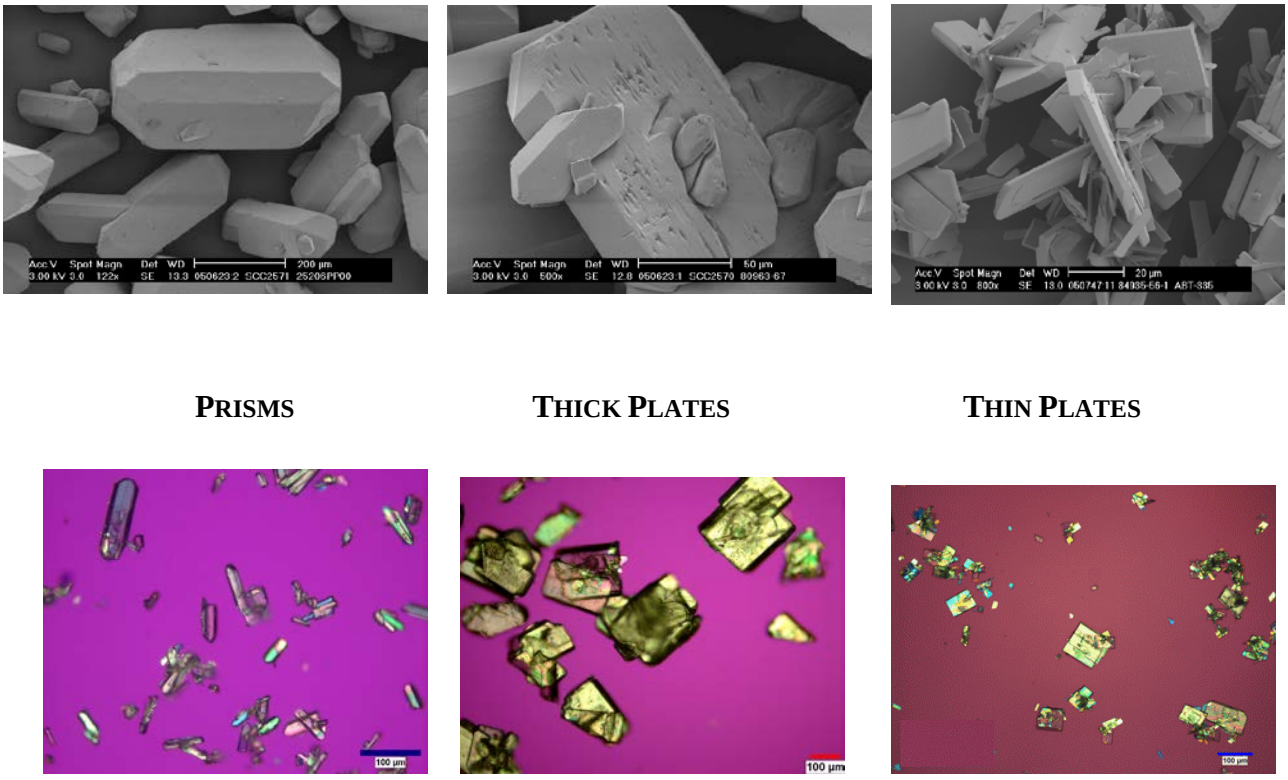


Figure 4. *SEM micrographs and Optical Microscope images of Choline Fenofibrate habits*

These experimental results validated our hypothesis about the role of supersaturation in defining the crystal habit of Choline Fenofibrate crystallized from MeOH-IPA solvent system. In addition, they provided the framework to design the crystallization process to deliver API with thick plate habit. The manufacturing process was designed as follows. The first isolation of Choline Fenofibrate followed the evaporative crystallization process from MeOH-IPA described earlier. The isolated API was dissolved in 80/20 MeOH/IPA at 60 °C at a concentration of 34 % by weight of the solution. The solution was gradually cooled to 50 °C to generate a supersaturation ratio of about 1.4 and seeded with 1 wt.% seed (relative to the total amount of API in solution). The seeds were added as a slurry in IPA. After seeding, a preheated charge of IPA was gradually added maintaining a temperature of 50 °C, to obtain a MeOH/IPA solvent

ratio of 30/70. The slurry was cooled to 20 °C over 2 hours. The MeOH content of the slurry was further reduced through a constant volume distillation under vacuum at ~20 °C. The constant volume was maintained by charging IPA during the distillation. The API was isolated by filtration and dried under vacuum at approximately 50 °C. These process parameters were chosen for optimal throughput and yield while maintaining good operational robustness. The distillation operation after the cooling step reduces the MeOH/IPA ratio and thereby offers a higher yield of the product without any negative impact on the thick plate crystal habit.

Other crystallization parameters were also studied for their effect on crystal habit. The effect of cooling rate was investigated by varying the cooling rate after IPA addition at 50 °C. Cooling rates of 5 °C/h and 15 °C/h both produced the target thick plate morphology. Also, crystallization experiments were conducted without seeding to determine the impact on crystal morphology. In the absence of seeds, the solution nucleates either during the IPA addition at 50 °C or during cooling to 20 °C. Thus, nucleation occurs at a higher supersaturation compared to the seeded process and results in prism morphology, which is also acceptable for the formulation process. Although these studies indicated robustness of the process to deliver the target crystal habit, seeding and controlled cooling at a predefined rate were incorporated in the manufacturing process, for consistency.

The Choline Fenofibrate manufacturing process was transferred to two manufacturing sites. One of these sites preferred not to use MeOH in their plant. In order to accommodate this need, other solvents were screened for use in the reaction and crystallization processes. The solvent system for salt formation reaction was switched from MeOH to IPA-water and the crystallization solvent was switched to ethanol (EtOH). We will briefly discuss the crystallization process using EtOH and the effect of supersaturation on crystal habit in this solvent. The first isolation of Choline Fenofibrate in this modified process occurs from a mixture of IPA-water (predominantly IPA with low concentration of water) and the filtered cake is washed with IPA. In order to streamline the unit operations in the process, the wet cake from the first isolation is carried directly into the crystallization process without drying. Similar to the earlier manufacturing process, the second crystallization using EtOH in this case, serves to control the crystal habit of the API. Since the product from the first isolation is not dried, it carries some amount of IPA into the next

crystallization. In light of this, we measured the solubility of Choline Fenofibrate in EtOH-IPA solvent mixture at various temperatures. The solubility data are shown in Figure 5.

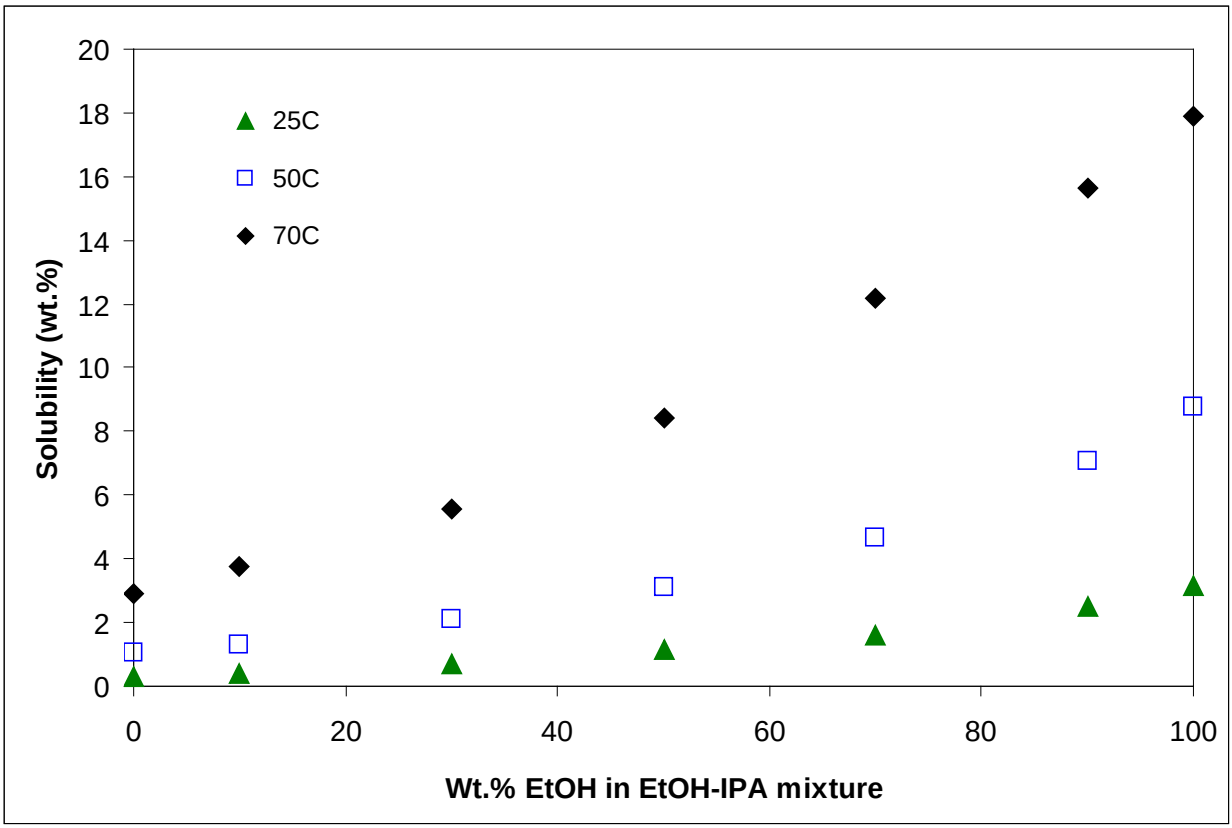


Figure 5. *Solubility of Choline Fenofibrate in EtOH-IPA as a function of temperature*

Additional solubility values at intermediate temperatures were calculated using the van't Hoff equation. Solubility at intermediate solvent compositions not experimentally measured, was estimated via interpolation of the above data. Using these data, a crystallization protocol was developed as follows. The Choline Fenofibrate isolated from the evaporative crystallization was dissolved in EtOH by heating to 75 ºC. The solution was cooled to a defined temperature to generate supersaturation. The supersaturated solution was seeded with 1-5 wt.% (relative to the total amount of API in solution) of finely milled Choline Fenofibrate seed. After seeding, the

crystallized slurry was cooled at a controlled rate to 0 ºC to recover more product. The API was isolated by filtration and dried using heat and vacuum.

The solution supersaturation at seeding is a function of the API concentration, EtOH/IPA ratio and temperature. Typical amounts of IPA brought in by the wet Choline Fenofibrate product from the first isolation resulted in less than 5 wt.% IPA relative to EtOH in the final crystallization process. The effect of supersaturation at seeding, on the API crystal morphology was investigated by conducting crystallization experiments at different levels of supersaturation. These experiments are summarized in Table 2. The supersaturation at seeding was varied by changing the API concentration in solution, the EtOH/IPA solvent ratio and the seeding temperature. Through various combinations of these three parameters, a range of supersaturation ratios from 1.07 to 1.89 was investigated. After seeding, the crystallization slurry was cooled to 0 °C and filtered. None of the experiments resulted in thin plate morphology. Unlike the MeOH-IPA crystallization process, thick plate morphology can be obtained at low supersaturation ratios ($C/C^*<1.1$) in the ethanol crystallization. This suggests that solvent interactions play a significant role in determining the crystal habit of Choline Fenofibrate. The effect of low supersaturation on crystal morphology is much less pronounced when EtOH is used as the crystallization solvent. This allows for a wider range of operating conditions for the EtOH crystallization process. Crystallization without seeding results in nucleation at a lower temperature during cooling. Since the supersaturation at the lower nucleation temperature is higher, the resultant API exhibits prism morphology. Other experiments indicated that varying the cooling rate during crystallization did not have an adverse effect on the crystal habit.

Table 2. *Crystallization Experiments using EtOH-IPA*

Experiment #	API Concentration[1] (wt.%)	EtOH/IPA Ratio[1]	Seeding Temperature (°C)	Supersaturation Ratio[1] (C/C*)	Product Morphology
1	18	95/5	60	1.53	Thick Plates
2	14	97.5/2.5	58	1.23	Thick Plates
3	14	100/0	58	1.18	Thick Plates
4	14	95.1/4.9	58	1.28	Thick Plates
5	17.3	97.5/2.5	58	1.52	Thick Plates
6	13.2	98/2	58	1.15	Thick Plates
7	14	99.5/0.5	52.5	1.45	Thick Plates
8	14	97.5/2.5	60	1.15	Thick Plates
9	18	95/5	70	1.07	Thick Plates
10	15	95/5	50	1.89	Prisms

[1]Value at Seeding Conditions.

The API solubility is not a strong function of solvent composition in the EtOH-IPA system at 0 ºC. As a result, there is no significant increase in the crystallization yield by going to a higher IPA/EtOH ratio. However, the volume efficiency of the process is negatively impacted at higher IPA/EtOH ratios. Hence the crystallization process in EtOH-IPA was designed to be a cooling crystallization process. The manufacturing process is operated at an API concentration of 14 wt. % in a 97.5/2.5 EtOH/IPA solution. The seeding temperature is 58 °C, which corresponds to a supersaturation ratio of about 1.2. About 1 wt.% seed (relative to the total amount of API in solution) is used. The seeds are added as a slurry in IPA. Following seeding, the slurry is cooled

to 0 °C over 4 h (linear cooling rate of 15 °C/h) and filtered. The product is dried under vacuum at approximately 50 °C with a nitrogen purge.

4. Effect of impurity on crystal habit of Choline Fenofibrate

During development of the manufacturing process for the API, low levels of a polymeric impurity were encountered in several lots of the starting material Fenofibrate. This impurity had an adverse effect on the crystal habit of Choline Fenofibrate. These observations will be discussed in this section.

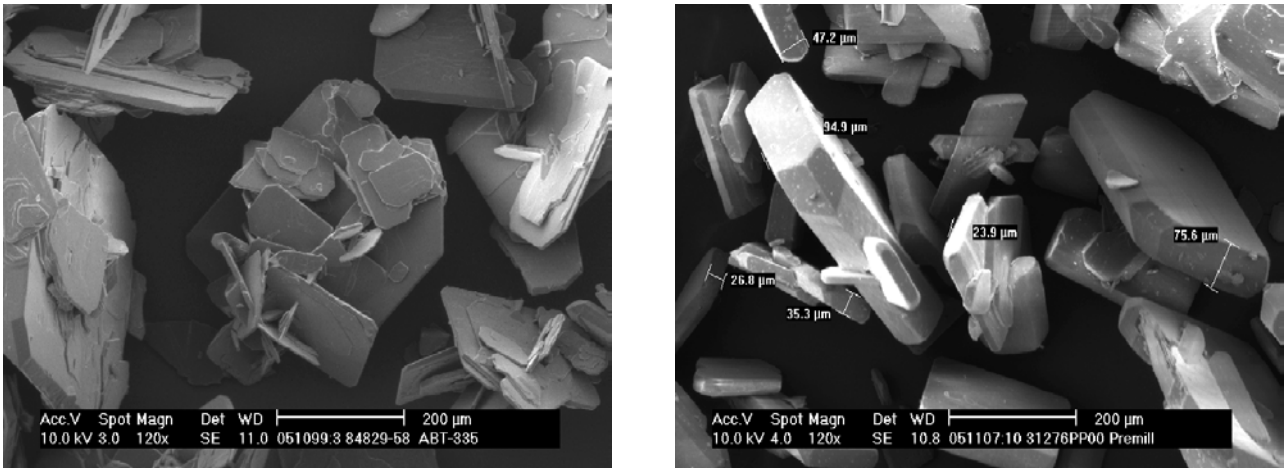
Isopropyl 2-bromo-2-methylpropionate is a starting material in the Fenofibrate synthesis. A polymeric impurity, poly-isopropylmethacrylate is formed in the Fenofibrate synthesis, from this starting material. The Fenofibrate process involves crude product isolation, followed by a recrystallization, which ensures removal of this polymeric impurity to undetectable levels. In order to increase the throughput of the Fenofibrate process, the manufacturer was considering removal of the Fenofibrate recrystallization. Fenofibrate lots made from the single isolation process contained significant levels of the polymeric impurity (up to 0.5 wt.%). Although the impurity levels were reduced during the first isolation of Choline Fenofibrate (evaporative process), the impurity was not completely removed. When these lots of API were carried forward through the second crystallization for habit control, thin plates were obtained. The polymer impurity inhibits growth of the most dominant crystal face of API, resulting in the formation of thin-plates. Several lots of Choline Fenofibrate from evaporative crystallization, with varying levels of polymer were crystallized using the MeOH-IPA process to determine the sensitivity of the morphology to polymer concentration. The polymer concentrations in these lots were determined by gravimetric analysis. This technique gives a conservative number for the polymer concentration since it measures the total mass of insoluble matter in the sample. The presence of polymer impurity was confirmed by IR spectroscopy. A few key crystallization experiments with Choline Fenofibrate lots containing polymer impurity are summarized in Table 3.

Table 3. *Effect of Polymer Impurity on API Crystal Habit*

Expt. #	Polymer Concentration in Choline Fenofibrate isolated from evaporative crystallization (wt.%)	API Concentration[1] (wt.%)	MeOH/IPA Ratio[1]	Seeding Temp. (°C)	Supersaturation Ratio[1] (C/C*)	Product Morphology
1	0.4	36	80/20	50	1.42	Thin Plates
2	0.3	36	80/20	50	1.42	Thin Plates
3	0.1	36	80/20	50	1.42	Thin Plates

[1]Value at Seeding Conditions.

These experiments indicate that the API crystal morphology is adversely affected by the polymer impurity even at a very low concentration (0.1 wt.% relative to Choline Fenofibrate). This phenomenon was confirmed by conducting crystallization experiments under identical conditions, using polymer free lots of Choline Fenofibrate spiked with a poly-isopropylmethacrylate standard with an average molecular weight of 100,000. The polymer standard was spiked at two different levels, 1.5 wt.% and 0.2 wt.% (relative to Choline Fenofibrate). Both experiments resulted in API with thin-plate morphology. A comparison of the API habits obtained from identical crystallization experiments, with and without the polymer impurity, is shown in Figure 6.



API crystallized in the presence of 0.2 wt. % polymer API crystallized in the absence of polymer

Figure 6. *Effect of Polymer Impurity on API Crystal Morphology*

Similar to the MeOH-IPA crystallization process, the polymer impurity had an adverse effect on the API crystal morphology for the EtOH based crystallization. Even crystallization experiments conducted at higher supersaturation using either process produced API with thin plate habit when the polymer impurity was present. We will provide some fundamental insight into the effect of this polymer impurity on crystal habit later in the paper.

As a result of these findings, the proposed modifications to the Fenofibrate process were abandoned. The recrystallization in the Fenofibrate process ensures removal of the polymer impurity, thereby eliminating risk to Choline Fenofibrate crystal morphology.

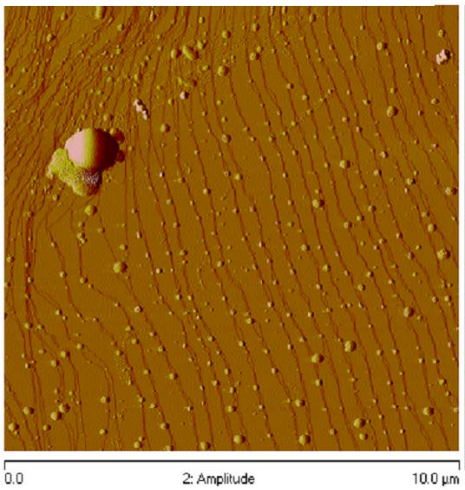
5. Experimental insights into the crystal growth mechanism of Choline Fenofibrate

The effect of supersaturation on crystal habit of Choline Fenofibrate crystallized using the MeOH-IPA process prompted us to probe the growth mechanism of the most dominant face of the crystal. A possible explanation for change in habit with supersaturation is a change in the growth mechanism of the most dominant face. A detailed discussion of the crystal lattice and

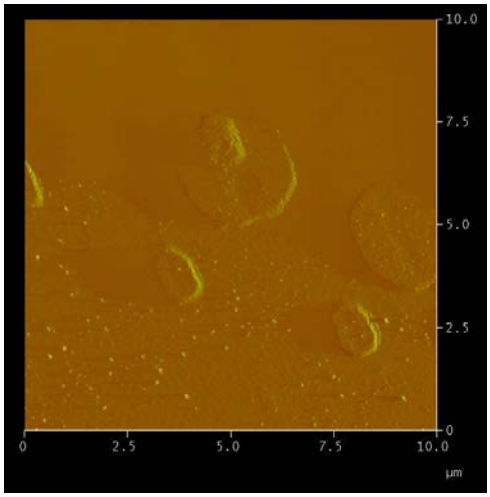
insights into the morphology are included in the next section of the paper. In this section, we present some experimental evidence for the growth mechanism.

We obtained AFM images of API crystals grown from pure methanol at a very low supersaturation. These images are shown in Figure 7. The images were obtained from different crystals grown in the same batch crystallizer. Image A shows steps with uniform spacing, which may be indicative of spiral growth originating from a screw dislocation [3]. Images B and C show 2-D nuclei on the dominant face of the crystal. The spacing between steps originating from 2-D nuclei depends on the nucleation rate and the step velocity, and may not be uniform [6]. It is likely that both spiral growth and 2-D nucleation mechanisms may be at play, either due to spatial variations in supersaturation in the batch crystallizer, or because the supersaturation is near the transition region between the two mechanisms (Figure 16).

A



B



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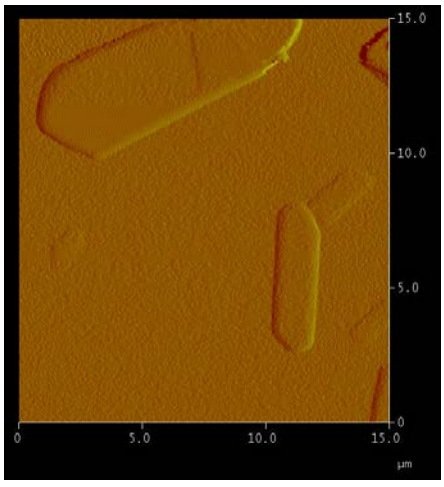


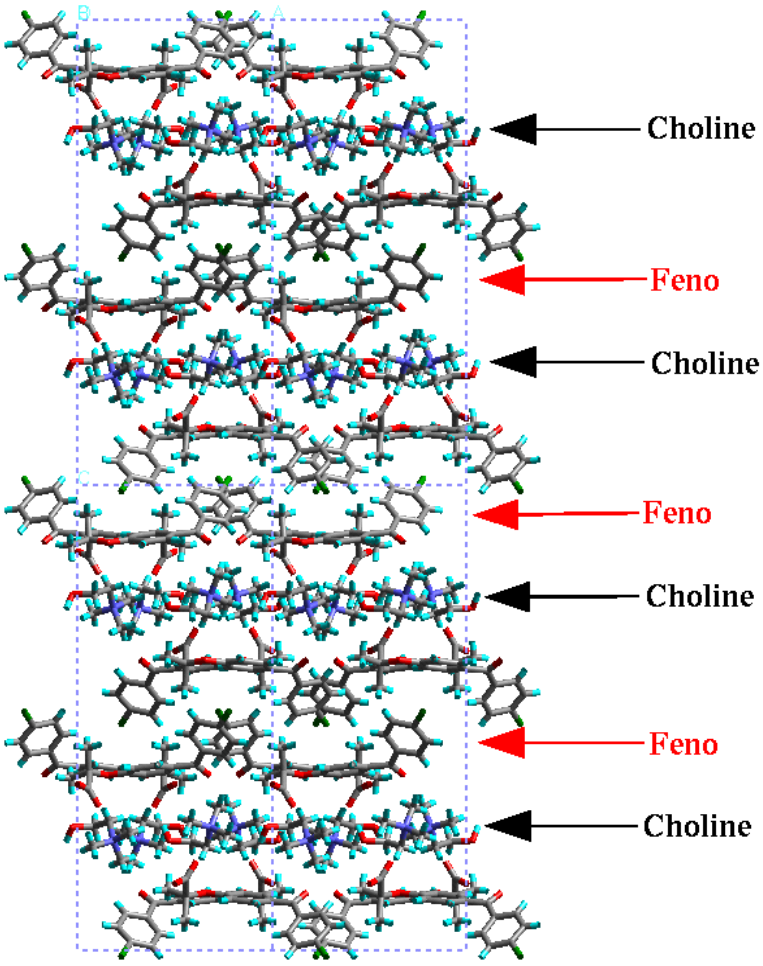
Figure 7. *AFM images of most dominant face of API crystal obtained from MeOH at very low supersaturation*

6. Mechanistic insights into the crystal habit of Choline Fenofibrate

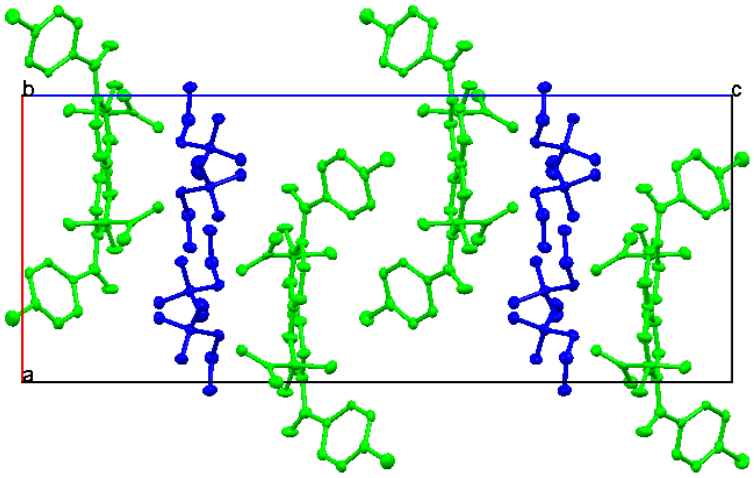
Although mechanistic/predictive studies on crystal morphology of organic salts are scarce in the open literature, it is a very important research focus for pharmaceutical companies. The classical attachment energy method that is most commonly used for morphology prediction is not mechanistic and does not give reliable predictions for certain systems such as needles. It also cannot explain the effect of supersaturation on crystal habits. The method developed for non-centrosymmetric growth units by Kuvadia & Doherty [4] applies conceptually to salt compounds. In this work, our primary aim is to identify accurately the morphologically relevant slow growing crystal faces of Choline Fenofibrate and based on this prediction, understand the fundamental reasons behind the interesting morphological behavior displayed by this system as described in the previous sections.

6.1 Crystal structure of Choline Fenofibrate

Choline Fenofibrate crystallizes in the space group Pbca (orthorhombic) with the lattice parameters a=12.009 Å; b= 12.275 Å and c =28.281 Å as identified by single crystal X-ray diffraction measurements. A single unit cell consists of 8 negatively-charged Fenofibrate ions and 8 positively charged Choline counter-ions, having 8 symmetry operators, as shown in Figures 8 a) and 8 b). Hence, the overall stoichiometry of the packing structure is 1:1 with respect to Choline and Fenofibrate and a total of 16 ions comprise one unit cell that can be translated to generate packing in all directions. The first step in the method for predicting the crystal morphology is to use a suitable force-field to estimate the solid-solid intermolecular interactions for this organic salt crystal. We first calculate the partial charge on each atom of the Fenofibrate and the Choline ions within the unit cell using GAUSSIAN 03 [7] and then use the AMBER force field [8,9] and HABIT 95 to calculate the intermolecular interactions within the crystal lattice. The calculated value of lattice energy using this approach is -125 kcal/mol which is in the range of values expected for organic salts; higher than the typical range for organic molecular crystals because of the high electrostatic component of the intermolecular interactions. This value of lattice energy is the converged value for a suitably large number of unit cells. (This is especially important to verify for ionic systems and provides confidence in the force field chosen).



a)



b)

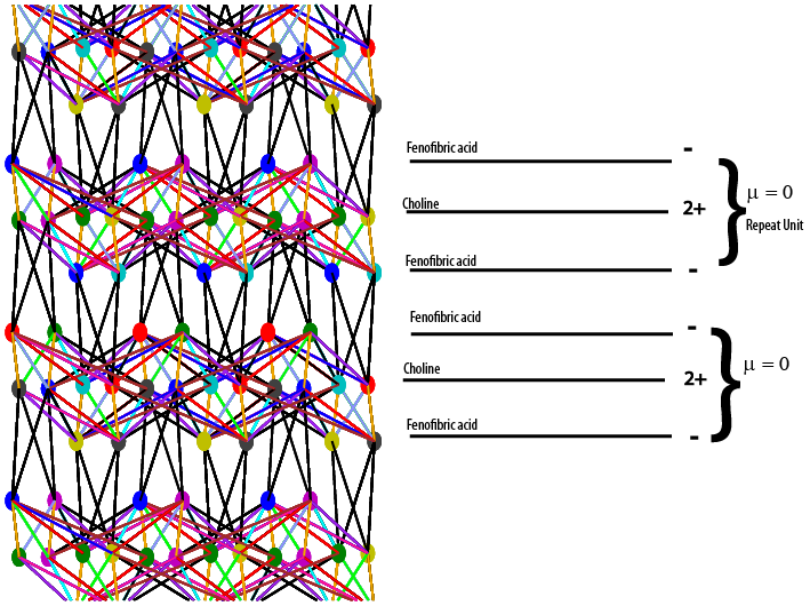
Figure 8*: Crystal packing structure of Choline Fenofibrate viewed perpendicular to the b axis.* ***a)*** *4 unit cells shown, coloring scheme used to show different elements (gray =Carbon, cyan=Hydrogen, violet=Nitrogen, Red=Oxygen).* ***b)*** *Coloring based on symmetric equivalence, green represents Fenofibrate ions and blue represents Choline ions.*

6.2 Morphology prediction of Choline Fenofibrate

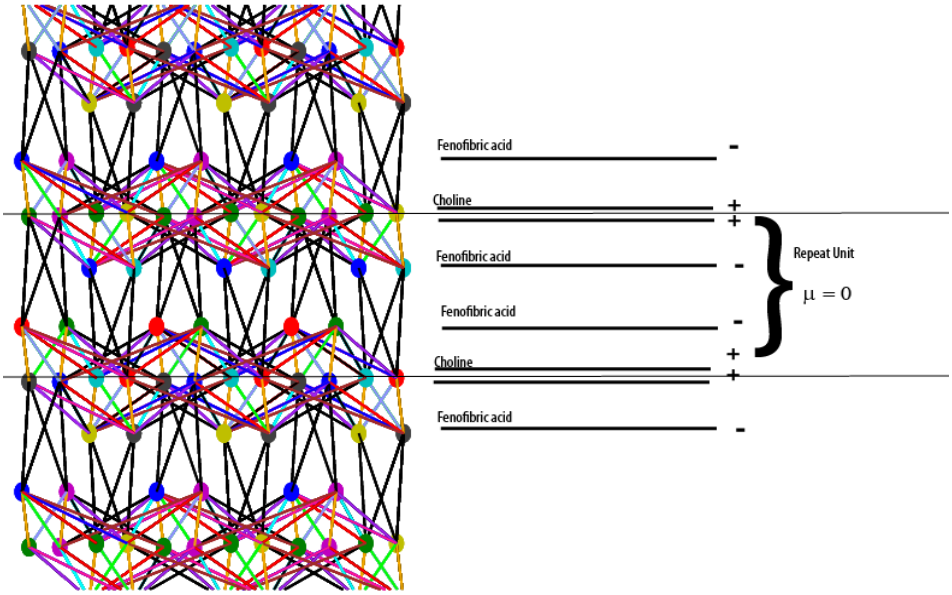
In order to obtain theoretical understanding of the crystal morphology, we need to identify the slow growing morphologically relevant faces based on the bonding structure. Since the compound is a salt (ionic compound), certain additional rules must be imposed to identify stable crystal slices (surfaces) in each direction based on the electrostatic dipole moment. According to Tasker [10], a stable slice must be stoichiometric in composition and also should not have any dipole moment perpendicular to the slice. Additionally, for the particular slice to be slow growing, the slice must contain periodic bond chains in at least two different directions [11].

Moving perpendicular to the c axis, there are two layers of Fenofibrate ions followed by two layers of Choline ions stacked along the {002} direction repeating to form the packing structure. We use the rules of stability of ionic crystal surfaces [10] to determine which is the stable slice in the {002} direction. Stable surfaces have either equal anions and cations on each plane (Tasker type 1) or charged individual planes with no net dipole moment perpendicular to the surface (Tasker type 2) [10,11]. The {002} planes are of type 2 and there are two possible

configurations, as shown in Figure 9. We select the slice with the least repulsive energy within the slice to be the most stable configuration (the repulsive interaction between the two Choline layers is significantly more than the repulsive interaction between the two Fenofibrate layers as the Choline ions are more closely packed in the unit cell due to their smaller size). The most stable slice configuration for the {002} planes is shown in Figure 10b). All the other morphologically relevant planes, {022}, {111}, {020} and {200} are Tasker type 1 surfaces.

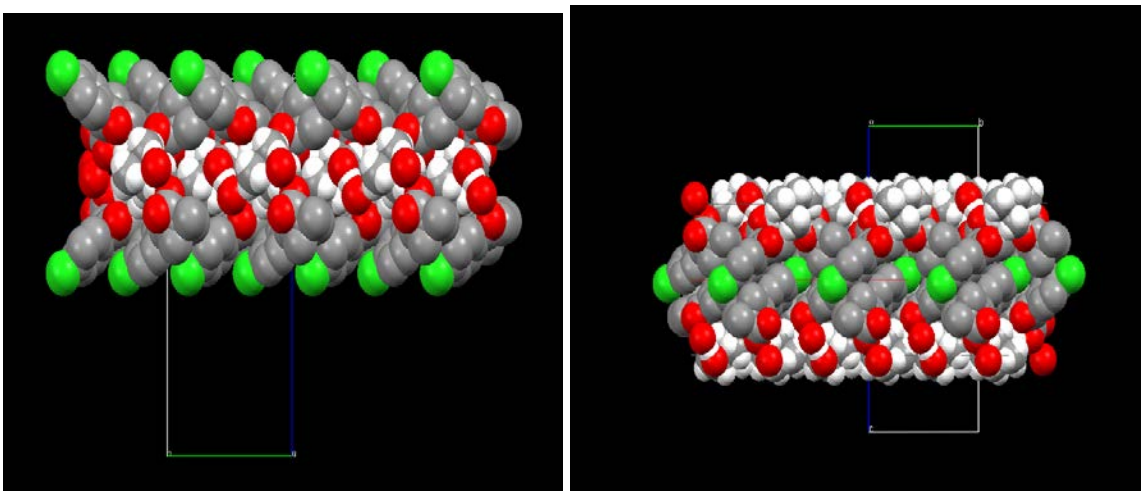


a)



b)

Figure 9a) and b). *Packing structure representation showing {002} slices and repeat units in terms of charged layers, viewed perpendicular to b axis. Two configurations which give zero dipole moment perpendicular to the surface. The molecules are represented by their centers of mass, shown by solid circles of different colors, and the lines represent intermolecular interactions.*



a) b)

Figure 10 a) and b). *Two configurations of the {002} slice based on slice shifting with zero dipole moment. b) shows the most stable slice with least repulsive interactions within the slice.*

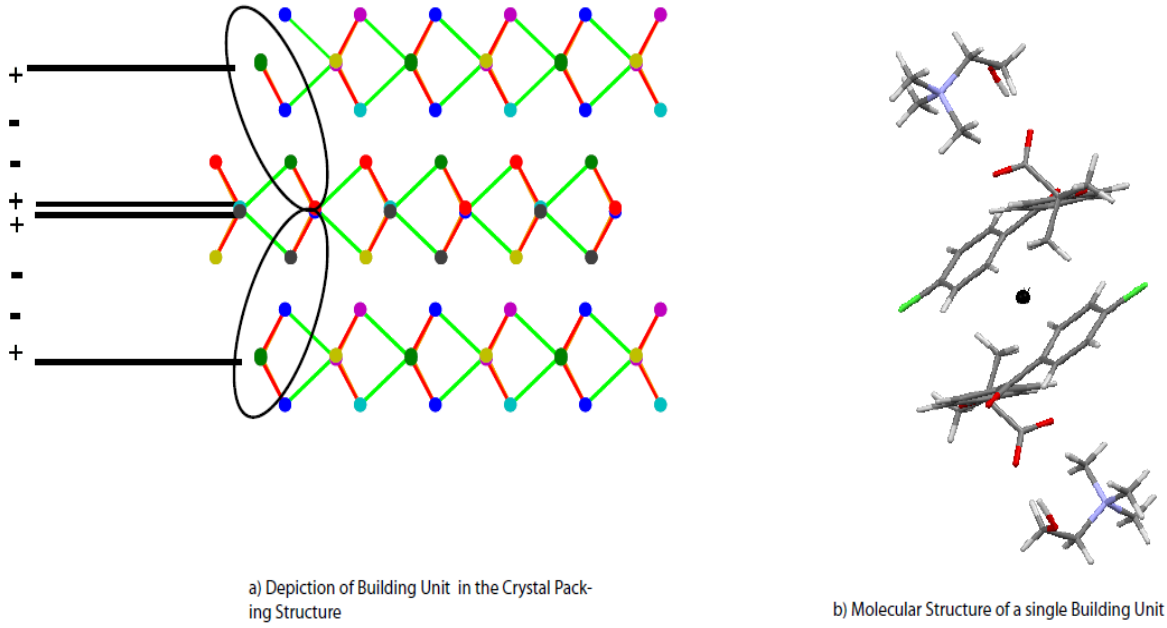


Figure 11. *Intermolecular interactions and the correct choice of a building unit for Choline Fenofibrate crystal.*

The periodic bond chains (PBCs) in Choline Fenofibrate crystal should satisfy all the properties of PBCs given by Hartman and Perdok [12]. Specifically, the PBCs should have stoichiometric composition and there should be no net dipole moment perpendicular to the PBC direction. The concept of a building unit has been proposed in the ionic crystal growth literature [13] that is used to identify the periodic bond chains in any ionic crystal. This concept was also used here to identify a building unit for the PBCs in Choline Fenofibrate.

A building unit is a stoichiometric arrangement of atoms in the solid-state such that mere translation of this arrangement in the symmetry-related directions in the lattice yields all the periodic bond chains in the lattice. The building unit should be stoichiometric and should have a zero dipole moment, only then can a single building unit generate PBCs in all directions in keeping with the slice stability rules. We select the building unit whose dipole moment is zero, as shown in Figure 11. It should be noted that the selected building unit contains an inversion centre within it, so that the entire bonding structure is transformed to a centrosymmetric one which is simpler to deal with.

It is important to note that the building units are not the exact growth units that actually attach to kink sites and new methods are being developed to enable a detailed mechanistic relationship between building units of periodic bond chains, growth units and kink densities and kink rates [14]. In this work, the building unit kink site approximation is made to get workable estimates for the crystal morphology of this complicated system.

Once the building unit is identified, all the PBCs that lie within the slice of any face of the crystal can be determined and PBC network diagrams can be drawn for each of the important faces of the crystal. The periodic bond chains for the slow growing F faces are shown in Figure 12. This is followed by the calculation of the PBC energies. In the case of organic salts, the presence of ions in the solid state makes it necessary to consider the long-range nature of the electrostatic interactions. Once a PBC direction has been identified, the interactions of a central building unit with all the other building units in that PBC direction were summed up to give the overall strength of intermolecular interactions along that PBC direction. The calculation of the PBC energies along with the PBC network diagram for each crystal face allows for an accurate prediction of the prominent edges on the growth spiral and the shape of the spiral.

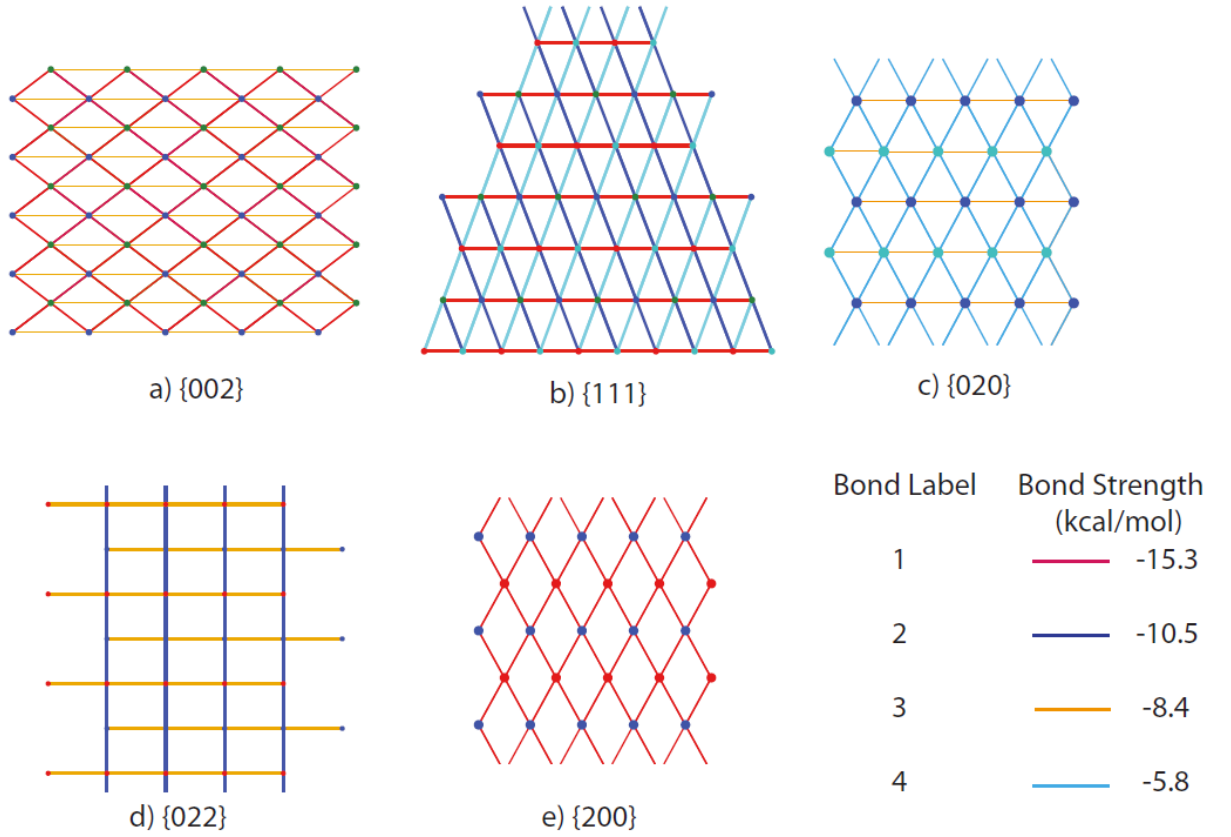


Figure 12. *The periodic bond chain representation for different F faces of Choline Fenofibrate using the building unit described in Figure 11.*

Thus, the periodic bond chain analysis using building units helps in predicting the set of slowest growing faces in Choline Fenofibrate and this can be combined with preliminary application of the spiral growth model [4] to predict the relative growth rates of each of those faces (Table 4) and estimate the steady-state crystal morphology of the material grown under low supersaturation conditions.

Table 4. *Spiral growth model calculations on all the F-faces of Choline Fenofibrate*

Face	Bond chain direction	Kink density	Step velocity (dimensionless)	Interplanar Spacing d_{hkl} (Å)	Relative Growth rate (R)
{002}	[110]	5.8E-06	5.1E-05	14.14	1
	[-110]	5.8E-06	5.1E-05		
	[100]	0.00184	0.01123		
{111}	[011]	0.0003	0.00264	8.21	4.8
	[110]	5.8E-06	9.1E-05		
	[101]	0.01554	0.14265		
{020}	[100]	0.00184	0.0257	6.13	551.3
	[10-1]	0.01554	0.18651		
	[101]	0.01554	0.18651		
{022}	[011]	0.0003	0.00362	4.635	39.0
	[01-1]	0.00184	0.02753		
{200}	[011]	0.0003	0.00465	4.635	27.1
	[01-1]	0.0003	0.00465		

We estimate the morphology of Choline Fenofibrate using the spiral growth mechanistic model to be plate-like (low to moderate thickness), with the {002} face being morphologically the most dominant face (Figure 13) followed by the {111} family. (All other faces grow out of the predicted final steady-state shape). This morphology is similar to that predicted using the attachment energy model (Figure S1a). However, it is well known that the spiral growth model provides a better mechanistic understanding of crystal growth of molecular crystals [4]. It is important to note once more that the building unit and periodic bond chain-spiral growth method used here is our first attempt to explain the growth mechanism of organic salts crystallized from

solution. The exact relation between kink sites and building units remains unknown at this stage. Also, this morphology estimation is carried out in vacuum. Despite the simple method adopted, it is one of the higher fidelity methods which correctly captures the behavior of F faces and identifies the morphologically relevant faces and their relative importance to morphology. There are ongoing efforts to develop the capability to understand the relationship between building units and actual kink site growth units, and also estimate the effect of mixed solvents on crystal morphology for these types of systems.

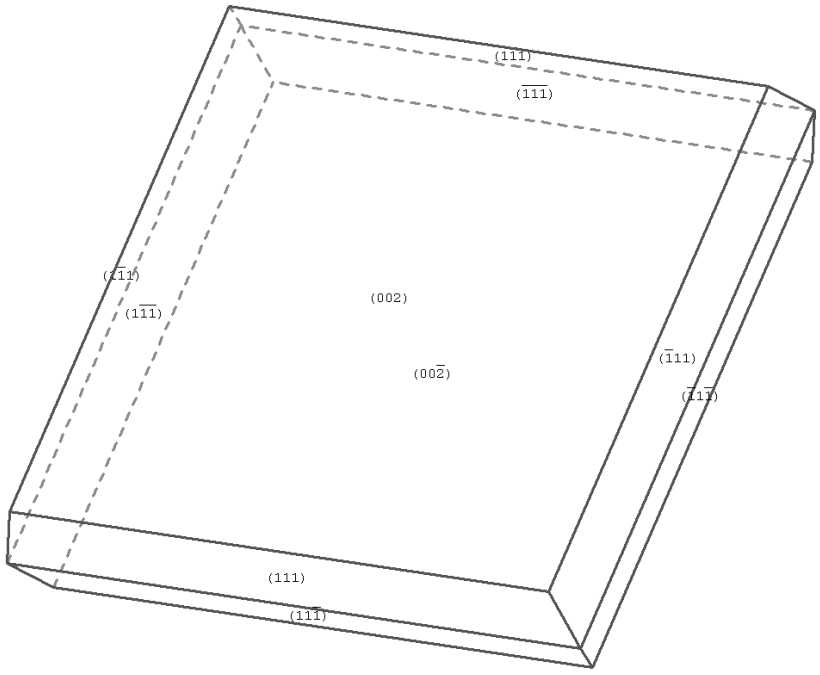


Figure 13. *Predicted morphology of Choline Fenofibrate crystal using the spiral growth model at low supersaturation.*

6.3 Change of morphology with impurity

Even a small amount of additive causes significant modification to the crystal habit. Since a morphology change can only be brought about if the additive affects the slow growing F faces

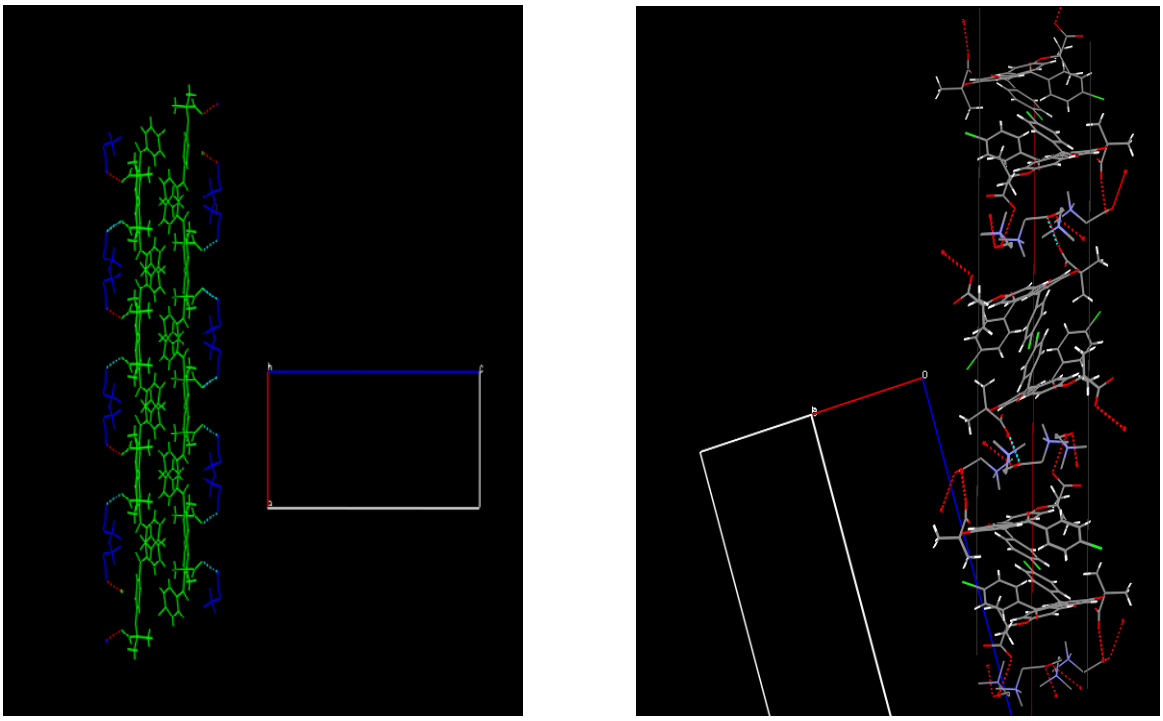
differently, our approach is to understand how the faces are inherently different in structure and behavior.

Materials Studio [15] was used to calculate the attachment energy for the slow growing faces using a Consistent Valence Force Field (CVFF) [16]. Using Materials Studio, the hydrogen-bond contribution and the van der Waals contribution of attachment energy of each face can be extracted (Table 5), which throws light on which faces are hydrophilic and which ones are hydrophobic. Even though the attachment energies by themselves lead to inaccurate relative growth rates, the relative H-bond contribution of the energy on each face yields useful qualitative information about the hydrophilic behavior of each crystal surface.

Table 5. *H-bond contribution of Attachment Energy on different crystal faces. All energy values are in kcal/mol.*

Face	Eatt(Total)	Eatt(vdw)	Eatt(H-bond)
{ 0 0 2}	-58.2	-58.1	**-0.1**
{ 1 0 2}	-129.3	-117.4	-11.9
{ 1 1 1}	-148.8	-134.1	-14.7
{ 1 1 2}	-168.5	-157.1	-11.4
{ 0 2 0}	-187.5	-171.6	-15.9

Although AMBER force field is more appropriate to model crystal growth of most organic molecules, CVFF uniquely allows the apportioning of the total interaction energy into van der Waals and hydrogen bonding contributions. The attachment energy values calculated using AMBER and CVFF force fields for the F-faces of choline finofibrate crystals are quite similar (Table S1). Therefore, our conclusions are independent of the force field that is applied.



a) {002} slice b) {111} slice

Figure 14*. Molecular arrangement of {002} and {111} slices to highlight the hydrogen bonding pattern on different faces, coloring scheme showing different elements*

From the values of H-bond contribution of attachment energy of each face and also from the packing structure of the {002} face (shown in Figure 8 a), we see that the {002} face is uniquely hydrophobic (as compared to all other faces) with all the hydrogen bonds directed completely inwards within the slice. Figure 14 shows the molecular arrangement and hydrogen bonds in the {002} slice as compared to the {111} slice, which ranks next in morphological importance after {002}. Also, it is known that the impurity, poly-isopropylmethacrylate, formed in the Fenofibrate synthesis, is hydrophobic in nature. Hence, we hypothesize that the polymeric impurity will be preferentially attracted to the hydrophobic {002} face compared to the other faces which are partially hydrophilic. Without restricting ourselves to any single mechanism of the effect on spiral growth of choline fenofibrate crystals, we expect that the impurity molecules adsorbed on the terrace may decrease the growth rate of {002} face. Hence, the polymer results in crystals growing in the form of very thin plates as shown in Figure 6.

6.4 Change of morphology with supersaturation - qualitative explanation

Reconstructing the steady-state relative growth rates of the different F-faces from the SEM images of the experimentally observed morphologies at varying supersaturations (Figure 15 a,b), it is inferred that the different crystal habits are mainly due to the change in relative morphological importance of the {002}face with respect to the other faces.

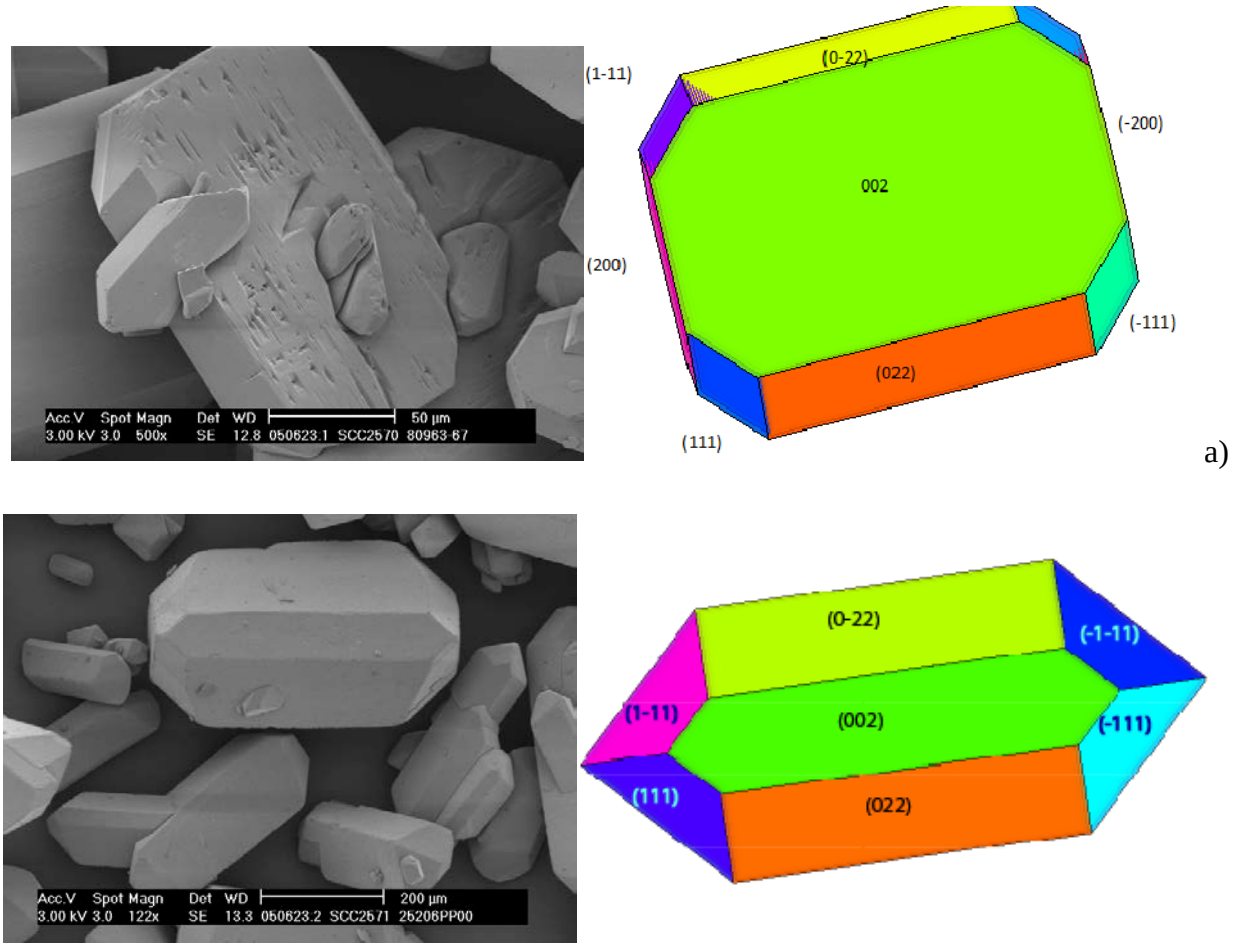


Figure 15*. SEM images used to reconstruct relative growth rates at different supersaturations. a) Lower Supersaturation- Plates b) Higher supersaturation- Prisms*

It is a well established general concept that at low supersaturation, crystals grow due to spirals emanating from screw dislocations on different faces. For the entire range of spiral growth

mechanism, step velocities and growth rate of faces change in such a way that they don't affect the morphology to a significant extent [4], as supersaturation does not affect spirals on different faces differently.

This suggests that this change in morphology is not due to changes on spiral polygons on different faces.

This leaves us with two possible explanations:

1) At low supersaturation, the {002} face experiences a dead zone of growth due to impurity inhibition causing individual step pinning by the Cabrera and Vermilyea mechanism [19] or by spiral pinning, i.e., growth reduction due to an increase in the rotation time of the spiral [18]. It is known that extremely low amounts of impurity concentration can affect the growth of crystal faces. Irrespective of the specific mechanism of inhibition due to immobile impurities, above a critical supersaturation, growth recovery occurs and the dead zone is overcome leading to much faster growth rate of this {002} face.
2) An alternate hypothesis is that the {002} face changes its dominant growth mechanism from spiral growth to 2D nucleation, causing it to grow much faster than the other faces, thus decreasing its morphological importance. When a face grows by spirals, the growth rate of that particular face has a quadratic dependence on supersaturation, whereas when the face grows in the form of 2D clusters, the growth rate varies exponentially with supersaturation [20-23] as shown in Figure 16 (image reproduced with permission from [21]). Hence, at some critical value of supersaturation, it is hypothesized that there is a sudden increase from a very low growth rate of the{002} face to a very high growth rate, thus leading to prismatic morphology at higher supersaturation.

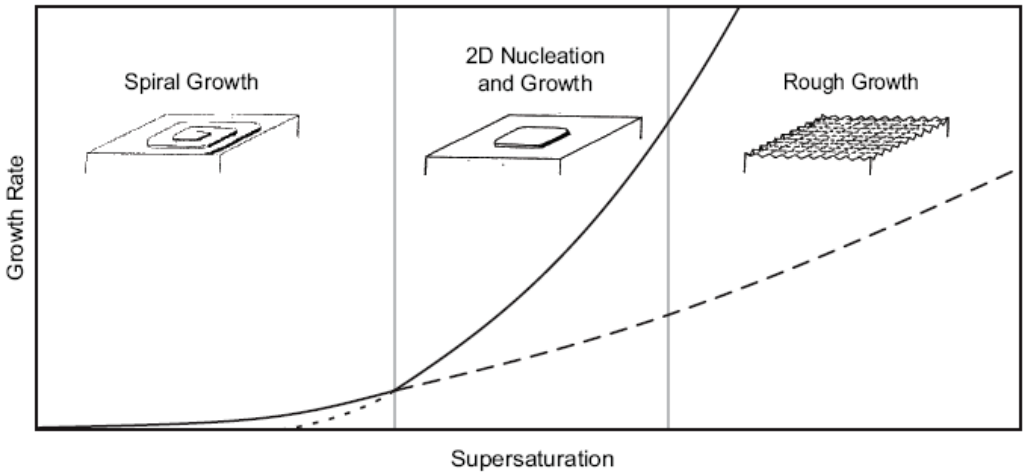


Figure 16*. Growth mechanisms for a flat (F) face, as a function of supersaturation. The solid line is the growth rate. The short dashed lines are the growth rates if two-dimensional (2D) nucleation continues to be dominant below its applicable supersaturation range. The long dashed line is the rate if spiral growth was the persistent mechanism above its applicable supersaturation range.*

7. Conclusions

In this article, we have discussed our observations on the morphological behavior of Choline Fenofibrate crystals and the relevance of crystal habit to the formulation process for this pharmaceutical product. The crystal morphology of this API is significantly influenced by supersaturation in the crystallization process using methanol and isopropanol. In particular, the growth rate of the {002} crystal face is slowed down at low supersaturation, resulting in undesirable thin plate crystals of the API. This observation at low supersaturation was less pronounced when the crystallization solvent was switched to ethanol. Also, the API crystal morphology was adversely impacted by low levels of a polymeric impurity which must be controlled in the upstream process to afford the desired crystal habit. These findings guided the design and development of a robust API crystallization process to consistently deliver the optimal crystal habit.

We further applied a mechanistic approach to identify the morphologically relevant slow growing faces of Choline Fenofibrate crystal using concepts of stability of surfaces, periodic bond chain and spiral growth theory, and fundamentally explain the interesting morphological behavior observed for this API. A basic first-pass workflow was introduced to predict morphology of organic salts and an attempt was made to qualitatively explain the effect of supersaturation and the polymeric impurity on the crystal habit of Choline Fenofibrate.

Disclosure

These studies were sponsored by AbbVie. AbbVie contributed to the design, analysis, and interpretation of data, writing, reviewing, and approving the publication. Shailendra Bordawekar and Samrat Mukherjee are employees of AbbVie. Zubin Kuvadia, Michael Doherty and Preshit Dandekar were collaborators on this research and were also involved in the analysis, interpretation of data, writing, reviewing, and approving of the publication. These collaborators are affiliated to the University of California, Santa Barbara; they have not received any personal compensation from AbbVie.

Acknowledgements

The authors acknowledge the following individuals: Russell Cink for his contributions to the API synthetic process development; Lara Sciaraffa for generating SEM images; Andrew Vogt for providing AFM images; Rodger Henry for solving the crystal structure of the API; Kevin Engh for conducting formulation trials with different API morphologies; Nandkishor Nere for mentoring Zubin Kuvadia during his summer internship at AbbVie.

Michael Doherty acknowledges support from the National Science Foundation (Grant number CBET-1159746).

Supporting Information Available

This information is available free of charge via the Internet at http://pubs.acs.org/.

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Interesting Morphological Behavior of Organic Salt Choline Fenofibrate: Effect of Supersaturation and Polymeric Impurity

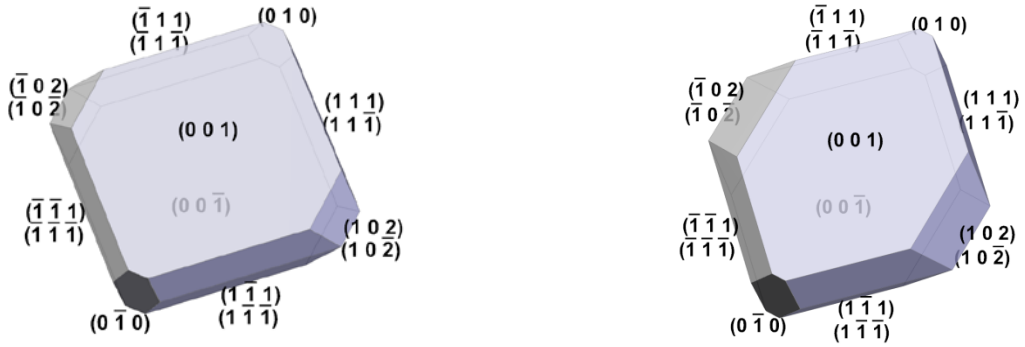
Supplementary Information

Shailendra Bordawekar, Zubin Kuvadia, Preshit Dandekar, Samrat Mukherjee and Michael Doherty

Table S1. *Comparison of attachment energy (E^{att}) values calculated from AMBER and CVFF force fields*

Face	E^{att} from AMBER (kcal/mol)	E^{att} from CVFF (kcal/mol)
{002}	-42.1	-58.2
{102}	-147.7	-129.3
{111}	-151.1	-148.8
{112}	-182.6	-168.5
{020}	-194.2	-187.5

The attachment energy values calculated using CVFF force field for {102}, {111}, {112} and {020} families of faces are within 10% of the values calculated using AMBER force field. There is a larger difference in the attachment energy values for the {002} faces, but it does not significantly affect the crystal morphology. Figure S1 shows the predicted crystal shapes using the two sets of attachment energy values. The crystal habit remains the same (thick plates dominated by {002} faces) for both force fields, with the surface areas of the {111} and the {102} families varying slightly between the morphologies obtained from AMBER and CVFF force fields. Therefore, the two force fields are equivalent in modeling the crystal growth and predicting the shape of choline fenofibrate crystals.



(a) (b)

Figure S1. *Predicted morphology of Choline Fenofibrate crystals using attachment energy model with (a) AMBER force field and (b) CVFF force field.*

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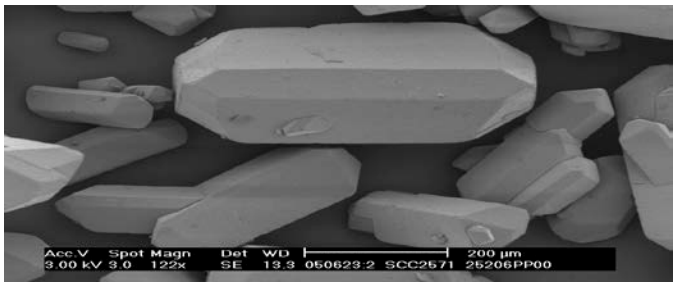
Interesting Morphological Behavior of Organic Salt Choline Fenofibrate: Effect of Supersaturation and Polymeric Impurity

Shailendra Bordawekar, Zubin Kuvadia, Preshit Dandekar, Samrat Mukherjee and Michael Doherty



This article discusses the effects of supersaturation and a polymeric impurity on the crystal habit of Choline Fenofibrate. The article also provides preliminary mechanistic insights into the crystal habit of this organic salt using an extension of the spiral growth model for morphology prediction of organic molecular crystals.