Anisotropic Crystal Growth Inhibition by Polymeric Additives: Impact on Modulation of Naproxen Crystal Shape and Size

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Abstract

This study investigated the effects of polymeric additives such as hydroxylpropyl methyl cellulose (HPMC) and polyvinylpyrrolidone (PVP)—commonly used in pharmaceutical formulations to stabilize fine crystalline suspensions and amorphous solid dispersions—on the growth kinetics of naproxen crystal, a model poorly water-soluble active pharmaceutical ingredient. Measurement of seed crystal growth rate in ethanol–water solution as a function of supersaturation suggested a spiral growth mechanism, with the \( b \) (needle) axis growth rate 5 times faster than the \( c \)-axis growth rate at 40\% relative supersaturation. At nearly equivalent supersaturations, growth along the \( b \)-axis was completely inhibited at one end of the seed crystal in the presence of either of the two polymeric additives. In contrast, growth at the other end of the \( b \)-axis was significantly accelerated in the presence of PVP. Molecular modeling revealed preferential interaction of the additives with the \{011\} faces of naproxen crystal, consequently leading to selective growth inhibition along the \( +b \) axis—this simulation result being consistent with the asymmetrical crystal growth observed experimentally. Growth promotion in the \( -b \) direction of naproxen crystal (in the presence of PVP alone) was explained based on hydrophobic–hydrophilic intermolecular interactions occurring at the crystal–solution interface. In the light of these findings, the use of polymeric additives, either singly or in combination, to modulate naproxen crystal shape and size was further explored.
1. Introduction

Polymeric additives are commonly used to modulate the morphology (shape) and size of organic crystals, with wide-ranging applications in pharmaceutical crystallization and formulation processes. One potential usage is in antisolvent precipitation\textsuperscript{1−4} of ultrafine crystals of poorly water-soluble active pharmaceutical ingredients (APIs). This formulation approach has been explored\textsuperscript{5} in recent years to overcome dissolution-limited bioavailability. Secondly, these additives can be used to avoid\textsuperscript{6−9} needle-like or platy crystal habits, which frequently cause problems in downstream processing. While supersaturation control and temperature cycling are normally carried out to improve the crystal shape and size distribution, these techniques at times fail to produce the desired outcome, particularly in API crystals that grow faster along certain faces due to the presence of strong directional hydrogen bonds in the crystal structure.\textsuperscript{10} Pharmaceutically accepted excipients (polymers) or a suitable solvent system\textsuperscript{10} can be used as additives to modulate such undesired crystal habits, without causing any structural (polymorph) modifications. A heuristic approach has been deployed in these applications to select polymeric additives for a given drug molecule. But for a few studies,\textsuperscript{2, 4, 11−14} the mechanisms underpinning the role of additives in mediating crystal nucleation and growth processes are not well-understood.

Generally, it is postulated\textsuperscript{6−9, 15−18} that polymer molecules adsorb on the surface of a growing crystal, and thereafter inhibit growth by retarding bulk diffusion or surface integration of the solute molecules. Polymeric additives also influence solution viscosity, possibly inhibiting crystal growth via a mass-transfer controlled mechanism. The effect of polymeric additives on crystal habit modification has been shown to depend on its molecular weight\textsuperscript{6, 15} (which, in turn, affects the polymer chain length), polymer chemistry,\textsuperscript{6, 9, 11} and additive concentration\textsuperscript{6}. A combination of polymeric additive and surfactant is often used in a precipitation process. Although the role of surfactant is usually associated with particle stabilization\textsuperscript{2, 19, 20} through steric and/ or electrostatic effects, in some cases, the polymer and surfactant can produce a synergistic effect\textsuperscript{14, 21, 22} on crystal growth inhibition.

While early studies on polymeric crystallization inhibitors proposed a hydrodynamic boundary layer mechanism,\textsuperscript{16} recent experimental and modeling work has provided insights into the interaction of polymeric additives on organic crystal surfaces at the molecular level. Selected case studies are reviewed here in context to the current work. Klapwijk et al.\textsuperscript{8} used small quantities of Pluronic P123—a triblock copolymer composed of a hydrophobic chain of poly(propylene glycol) (PPG) flanked by two hydrophilic chains of poly(ethylene glycol)
(PEG) to modify succinic acid crystal morphology from platy/needle-like to block-like. By analyzing molecular packing arrangement in the crystal structure, and based on the crystal habit modifications observed experimentally, the authors proposed that the hydrophobic PPG block of the copolymer interacts favorably with the \{111\} crystal faces, which exposed hydrophobic CH$_2$ groups on the surface. Wen \textit{et al.}\textsuperscript{18} monitored etch-patterns on acetaminophen crystal surface developed during partial dissolution using atomic force microscopy (AFM). The experimental observations revealed that directional hydrogen bonding interactions influenced adsorption of the polymeric additives on the crystal surface.

In producing micron-sized salbutamol sulfate (SS) crystals by antisolvent precipitation method, Xie \textit{et al.}\textsuperscript{6} found that polyvinylpyrrolidone (PVP) modified the morphology of SS crystals from needle-like to block-like with a lower aspect ratio. Through molecular dynamics (MD) simulations,\textsuperscript{23} the growth-inhibitory effect was attributed to the propensity of PVP to form hydrogen bonds with SS crystal faces along the needle axis. Zhu \textit{et al.}\textsuperscript{22} carried out MD simulations to study the interaction mechanism of hydroxypropyl methylcellulose (HPMC) and Pullulan (a polysaccharide consisting of maltotriose units) with griseofulvin (an API with low aqueous solubility) crystal surface. Between the two additives, HPMC exhibited stronger binding affinity with the (hydrophobic) crystal surface due to the presence of a longer hydrophobic branch in the additive molecule. Overall, these studies have shown that polymer interactions with the crystal surface can be influenced by both hydrophobic/ vander Waals (vdW) interactions and the presence of hydrogen bond donors or acceptors in the additive molecule and on the crystal surface.

Some recent experimental investigations\textsuperscript{7,11,24,25} have evaluated the effects of polymeric additives on crystal growth and nucleation by measuring desupersaturation profile in a seeded crystallization experiment. These studies were able to demonstrate additive-mediated crystal growth mechanisms in relationship to the physicochemical properties of the additives (such as hydrophobicity and amphiphilicity). However, they provided limited insights into interaction of the additives with the drug crystal surface at the molecular level. Further, this methodology calls for a comprehensive experimental design decoupling crystal growth from other crystallization phenomena (such as nucleation, attrition and agglomeration).

Our recent work\textsuperscript{13} elucidated the mechanisms by which polymeric additives (HPMC and PVP) influenced the nucleation kinetics of naproxen crystal (a poorly water-soluble model drug) at moderate supersaturation conditions. Nucleation rate was calculated from probability distribution of the induction times measured in small-volume batch solutions. The effect of additives on crystal nucleation and growth stages was decoupled in a qualitative manner by...
explicitly considering a growth time \((t_g)\) parameter in the nucleation rate equation. By comparing relative percentage increase (or decrease) in the nucleation rate and growth times, it was found that PVP promoted both nucleation and crystal growth. While the effect of HPMC on nucleation kinetics was supersaturation-dependent, the additive inhibited crystal growth in the entire range of supersaturation investigated. Building on these observations, the current study aims to determine the mechanisms by which the polymeric additives mediate naproxen crystal growth. In-situ optical microscopy was used to measure seed crystal growth rates in supersaturated ethanol–water solution, both in the absence and presence of the additives. From the growth kinetics data, the interfacial crystal growth mechanism within a definite range of supersaturation was characterized. The experimental observation on the effect of additives on crystal growth was supported by molecular modeling and calculation of intermolecular interaction energies between the additives and crystal faces. Finally, the use of polymeric additives, either singly or in combination, to modulate naproxen crystal shape and size was further explored.

2. Experimental Section

2.1. Materials. \((\delta)\)-Naproxen ((+)2-(6-Methoxy-2-naphthyl)-propionic acid, 99% purity) was purchased from Afine Chemicals Ltd. (China). Hydroxypropyl methylcellulose (HPMC, grade 4000 cP, average MW 86000 g/mol) and polyvinylpyrrolidone (PVP, grade K16–18, average MW 10000 g/mol) were obtained from Sigma Aldrich and used as polymeric additives. Their molecular structures and the crystal structure of naproxen (obtained from Cambridge Structural Database (CSD) reference code COYRUD11) are shown in Figure 1. Analytical grade ethanol (VWR International) and ultrapure water were used to prepare naproxen solutions.

2.2. Crystal Growth Measurement. Initially, naproxen seed crystals were grown from ethanol–water solution by slow solvent evaporation. A supersaturated solution of naproxen \((\sigma = \frac{C}{C^*} - 1\), where \(C\) and \(C^*\) are the actual and equilibrium concentration of naproxen in 41.5 wt. % ethanol–water mixture) was prepared by dissolving a known amount of naproxen in the cosolvent mixture at an elevated temperature and cooling it down to 23 °C. About 2.5 ml of the solution was injected into a glass cuvette preloaded with a naproxen seed crystal. The injection port of the glass cuvette was tightly capped to avoid any solvent evaporation. Growth of the seed crystal was monitored using an optical polarizing microscope (Olympus BX51 connected to a CCD camera) in a temperature-controlled environment (~23 °C). The
crystal images were recorded at regular time intervals using Stream Basic image capture software. Growth rate along the $b$ (length) and $c$ (width) axes of a naproxen seed crystal was obtained by plotting the axis dimension against time and calculating the slope of the resulting straight line (regression coefficient $R^2 > 0.93$).

Solubility of naproxen in pure ethanol–water cosolvent mixture and in the presence of polymeric additives was determined in our previous work$^{11}$ by density measurement technique. At 23 °C, the polymeric additive (HPMC or PVP at the concentration 0.283 mg/g of cosolvent) increased the solubility of naproxen by ca. 15%. Solubility of naproxen in the presence of combination of the additives (a mixture of HPMC and PVP, with individual additive concentration 0.14 mg/g of cosolvent) was determined in this work using the analytical method reported before.$^{11}$ The solubility of naproxen was found to increase by ca. 13% compared to the pure solution. These solubility changes were factored in while preparing supersaturated solutions for crystal growth experiments.

Figure 1. Molecular structures of naproxen (a), HPMC (b) and PVP (c); (d) and (e) crystal structure of naproxen (CSD reference code COYRUD11) viewed along the $c$ and $a$ axes respectively. Hydrogen bonding interactions in the crystal structure are shown by the dashed (cyan blue) lines.

2.3. Batch Crystallization and Crystal Size Measurement. Small volume (10–30 ml) batch crystallization experiments were carried out under similar supersaturation conditions to evaluate the effect of polymeric additives on naproxen crystal shape and size. Three different experimental procedures were followed: (a) slow cooling without stirring: a supersaturated solution of naproxen ($\sigma = 0.3$) was prepared at an elevated temperature and naturally cooled
to room temperature (~23 °C) in an enclosed glass crystallization dish; (b) slow evaporation: the supersaturated solution was allowed to evaporate slowly (at room temperature) through a few holes drilled on the aluminium foil used to cover the crystallization dish; (c) slow cooling with stirring: the solution was cooled at 0.5 °C/min in a jacketed glass vessel connected to a water circulator until the crystals nucleated out. The crystals obtained by procedures (a) and (b) were directly imaged using the optical microscope (Olympus BX51), whereas the crystals obtained by procedure (c) were vacuum filtered and dried before imaging using a field emission scanning electron microscope (FESEM, JEOL, JSM-6700F). As the polymeric additives influenced both the nucleation and growth kinetics of naproxen crystals, the batch experiments were performed at relatively low supersaturation level, in order to minimize nucleation and discern the effect of additives specifically on crystal growth—and, in turn, the crystal habit.

As noted in our previous work, naproxen crystal size characterized using conventional analytical techniques based on light scattering principle was inconsistent with linear dimensions of the crystals (length and width) measured from microscopic (optical or SEM) images. We reason that this discrepancy primarily arises due to the thin, needle-like habit of naproxen crystallized from ethanol–water solution. Therefore, in the current study, the changes in crystal size induced by the polymeric additives were determined by measuring the crystal length and width (typically 100–200 crystals were sampled) from SEM and optical microscope images. In characterizing the crystal size by this method, the crystals were often found to be overlaid on each other, making it difficult to identify individual crystals from the images. While this particle sizing method does not ensure statistical representation of the population of crystals, the 2-dimensional size data provided qualitative assessment of the effect of additives on naproxen crystal habit modification.

3. Molecular Modeling

Initially, the crystal habit of naproxen was simulated from its internal crystal structure (CSD reference code COYRUD11) in Materials Studio modelling software. Both the BFDH (Bravais-Friedel-Donnay-Harker) and attachment energy models simulated a similar crystal habit, although the latter crystal habit was elongated along the b-axis. This result is in line with the underlying crystal habit modelling theory, as the attachment energy model considers intermolecular interaction energies within the crystal structure while the BFDH model is based solely on crystallographic factors. The simulated crystal habit (Figure S1 in
the Supporting Information) was compared with the experimental crystal habit assigned with
the face indices (Figure S2 in the Supporting Information) to identify the dominant crystal
faces: (011) and (011) in +b direction, (0[11]) and (0[11]) in −b direction, (100) and (100)
in ±a direction and (001) and (001) in ±c direction, respectively.

A molecular model of naproxen crystal surface was built by cleaving the (hkl) face from
the crystal structure to a depth of 1–3 unit cells, and extending the surface to m × n unit cells.
By this procedure, a flat face, without any step or kink sites, was generated. The dimension
of the crystal surface was set appropriately so that the polymer (additive) molecule can orient
on the crystal surface along different conformations during MD simulation. A vacuum slab of
appropriate thickness was built above the crystal face, with periodic boundary conditions
imposed on the system. A single chain polymer molecule, with molecular weight 10000 g/mol, was built with 90 and 62 repeat units for PVP and HPMC, respectively. The additive
molecule was geometry optimized using the COMPASS forcefield (with forcefield-
assigned partial atomic charges) and subsequently placed on the crystal surface.

MD simulation for polymer–crystal surface interaction was carried out in the Discover
module in Materials Studio. The COMPASS force field was used to model atomic
interactions in the crystal structure of naproxen as well as in the polymer molecule. The
Verlet velocity algorithm, with an integration timestep of 1 femtosecond, was used to
integrate the equations of motion. Ewald summation was used to enable calculation of long
range interactions. An energy minimization procedure was first done after placing the
polymer molecule on the crystal surface; this step evades any unrealistic physical interactions
between the additive and the crystal surface prior to MD simulation. During the simulation,
the crystal surface is kept fixed and only the additive molecule is mobile. MD simulations
were carried out in the NVT (constant number of particles, constant volume, and constant
temperature) ensemble at 298 K for at least 500 picoseconds. The Nose/Hoover thermostat
was used to control the temperature. The equilibrated structure was then minimized with a
geometry optimization procedure, and the interaction energy between the additive molecule
and the crystal surface was obtained by the following expression:

\[ E_{\text{interaction}} = E_{\text{total}} - (E_{\text{surface}} + E_{\text{additive}}) \]

in which \( E_{\text{total}} \) is the total interaction energy of the system (includes all atoms of the first
layer of crystal surface and the additive molecule), \( E_{\text{surface}} \) is the interaction energy of the
atoms on the surface, and $E_{\text{additive}}$ is the interaction energy of atoms of the additive molecule itself.

Note that, while this modelling approach provides an assessment of interaction energies associated with the adsorption of an additive molecule on a molecularly smooth surface, the role of surface defects (step density) in the adsorption process is not being considered.

\[\text{Figure 2. Naproxen seed crystal growth rates measured in ethanol–water solution at different supersaturation levels. The experimental data is fitted to kinetic model equations corresponding to different crystal growth mechanisms. The error bars denote standard deviation (SD ≤ 20%) of at least three growth data points.}\]

4. Results and Discussion

4.1. Naproxen crystal growth mechanism in ethanol–water solution. Naproxen, characteristically, exhibits a hexagonal, thin elongated crystal habit (see inset in Figure 2). Growth rates along the $b$-axis of naproxen seed crystal (delineated by the \{011\} faces) measured in the supersaturation range $\sigma = 0.15–0.4$ are shown in Figure 2. At $\sigma > 0.4$, many new crystals formed in the solution depleting the solute concentration significantly. At $\sigma < 0.15$, crystal growth along the $b$-axis was too slow to be measured precisely within a reasonable experimental time. Naproxen crystal growth mechanism was determined by fitting
the growth data to kinetic model equations\textsuperscript{31} relating face growth rate and supersaturation. The analysis revealed that the \{011\} face grows by a spiral growth mechanism—with the kinetics data exhibiting a good fit to the BCF (Burton, Cabrera and Frank) growth rate expression (blue colored solid curve in Figure 2). As per this mechanism, growth proceeds with the emergence of screw dislocations on the crystal surface, leading to the formation of steps and kinks. Growth rate is primarily a function of step velocity and density—with step velocity determined by the flux of growth units at the kink sites, which may be controlled either by diffusion from bulk solution directly to the kink site or by two-dimensional diffusion across the crystal surface. As step density increases with supersaturation, growth rate exhibits a parabolic and linear relationship with supersaturation at low and high supersaturations, respectively. In contrast, the surface nucleation growth mechanism is typically characterized by a region of supersaturation with ‘no growth’ followed by an exponential increase in the growth rate. The continuous growth mechanism normally operates at higher supersaturation at which the growth interface undergoes surface roughening to produce abundant kink sites, leading to much higher growth rates.

Growth rate along the \textit{c}-axis of naproxen crystal was less sensitive to supersaturation when compared to the \textit{b}-axis growth. In the supersaturation range $\sigma = 0.15$–$0.4$, the \textit{c}-axis growth rate increased about 3 times with increase in supersaturation, as compared to a 6-fold increase in the \textit{b}-axis growth rate. Besides, in this supersaturation range, the \textit{b}-axis growth rate was approximately 5 times faster compared to the \textit{c}-axis growth rate. Intriguingly, these growth kinetics data concur well with the elongated plate-like crystal habit of naproxen obtained experimentally.

A detailed study on the mechanism of naproxen crystal growth from solution has not been reported before (to the best of our knowledge). In view of this, we compare our current results with two recent studies\textsuperscript{7, 32} on the growth mechanism of \textit{RS}-ibuprofen crystal (racemic compound), whose molecular structure is somewhat similar to naproxen. Naproxen (S enantiomer, (+)-2-(6-methoxy-2-naphthyl) propionic acid, C\textsubscript{14}H\textsubscript{14}O\textsubscript{3}, MW 230.26 g/mol) and ibuprofen (2-(4-isobutyl-phenyl) propionic acid, C\textsubscript{13}H\textsubscript{18}O\textsubscript{2}, MW 206.28 g/mol) belong to the propionic acid class drugs. Both the materials crystallize in a monoclinic crystal structure with space group \textit{P21} and \textit{P21/c} for naproxen and ibuprofen respectively. Both naproxen and ibuprofen exhibit a hexagonal plate-like shape with their crystal habits delineated by \{011\}, \{100\} and \{001\} faces. The \textit{b}-axis is the fast-growth direction in both these crystals. Note that the below analysis is not intended to directly compare the growth rates of naproxen and
ibuprofen but to highlight that the two compounds exhibit the same growth mechanism when grown from the same solvent system (although of a different composition) under similar supersaturation conditions.

In the first study, Nguyen et al. measured growth rates of spontaneously nucleated ibuprofen crystals in 95 wt. % ethanol–water solution using in-situ optical microscopy. In the supersaturation range $\sigma = 0.66–1.17$, growth rates of the {011} faces varied between $8.5\pm2.1$ and $21.6\pm1.3 \, \mu m \, min^{-1}$. In comparison, in the supersaturation range $\sigma = 0.15–0.4$, growth rates along the $b$-axis of naproxen crystal (this study used 41.5 wt. % ethanol–water solution) ranged from $0.2\pm0.03$ to $1.03\pm0.1 \, \mu m \, min^{-1}$. These data show that ibuprofen crystal growth is approximately 3 times faster than naproxen at the same supersaturation level ($\sigma = 0.66$). The difference in growth rates between the two systems can be attributed to several factors, including differences in the crystal surface chemistry and the interaction of surface functional groups with the solvent, defect densities on the seed crystal surface, variation in solvent composition, seed crystal size and solution volume used during crystal growth experiments. Notwithstanding these differences, the spiral growth (BCF) model was shown to fit the growth kinetics data satisfactorily in both the crystal systems. However, in the other solvents investigated (acetonitrile, toluene, and ethyl acetate), the birth and spread model (viz. surface nucleation and growth mechanism) was observed to best fit the growth kinetics data.

In the second study, Vetter et al. determined ibuprofen crystal growth kinetics in 50 wt. % ethanol–water solution by measuring the rate of desupersaturation in seeded batch experiments. In-situ ATR-FTIR (attenuated total reflectance Fourier transform infrared) spectroscopy was used to measure the solute concentration. The overall crystal growth rate was calculated by solving population balance models. Analysis of the growth data revealed that surface integration controlled growth mechanism (birth and spread model) was in action. Whilst this approach for investigation of crystal growth mechanism considered growth kinetics determined at the process scale (500 mL stirred vessel), in the work by Nguyen et al., the growth solution volumes used were in micro to milliliter range.

### 4.2. Asymmetrical crystal growth in the presence of polymeric additives

Figure 3 shows time series images of naproxen seed crystal acquired in a typical growth experiment. At supersaturation $\sigma = 0.2$, in pure solution (without any additives), axial growth along the $b$-axis occurred at both capped ends of the seed crystal (Figures 3a and b). At the same supersaturation level, in the presence of HPMC additive, the seed crystal grew at only one of
the capped ends (Figures 3c and d). Likewise, a unidirectional growth along the $b$-axis of naproxen seed crystal was observed in the presence of PVP additive. However, in this case, crystal growth at the other end of the $b$-axis was accelerated. In comparison to the effect of additives on the $b$-axis growth, the additives had a minor effect on crystal growth along the $c$-axis. At equivalent supersaturation, the $c$-axis growth rate was slightly higher and lower than the pure system in the presence of HPMC and PVP respectively (data not shown). However, these minor differences in growth rates are attributed to the effect of local supersaturation at the crystal faces rather than specific additive interactions at the crystal surface.

**Figure 3.** Optical microscope images of naproxen seed crystal growth in ethanol–water solution at supersaturation $\sigma = 0.2$; (a) and (b) correspond to growth from pure solution (no additives), (c) and (d) correspond to growth in the presence of HPMC additive. Arrow symbols represent growth direction along the $b$-axis of naproxen crystal. Dashed lines are drawn to indicate advancement of the crystal growth front with time.

Subsequently, seed crystal growth rates were measured at different supersaturation levels in the presence of both individual and combination of the polymeric additives (Figure 4). At a given supersaturation, the effect of additives on growth kinetics was evaluated by calculating percentage increase or decrease in growth rate compared to the pure system. In the supersaturation range $\sigma = 0.15–0.25$, naproxen crystal growth was significantly accelerated ($ca. 50\%$ increase) in the presence of PVP additive. However, at $\sigma \geq 0.3$, the measured
growth rates were either equal to or slightly lower compared to pure system. As PVP additive also promotes\textsuperscript{13} nucleation kinetics of naproxen crystals, many new crystals were formed in the growth solution causing a decrease in supersaturation. Therefore, the values of seed crystal growth rates measured at the higher supersaturation were lower compared to the growth rate of the pure system.

![Diagram of crystal growth rates]

**Figure 4.** Naproxen seed crystal growth rates (in the $b$ direction) measured in ethanol–water solution at different supersaturation levels and in the presence of polymeric additives. Growth rate for pure system (no additives) is derived by fitting experimental growth data to the spiral growth model and is represented by the solid (blue) line. The error bars denote standard deviation (SD $\leq$ 20\%) of at least three growth data points.

In contrast to the effect of PVP additive, in the supersaturation range $\sigma$ = 0.15–0.4, naproxen crystal growth along the $b$-axis was inhibited in the presence of HPMC additive (Figure 4). Notably, the effect of additive on growth inhibition was stronger at higher supersaturation. These results are consistent with the effect of polymeric additives on the growth time ($t_g$)—a parameter in the nucleation rate equation\textsuperscript{33} which accounted for the time
needed for the crystal nucleus formed in solution to grow to a detectable size—of naproxen crystal determined in our previous study.13

Earlier works34−38 have reported a unidirectional growth behavior in polar crystals—acentric crystals comprising polar molecules packed in non-centrosymmetric space group. The mechanism of asymmetrical growth in polar crystals (α-resorcinol being a classic example) is generally attributed to solvent interactions at the crystal–solution interface37, 38 or to the intrinsic property of the crystal leading to distinct growth mechanism34−36 on the hemihedral faces at the opposite ends of the polar axis. Besides, other studies39−41 have shown auxiliary molecules (like organic small molecule and inorganic salts) inhibiting growth at one end of the polar crystal, a phenomenon caused by specific intermolecular interactions at the crystal faces. The current work, for the first time (to the best of our knowledge), has revealed anisotropic growth inhibition in an organic crystal by polymeric additives.

Next, we investigated the effect of combination of the additives—a mixture of PVP and HPMC, each of concentration 0.14 mg/g co-solvent mixture—on naproxen crystal growth. Note that the total additive concentration (0.28 mg/g co-solvent mixture) is the same as that used previously in crystal growth experiments with the individual additives. This set of experiments was intended to clarify a specific aspect relating to the effect of additives on naproxen crystal growth: do the individual additives inhibit b-axis crystal growth at the same capped end faces or capped end faces in the +b and −b directions, respectively? In the presence of the additive mixture, a unidirectional growth along the b-axis of naproxen crystal was observed, similar to the effect produced by the individual additives. This experimental result elucidates that the action of PVP and HPMC additive is most likely confined to the hemihedral faces at the same crystal end. On the other hand, if the additive effect has been pronounced at both the capped end faces, growth inhibition would occur in both +b and −b directions. Nevertheless, in the supersaturation range σ = 0.2–0.4, crystal growth rates measured in the presence of the additive mixture was somewhat slower compared to that with HPMC alone (Figure 4). This result will be further discussed in the context of intermolecular interaction of the additives at naproxen crystal surfaces in the next section.
Table 1. Interaction energies (kcal/mol) between polymeric additives and naproxen crystal faces.

<table>
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<tr>
<th>Additive</th>
<th>Crystal face</th>
<th>(011)</th>
<th>(01̅1)</th>
<th>(100)</th>
<th>(00̅1)</th>
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<td></td>
<td>(-b axis)</td>
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<tr>
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<td></td>
<td>(+b axis)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Total interaction energy</td>
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<td></td>
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<tr>
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<td>-138.39</td>
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<tr>
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<tr>
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4.3. Interaction of polymeric additives with naproxen crystal faces. Intermolecular interaction energies between the polymeric additives and dominant faces of naproxen crystal are shown in Table 1. Note that a negative value for the interaction energy generally indicates favourable interactions between the additive molecule and crystal face, with a higher absolute value of interaction energy denoting stronger intermolecular interactions. The simulation results show that PVP and HPMC respectively exhibit much stronger interactions with the {011} faces ((011) and (01̅1) symmetrically-related faces in +b direction) compared to the {01̅1} faces ((01̅1) and (01̅̅1) symmetrically-related faces in −b direction). Besides, the +b axis total interaction energies for the two additives are significantly greater than that for the (100) and (00̅1) faces (along the a-axis and c-axis), respectively. The contribution from van der Waals (vdW) and electrostatic interaction forces to the total interaction energy of the additives is now evaluated. The vdW interaction energy accounts for 64–93% of total interaction energies between PVP and the dominant faces of naproxen crystal. Likewise, the vdW interaction energy accounts for 63–100% of total interaction energies between HPMC and the crystal faces. In comparison, the electrostatic interaction energy, which is primarily contributed by hydrogen bonding interactions, only accounts for 0–8% of the total interaction.
energies. However, for the \((01\overline{1})\) face (along the +\(b\) axis), the electrostatic interaction energy accounts for ca. 30\% of total interaction energy.

![Figure 5](image-url)  
**Figure 5.** Molecular topology of naproxen crystal faces: (a) \((0\overline{1}1)\) face in \(-b\) direction; (b) \((01\overline{1})\) face in +\(b\) direction; (c) \((\overline{1}00)\) face in \(-a\) direction; (d) \((00\overline{1})\) face in \(-c\) direction.

Differences in the calculated values of interaction energies, in part, could be explained based on surface chemistry of naproxen crystal faces and the resulting intermolecular interactions with the polymeric additives. While non-polar methyl and naphthyl functional groups are expressed the \((0\overline{1}1)\) face (Figures 5a), the \((01\overline{1})\) face expresses both naphthyl and carboxylic acid functional groups (Figure 5b). In a typical MD simulation run, a PVP molecule formed 1–2 long-lived \(O\cdots H_{naproxen} \cdots O=C_{PVP}\) hydrogen bonds (of lifetime ranging 70–450 ps) and around 50–80 short-lived hydrogen bonds (of lifetime < 2 ps) on the \((01\overline{1})\) surface. In contrast, no hydrogen bonds were formed between PVP molecule and the \((0\overline{1}1)\) face. A HPMC molecule formed 1–4 long-lived hydrogen bonds \((O\cdots H_{naproxen} \cdots O\cdots H_{HPMC})\) and around 200–400 short-lived hydrogen bonds on the \((01\overline{1})\) surface. In comparison, the additive molecule formed around 40–60 short-lived hydrogen bonds on the \((0\overline{1}1)\) face. These analyses indicate that the additives interact more strongly with the \(\{011\}\) hemihedral faces bounding the +\(b\) axis though hydrogen bonds. Subsequently, the adsorbed polymer molecule imposes barrier to surface integration of the solute molecules, resulting in growth...
inhibition along that direction. Between the $(\bar{1}00)$ and $(00\bar{1})$ faces (Figures 5c and d), the $(\bar{1}00)$ face expresses polar (carboxylic acid) functional group resulting in stronger (electrostatic) interaction with HPMC additive (cf. Table 1).

It is encouraging to note that the calculated values of interaction energies and the underlying crystal surface and polymer (additive) chemistry are consistent with the experimental observations on additive-mediated crystal growth. However, we did not observe such a direct correspondence between the crystal surface chemistry and naproxen crystal habits obtained from additive-free solution. Analysis of functional groups oriented on the $\{011\}$ faces showed that both polar and non-polar groups are expressed on the $(01\bar{1})$ face ($+b$ direction) whereas non-polar groups are expressed on the $(0\bar{1}1)$ face ($-b$ direction). Based on this analysis, it is expected that the $(01\bar{1})$ face will experience stronger interactions with the solvent (ethanol–water mixture) and, consequently, grow slower compared to the $(0\bar{1}1)$ face. Contrast to this notion, previous observations of naproxen seed crystal growth has shown comparable growth rates at the $+b$ and $-b$ ends. Accordingly, equally developed $\{011\}$ hemihedral faces were often observed in the experimental crystal habit. On the other hand, a plate-like crystal habit with dominant $\{100\}$ face could be attributed to strong interactions between carboxylic acid functional groups exposed on this face and the solvent molecules.

The current work simulated interaction of polymeric additives with naproxen crystal surface in vacuum since explicit modelling of the solvent environment can considerably increase complexity of the system. However, it is well-recognized that additive–crystal interactions could be strongly influenced by the presence of solvent at the crystal interface. Particularly, in the case of water-soluble polymers interacting with weakly water-soluble drug molecules, the dominant forces of intermolecular interactions can be quite different with solvent molecules present at the crystal interface. Gao and Olsen$^{42}$ studied the interaction of an amphiphilic block copolymer, poly(ethylene glycol)-block-poly(lactic acid) (PEG-b-PLA), with tolazamide (a poorly water-soluble drug) crystal in water using MD simulation. Their simulation results revealed that hydrophobic and vdW interactions accounted for more than 90% of the total interaction energies. As tolazamide molecules in the crystal structure are dimerized by intermolecular NH–O hydrogen bonds, limited hydrogen bonding sites are accessible on the crystal surface. Consequently, hydrophobic interactions
rather than hydrophilic interactions contributed predominantly to the intermolecular interactions. In this simulation, hydrophobic interaction energy resulted from a thermodynamic effect caused by varying amounts of water molecules present on the crystal (hydrophobic) surface at any instance during crystal growth. Accordingly, a reduction in solvent accessible surface area favored more hydrophobic interaction between the polymeric additive and crystal surface.

Next, we probe into the mechanism underpinning naproxen crystal growth promotion (along the \(-b\) axis) in the presence of PVP. Little previous work on additive-mediated promotion of crystal growth is available in literature to aid our understanding of this phenomenon. Also, a detailed (molecular) simulation study on this aspect is beyond the scope of this work. Herein, we provide some insights into this effect based on the molecular mechanism\(^{40}\) proposed earlier to explain the role of impurities (organic small molecules) in accelerating crystal growth. In the case of \(\gamma\) glycine (exhibiting a polar crystal morphology), growth rate acceleration at one end of the polar axis was associated with disruption of solvation layer by the impurity molecules (aspartic and malonic acids). The impurity reduces the activation energy for desolvation through two different pathways: first, by protonating the surface carboxylate sites (pH effect); second, by decreasing the concentration of hydrated glycine molecules on the crystal surface due to enhanced additive–glycine interactions. Building on this proposition, the role of PVP in promoting naproxen crystal growth is reasoned. Owing to its amphiphilic nature, the additive experiences both lipophilic interactions with the \((0\bar{1}1)\) face of naproxen crystal (through vdW forces), and also has a tendency to associate with the solvent molecules (ethanol and water) due to its hydrophilic nature. Note that, between the two polymeric additives, PVP is 10-fold more soluble in water/ethanol compared to HPMC. In fact, HPMC is nearly insoluble in ethanol. On the other hand, naproxen molecules on the \((0\bar{1}1)\) surface will have weaker interactions with the polar solvent molecules. Retrospectively, relative strength of these intermolecular interactions could promote integration of the solute molecules on the crystal surface in the presence of weakly-adsorbed PVP, thereby catalyzing growth. In contrast, HPMC is likely to have relatively stronger interaction with the crystal surface and weaker interaction with the solvent medium.

4.4. Relating crystal growth kinetics to modulation of crystal shape and size. Figure 6 shows representative images of naproxen crystallized by slow solvent evaporation method.
The crystals obtained in the absence of additives exhibit a prismatic habit elongated along the $b$-axis (Figure 6a). With PVP additive, thin, needle-like crystal habit was obtained (Figure 6b). The crystal habits obtained in the presence of HPMC (Figure 6c) and a mixture of PVP and HPMC additives (Figure 6d) respectively were relatively shorter along the needle-axis.

**Figure 6.** Microscopy images (cross-polarized mode) of naproxen crystallized by slow solvent evaporation in the absence (a) and in the presence of additives: PVP (b), HPMC (c) and a mixture of PVP and HPMC (d).

Now, we evaluate the effect of additives on naproxen crystal shape and size by comparing the crystal length and width at 80% cumulative frequency ($L_{80}$ and $W_{80}$) obtained by histogram analysis of the linear dimensions (Table 2). From both slow evaporation and slow cooling (without stirring) experiments, smaller crystals were obtained in the presence of HPMC alone and HPMC+PVP additive mixture. Naproxen crystallized in the presence of PVP additive was too needle-like (elongated along the $b$-axis) to measure the crystal length from microscope images. Nevertheless, the size data indicated that the width of naproxen crystals obtained with PVP additive was significantly reduced (compared to the pure system).
Table 2. Size of naproxen crystallized in the absence and presence of polymeric additives.

<table>
<thead>
<tr>
<th>crystal size (µm)</th>
<th>slow evaporation</th>
<th>slow cooling (without stirring)</th>
<th>slow cooling (with stirring)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>length (L_{80})</td>
<td>width (W_{80})</td>
<td>length (L_{80})</td>
</tr>
<tr>
<td>No additive</td>
<td>2280</td>
<td>200</td>
<td>1030</td>
</tr>
<tr>
<td>HPMC</td>
<td>1590</td>
<td>112</td>
<td>660</td>
</tr>
<tr>
<td>PVP*</td>
<td>...</td>
<td>90</td>
<td>...</td>
</tr>
<tr>
<td>HPMC+PVP</td>
<td>1360</td>
<td>102</td>
<td>980</td>
</tr>
</tbody>
</table>

*Naproxen crystallized with PVP additive was too needle-like (elongated along the \(b\)-axis) ruling out statistical measurement of the crystal length from the microscope or SEM images.

Naproxen crystallized by slow cooling ethanol–water solution under stirred conditions is shown in Figure 7. In general, compared to crystallization from quiescent solutions, more number of crystals is formed due to enhanced primary and secondary nucleation rates. Consequently, with limited supersaturation available for growth, naproxen crystals obtained are generally smaller compared to that formed from unstirred solutions. Yet, the effect of additives on the crystal habit was apparent. While elongated needle-like crystals were obtained in the presence of PVP (Figure 7b), comparatively shorter crystals (along needle-axis) were produced in the presence of HPMC (Figure 7c) or a mixture of HPMC and PVP (Figure 7d). These observations are analogous to the results obtained in slow evaporative and cooling (without stirring) experiments. Besides, the effect of additives on the crystal size concurs with the trends observed in the previous batch experiments (*cf*. Table 2). Powder X-ray diffraction analysis of naproxen crystallized from both the stirred and unstirred experiments confirmed that the additives did not induce any changes in the polymorphic form (Figure S3 in the Supporting Information).
Figure 7. SEM images of naproxen crystallized by slow cooling under stirred conditions in the absence of additives (a) and in the presence of additives: PVP (b), HPMC (c) and a mixture of PVP and HPMC (d).

From the above data on the effect of polymeric additives on naproxen crystal shape and size, the following inferences were drawn. Firstly, the additive-mediated modification of naproxen crystal length is generally in line with the effect of additives on the $b$-axis growth kinetics (cf. Figure 4). Secondly, since the additives can inhibit naproxen crystal growth effectively at only one end of the needle ($+b$) axis, it is unlikely to avoid needle shapes by using either a single or combination of the additives. Taking clues from the molecular modeling results, an additive that is capable of forming stronger hydrophobic interactions with the $-b$ end of the needle axis—in combination with PVP or HPMC which interacts strongly with the hemihedral faces at the $+b$ end through hydrogen bonding interactions—can provide an effective crystal growth inhibitor system.
Figure 8. Optical microscope images of naproxen crystal (spontaneously nucleated) growth in ethanol–water solution at $\sigma = 1.4$; (a) and (b) are in pure solution (no additives), (c) in the presence of HPMC additive. Arrow symbols represent growth direction along the $b$-axis of naproxen crystal. Dashed lines are drawn to indicate the advancement of crystal growth front with time.

Lastly, growth of a spontaneously nucleated naproxen crystal was monitored in the absence and presence of the polymeric additives, with the aim to compare the growth behavior with that observed earlier during seeded crystal growth. In pure solution (no additives), a newly formed crystal grew in the $+b$ and $-b$ directions (Figures 8a and b); whilst the crystal shown in Figure 8a develops a prismatic shape with capped edge faces, the crystal shown in Figure 8b retains needle shape with further growth. In the presence of HPMC, the crystal grew only at one end of the needle axis (Figure 8c). A similar growth behavior was observed with PVP additive and in the presence of the additive (HPMC+PVP) mixture, respectively. Now, the $b$ and $c$ axes growth rates were determined by measuring linear displacements with time in randomly nucleated crystals. In pure solution, at equivalent supersaturation conditions, the $b$-axis to $c$-axis ($b/c$) growth rate ratio for a spontaneously nucleated crystal was around 16, compared to a ratio of 6 for the seeded crystal growth. In the presence of PVP, HPMC and HPMC+PVP additives, $b/c$ growth rate ratios for the spontaneously nucleated crystal were determined to be 46, 20, and 36, respectively. In comparison, $b/c$ growth rate ratios for the seeded crystal in the presence of PVP, HPMC and HPMC+PVP additives were 7, 2.6, and 2.6, respectively. These results indicate that, growth inhibitory effect of the additives was less pronounced in the case of a nucleated crystal. This comparative analysis shows that the effect of additives on naproxen crystal growth could
depend on the growth morphology and local supersaturation at the growth front. While the former factor may influence the strength of intermolecular interactions between the additive and crystal faces (for instance, through defect density), local supersaturation at the crystal–solution interface affects the growth rate through kinetic (generation of steps on the crystal surface) and thermodynamic (interfacial free energy) factors.\textsuperscript{31}

5. Conclusions

Two-dimensional growth of a single seed crystal of naproxen in ethanol–water solution at nearly constant supersaturation was monitored using optical microscopy. The spiral growth model was shown to fit the needle \((b)\) axis crystal growth rate versus supersaturation data very well. In the presence of small quantities of polymeric additives like hydroxylpropyl methyl cellulose (HPMC) and polyvinylpyrrolidone (PVP) dissolved in the solution, growth along the needle axis was selectively inhibited at one end of the seed crystal \((+b\) direction). In the supersaturation range \(\sigma = 0.15–0.4\), the overall \(\beta\)-axis growth rate was slowed down in the presence of HPMC additive; in contrast, PVP promoted the \(\beta\)-axis growth rate (selectively in \(-b\) direction) significantly.

The mechanism underpinning naproxen crystal growth inhibition was probed by modeling intermolecular interactions between the polymeric additive and crystal surface. Molecular dynamics (MD) simulation results revealed that the hemihedral faces capping \(+b\) and \(-b\) axis of naproxen crystal differ in their surface chemistries, and consequently influence interaction energies of the additives with the crystal faces. The additives (PVP and HPMC) form stronger hydrogen bonds with the \(\{011\}\) faces in \(+b\) direction—ca. 30\% of the total interaction energy, as compared to less than 8\% for the \(\{0\overline{1}1\}\) faces in \(-b\) direction. Consequently, the additive molecule adsorbs strongly on the \(\{011\}\) faces, and, in turn leads to growth inhibition via diffusion-controlled mechanism. This simulation result differs from the viewpoint\textsuperscript{8, 11, 22, 24} that hydrophobic and van der Waals interactions play a dominant role in inhibiting crystallization of poorly water-soluble drugs by water-soluble polymeric additives. While, in this study, MD simulations were carried out in vacuum, the presence of solvent is expected to influence the interaction of additives with the crystal surface. More specifically, as the polymeric additives can strongly interact with water/ethanol molecules, the drug–polymer interactions at the crystal surface could be significantly altered. This aspect will be investigated potentially in our future work. Nevertheless, current experimental
observations on the effect of polymeric additives on naproxen crystal growth appear to be in good agreement with the underlying crystal surface chemistry.

Based on the insights obtained from crystal growth experiments and molecular modeling, both individual and combination of the polymeric additives were used to modulate naproxen crystal shape and size. Naproxen crystallized in the presence of HPMC and a mixture of HPMC and PVP additives respectively was somewhat shortened along the needle axis. In contrast, PVP produced a crystal habit much elongated along the b axis. These changes in the crystal habit are in line with the growth kinetics data. While the crystal width (c-axis) and thickness (a-axis) were reduced in the presence of the additives, these specific habit modifications were attributed to the effect of additives on enhancement of crystal nucleation kinetics (as shown in our previous work\textsuperscript{13}) rather than growth inhibition.

Supporting Information

Naproxen crystal habit simulated from its crystal structure, experimental assignment of face indices for naproxen crystal, and powder X-ray diffraction analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgement

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Anisotropic Crystal Growth Inhibition by Polymeric Additives: Impact on Modulation of Naproxen Crystal Shape and Size

Sendhil K. Poornachary, Vernissa D. Chia, Yani Yin, Guangjun Han, Pui Shan Chow, and Reginald B. H. Tan

The mechanisms by which polymeric additives (HPMC and PVP) caused anisotropic growth inhibition along the needle axis of naproxen crystal was probed through seed crystal growth rate measurements and by modeling intermolecular interactions between the additives and crystal faces.