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The Challenges of Developing an API Crystallization Process for a Complex Polymorphic and Highly Solvating System. Part I

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Abstract:

Developing a robust crystallization process for an active pharmaceutical ingredient (API) molecule with a complex polymorphic profile can present a significant challenge. The presented case illustrates an unusual crystallization development problem where a polymorphically complex API has the additional obstacles of poor solubility in standard crystallization solvents as well as a propensity for forming solvates. After early polymorph screening of this candidate highlighted the potential for a complex solid form profile, a variety of experimental approaches was utilized to determine the low-energy polymorph and characterize the various solvates formed. Characterization of the API crystallization process identified a critical solvent composition range for the transformation from a metastable solvate form to the desired polymorph. During subsequent crystallization process development studies, a new lower-energy polymorph was discovered. Examination of the crystal structures led to a rationale for the formation of solvates and the existence of a new lower-energy form.

1. Introduction

From a crystallization standpoint, the development of a drug candidate is fraught with challenges. The practitioner must develop a robust crystallization process that delivers the active pharmaceutical ingredient (API) with both high yield and appropriate attributes that are conducive to drug product development (e.g., purity, polymorph, and particle size distribution). These requirements typically become more acute while optimizing the chemical process in parallel as subtle variations in impurity profiles must be anticipated in order to develop a robust API isolation process. If utilizing a "Quality by Design" approach to developing and filing a process, the practitioner must develop a robust crystallization process that can demonstrate an assurance of all quality attributes via the multidimensional combination of starting material attributes and process parameters.[1]

The crystalline polymorph is a quality attribute that is assured by the API crystallization and isolation process. Polymorphism can be thought of as the condition in which a solid chemical compound exists in more than one crystalline form,[2] with only one polymorph being the thermodynamically most stable form at any given temperature. Different polymorphs can have differences in certain properties, such as solubility and stability, that can often have a significant impact on bioavailability and overall drug product performance. A number of excellent texts on polymorphism and their influence on pharmaceutical development are available.[3] There are numerous examples from the literature[4] that describe the appearance of lower-energy polymorphs at late stages in development. Thus, evaluating the polymorph landscape of a new API through well-designed screening experiments and identifying the most stable crystalline polymorphic form at an early developmental stage is critical for API and drug product development. Significant effort has been spent in the pharmaceutical industry over the past decade on developing and utilizing numerous screening protocols,[5] including efforts to develop robust computational methods to predict crystal structures from a molecular starting point.[6,7] More recently, a knowledge-based model that utilizes insights on the intermolecular interactions derived from the crystal structure has shown promise in advancing understanding of the differences between polymorphic forms and solvates at the molecular level.[8]

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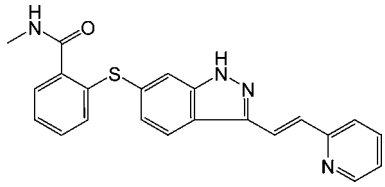

Figure 1. **Axitinib.**

Axitinib (Figure 1) is an oncology candidate under development at Pfizer. This candidate targets the vascular endothelial growth factor (VEGF) to prevent the growth and proliferation of cancer cells via interruption of tumor angiogenesis (formation of vascular supply tissue). This compound has shown promise in the treatment of carcinomas in a number of target tissues and organs and is currently in late-stage clinical development.[9] The development of axitinib required new approaches due to the propensity of the molecule to solvate and the appearance at a late stage of a more stable, lower-energy polymorph. Progress in identifying crystallization conditions to reproducibly isolate this new form and examination of the crystal packing of the API to explain the observations and challenges in polymorph screening of this compound are described.

2. Results and Discussion

2.1. Early Development Polymorph Discovery. Two polymorphic screening studies of axitinib had been performed during the preclinical development stage. Though it is common for typical drug molecules to exhibit some degree of polymorphism, these early investigations suggested axitinib to be highly polymorphic. In addition, preliminary salt screening studies yielded salt forms which were hygroscopic and also polymorphic; thus, the decision was made to advance the free form. Seven crystalline free base forms, designated as Forms I−VIII, were discovered in early process development studies (no polymorph was given the designation Form V). Methods used in these studies included solid slurries, evaporative crystallizations, and pH-adjustment experiments using a set of seven solvents.[10] All the solid forms were unique based on distinctive powder X-ray diffraction (PXRD) patterns and different thermal characteristics such as melting onset, enthalpy of melting, and desolvation/dehydration temperatures as measured by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). This group of solid forms included three anhydrous forms, a potential hydrate, and several solvates including ethyl acetate, dioxane, and THF. Characterization of the solvate/hydrate forms using TGA suggested nonstoichiometric solvent levels in some instances.

The anhydrous Form IV had favorable physical and chemical properties and was selected as the development form. This form was the highest melting of the anhydrous forms and was also shown to be nonhygroscopic and physically and chemically stable. Thus, Form IV was characterized as a robust developmental form with acceptable solid-state properties. A successful solid dosage form utilizing Form IV was manufactured for early clinical studies.

Table 1. **Room temperature (20−25 °C) solubility measurements of axitinib Form IV**

solvent	solubility (mg/mL)
acetic acid	10
acetone	<1
acetonitrile	0.1
DMF	16
ethanol	5.0
ethyl acetate	<1
hexanes	0.3
methanol	1.0
octanol	2.7
THF	<1
water	<0.1

A second, more expanded polymorph screen using Form IV was later performed in 45 individual solvents and binary solvent mixtures using common crystallization techniques. This study resulted in the generation of over 20 unique PXRD patterns showing crystalline or partially crystalline material. Due to limited material generated from the screen, extensive characterization was not performed, though later findings indicated that many of these were solvated forms. It was clear from these early studies that axitinib had a large polymorph space and a complex solid-form profile. In addition, a set of initial solubility measurements for Form IV demonstrated that axitinib had low solubility in a range of solvent systems (see Table 1.)

2.2. Later-Stage Polymorph Screening with Form IV and Form IX. Form IV API and drug product had been successfully manufactured throughout early development and early clinical trials. However, the initial form screens were based on a limited number of solvents; thus, our understanding of the polymorphic environment was not sufficient to have high confidence that Form IV was the lowest-energy form. Consequently, more comprehensive polymorph screens were undertaken to further delineate the polymorph landscape and confirm Form IV as the low-energy form suitable for commercial development. Many techniques are commonly employed in screening studies to uncover additional metastable and low-energy polymorphic forms. These include evaporation of API solutions to dryness, antisolvent addition to API solutions, cooling of API solutions to induce precipitation, and slurrying of solid API in a variety of solvents.[11] All of these methods were employed in the following screens.

2.2.1. Polymorph Screening with Form IV. Two extensive polymorph screens were performed simultaneously using Form IV as the starting form. The material used for these screens was of known high purity, generally greater than 98%, with no single impurity greater than 0.5%. The first screen utilized primarily slurrying the API in numerous solvents using a temperature cycling protocol. For example, solids were slurried at 25 °C for three days and then subjected to temperature cycling at designated time intervals from 25 to 40 °C for an additional three days. A total of 56 solvents or cosolvents spanning a broad range of polarities and chemical composition were screened

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(11) Quallich, G. In *Early Clinical Drug Development: From Synthesis Design to Formulation*, Abdel-Magid, A. Caron, S., Eds.; John Wiley and Sons: New York, 2006.

Table 2. **List of solvents employed in late-development polymorph screens**

acetone[b,c]	octane	1-butanol/water, 1:1
2-propanol[b]	methylene chloride[b,c]	DMF/octanol, 1:1[b]
toluene[b,c]	1-octanol[b]	acetic acid/ toluene, 1:1
chloroform[b]	acetic acid[b]	IPA/water, 2:8
1,2-dimethoxyethane	pyridine[b]	IPA/water, 7:3
acetonitrile[b,c]	1-pentanol[b]	IPA/water, 8:2
cyclohexane	*n*-methyl-pyrrolidine[b]	IPA/water, 9:1
ethyl acetate[b,c]	allyl alcohol[b]	methyl benzoate[b]
heptane	3-methyl-1-butanol	*o*-xylene
MTBE	trichloroethylene[b]	dioxane[b]
THF[b,c]	ethanol/water, 1:1[c]	nitromethane
water[b,c]	DMF/water, 1:1[c]	1-butanol[b,c]
1-methoxy-2-propanol	DMSO/water, 1:4[b]	pentane
methanol[b,c]	acetone/water, 1:1[c]	DMSO[b]
ethanol[b,c]	methanol/ water, 1:1[b,c]	DMF[b]
hexane[b,c]	IPA/water, 1:1[c]	benzyl alcohol[b]
IPE[b]	acetonitrile/ water, 1:1[b,c]	1-methoxy-2-propanol/water, 1:1
MIBK[b]	THF/water, 1:1[b,c]	*n*-propanol/ water, 1:1
1-propanol	2-butanone[b,c]	

[a] All solvents listed were used in the first polymorph screen with Form IV. [b] Solvents used in the second polymorph screen with Form IV. [c] Solvents used in polymorph screen with Form IX.

(refer to Table 2). Solids were also evaluated from evaporation and cooling experiments in the screen. The second form screen utilized room temperature and 60 °C temperature slurry experiments, temperature cycled slurries, evaporation and cooling experiments at different rates, and antisolvent addition crystallization studies, on 25 varied solvents (mostly a subset of the solvents listed in Table 2) to test the form robustness of Form IV. Thus, the second screen utilized a smaller solvent set, but focused on more diverse techniques to attempt to generate a high population of solid forms. All solids isolated from both screens were characterized by PXRD, Raman spectroscopy, DSC, TGA, microscopy, and NMR spectroscopy. Between these two studies, a significant number of new PXRD patterns not observed in the two previous form screens were obtained, and a new set of solid forms based on these patterns were deemed Form IX through Form XXIV (refer to Table 3). Form IV remained the form most suitable for commercialization, due to its ease of preparation and the fact that no lower-energy form had been found from the aforementioned screens.

2.2.2. Polymorph Screening with Form IX. At this point, a different tack was taken; considering the extensive number of solid forms discovered to date, a polymorph screen was performed using a different in-going form, Form IX (a hydrate). This form was chosen because the hydrate form should be metastable to Form IV in anhydrous solvent systems, which may lend to spawning additional forms that may not be kinetically or thermodynamically achievable starting with Form IV. This new study employed a total of 20 different solvent or cosolvent mixtures that were slurried at 45 °C for 3 days. Solids were obtained from the resultant slurries, or from evaporation of their respective filtrates. However, in this case, no new PXRD patterns that had not been previously observed were obtained from the study.

Table 3. **Axitinib polymorph designations**

name	form	solvent
Form I	anhydrate	–
Form II	hydrate	water
Form III	solvate	ethyl acetate (EtOAc)
Form IV	anhydrate	–
Form VI	anhydrate	–
Form VII	solvate	isopropyl alcohol (IPA)
Form VIII	solvate	dioxane, isomorphic with tetrahydrofuran
Form IX	hydrate	water
Form X	solvate	dimethylformamide (DMF)
Form XI	solvate	THF/water, THF
Form XII	solvate	ethanol (EtOH), isomorphic with dichloromethane
Form XIII	solvate	acetonitrile (ACN)
Form XIV	solvate	acetic acid
Form XV	solvate	EtOH
Form XVI	solvate	IPA
Form XVII	solvate	acetone
Form XVIII	solvate	methylisobutylketone (MIBK)
Form XIX	solvate	methylethyl ketone (MEK)
Form XX	solvate	methyl benzoate
Form XXI	solvate	2,2,2-CF_3CH_2OH
Form XXII	solvate	1-pentanol
Form XXIII	solvate	pyridine
Form XXIV	solvate	chloroform

2.2.3. Summary of Axitinib Polymorphs and Solvates Discovered in Screening Experiments. No new anhydrous polymorphs had been discovered, as all of the new forms discovered from these three last polymorph development studies were solvated forms. Axitinib had a propensity to form relatively stable solvated structures, as a number of the newly discovered forms were characterized as possessing relatively high temperatures of desolvation (desolvation temperatures higher than the normal boiling point of the corresponding solvent), suggesting a high degree of strong intermolecular bonds within the crystal structure. Yet, some solvated forms had solvent not tightly bound as evidenced by moderately low temperatures of desolvation. This suggested that these solid forms are "fragile solvated" systems where the solvent may be more loosely bound, allowing the solvent to readily leave the structures. Also, many solvates formed from different solvent systems demonstrated very similar PXRD patterns suggesting similar crystal structures, known as isomorphs,[12] which made differentiation of solid forms all the more complex. In addition, multiple polymorphs of solvates were observed from the same solvent, such as ethanolate Form XII and Form XV as evidenced by PXRD and TGA.

A total of 23 forms had been identified and characterized, with three anhydrous forms identified and the remainder as solvates in all of the screening studies (comprising greater than 300 experiments). No new anhydrous forms had been discovered. All solvates were found to desolvate to Form IV upon heating from DSC experiments. Form IV remained the predominant anhydrous form and was deemed suitable for continued development.

(12) Mullin, J. W. *Crystallization*, 4th ed.; Butterworth-Heinemann: Oxford, 2001; Sect. 1.8, pp 16−18.

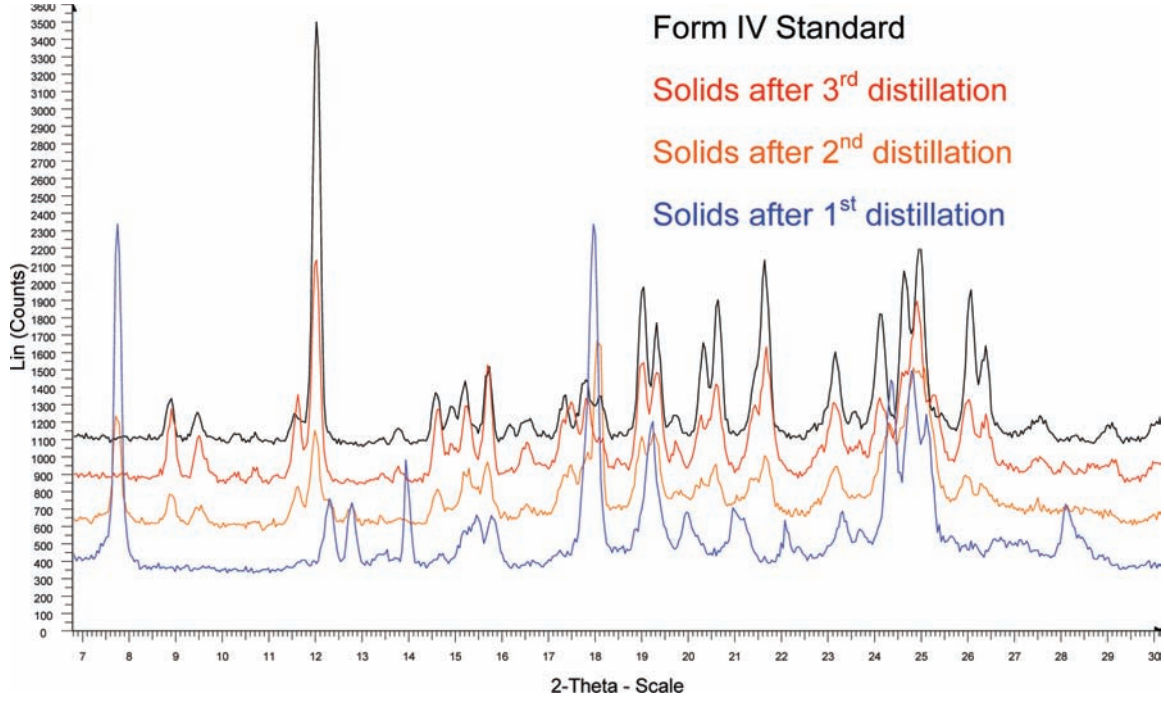

Figure 2. **Conversion of Form XIV to Form IV during acetic acid/xylenes distillations.**

2.3. The Development of a First-Generation Form IV Crystallization Process. The development of a polymorph control process for axitinib was challenged by the propensity of this compound to form solvates with most standard API crystallization solvents while also exhibiting poor solubility in most standard solvent systems. As described previously, the majority of reslurry and recrystallization studies conducted as part of the form screening for this compound resulted in the isolation of a solvate form. A previous article in this journal describes the first-generation process for producing axitinib as well as the challenges of developing an efficient palladium removal process due to the poor API solubility in most solvent systems.[13]

For this first-generation process, after the sequential Pd removal and purification steps, the solid form of axitinib was controlled by the following process. The penultimate form of the API was dissolved in a mixture of acetic acid and methanol by heating. The resulting solution was speck-free filtered and then distilled to remove the MeOH and induce supersaturation. A portion of xylenes was added next, and the resulting slurry was concentrated back to the original volume by vacuum distillation. This xylenes strip-and-replace process was repeated until PXRD indicated conversion to the desired polymorph, Form IV. Although this was a complex and solvent-intensive method for controlling the solid form, the process was "fit for purpose" as it delivered consistently the desired anhydrous solid form. As the clinical program required a rapid turnaround prior to the subsequent campaign, a decision was made to keep the existing first-generation process for the next manufacture. Therefore, the initial focus of the studies on the final API step was focused on characterizing the existing process to understand the mechanism of the polymorph control and thereby reduce any risk of solid form control upon scale-up.

An initial crystallization trial was run to determine the location of the various physical transformations during the process as well as to identify any metastable forms that nucleate during the process. Once in solution by heating in a mixture of acetic acid and methanol, the resulting solution could be cooled to 28 °C without any observation of nucleation, indicating that there was a wide metastable zone-width in which speck-free filtration could be run. Controlled distillation of the resulting solution resulted in the precipitation of some sticky solids toward the end of distillation. These sticky solids were redissolved upon heating after the addition of xylenes. Subsequent distillation resulted in the precipitation of crystalline solids; analysis of this solid form indicated a powder pattern of a crystalline solid form (this form was later designated Form XIV) that did not match the desired Form IV, so a second xylenes addition and distillation cycle was completed. Analysis of the solid form at the end of this distillation cycle indicated a mixture of Form XIV and Form IV, suggesting partial conversion to the desired form. A third xylenes strip-and-replace cycle was completed, and analysis of the solids upon cooling indicated a complete match to Form IV as seen in Figure 2 which shows the PXRD pattern from each of the three samples as well as the Form IV standard pattern. This initial pilot highlighted the significant limitations of this enabled process for controlling the solid form as it was highly solvent- and time-intensive and utilized a complicated distillation scheme to control the solid form.

PXRD analysis of the sticky solids that precipitated during the initial volume reduction showed a highly disordered solid form. Analysis of the intermediate crystalline solid form isolated after the xylenes distillation cycle indicated an apparent acetic acid solvate, which was designated as Form XIV. Thermogravimetric analysis (TGA) showed a 20.8% weight loss event

(13) Flahive, E. J.; Ewanicki, B. L.; Sach, N. W.; O'Neill-Slawecki, S. A.; Stankovic, N. S.; Yu, S.; Guinness, S. M.; Dunn, J. *Org. Process Res. Dev.* **2008**, *12*, 637.

Table 4. **Acetic acid content of solvent mixture and solid form during xylenes addition and distillation process[a]**

process step	wt % acetic acid in solvent mixture (HPLC)	solid form (PXRD)
after 1st xylenes addition + distillation	67.3	XIV
after 2nd xylenes addition	32.5	XIV
after 2nd distillation	17.0	XIV
after 3rd xylenes addition and distillation	1.9	IV

[a] All samples were taken at 25 °C.

with an onset temperature of approximately 85 °C. This weight loss result agrees closely with the acetic acid content of Form XIV also assessed by HPLC, which indicated a similar value as the TGA of 20.5 wt %. Due to the small pK_a value difference between axitinib and acetic acid, Form XIV was not expected to be an acetic acid salt form, as typically pK_a values 2−3 units apart are necessary to facilitate salt formation.[14] Identification of this material as a solvated free base form was ultimately confirmed by single-crystal X-ray analysis. Knowing that the polymorph control process entailed the conversion of the acetic acid solvate to the desired anhydrous form, research focused on identifying the critical acetic acid composition level to allow for this transition. For a crystallization system where an anhydrous form and solvate form can be produced, there exists a critical solvent activity and therefore a critical solvent composition (which is dependent on temperature) that defines the phase boundary between the solvate and an anhydrous form.[15]

A second pilot of the polymorph control process was run to identify this transition point in the process where the conversion from the acetic acid solvate (Form XIV) to Form IV occurs. Slurry samples were removed at different points through the process and filtered (each sample was taken when the reactor temperature was 25 °C). The isolated solids were assessed for form by PXRD; the mother liquor samples were analyzed by HPLC to determine the acetic acid content of the solvent mixture. Table 4 demonstrates that as the acetic acid content of the solvent mixture is reduced from 17.0 wt % to 1.9 wt % during the third distillation cycle the form conversion to Form IV occurs. This indicates that the process crossed a critical acetic acid composition during this step. Results from additional experiments help to further define the window for the critical acetic acid content for the Form XIV/Form IV conversion in the range of 4−10% (wt % acetic acid) near 25 °C.

These studies demonstrated that the first-generation process initially nucleated a stable solvate form (Form XIV, acetic acid solvate) and then through multiple distillation cycles changed the solvent composition to such an extent that the thermodynamically favored form was Form IV. This process for producing axitinib Form IV was successfully scaled up to a 33.3 kg-basis in the pilot plant. The dissolution and speck-free operation performed as expected with the API dissolving in the acetic acid and methanol mixture by heating to 50 °C. After filtering the warm solution, the methanol was removed by distillation, and the acetic acid was gradually displaced with four xylenes strip-and-replace cycles. After the fourth distillation cycle was completed, PXRD analysis indicated that the desired final form was reached; 24.3 kg of Form IV was isolated. One process change implemented for this campaign was the use of a final *n*-heptane wash in order to displace the xylenes and allow for a more efficient drying process. Previous lab studies had been challenged to reach the ICH limit for xylenes (2170 ppm) by drying at 60 °C under vacuum for 48 h without the use of heptane reslurry. Incorporating the heptane reslurry, the residual xylenes were measured at 0.1% after 28 h of drying under vacuum in the plant.

2.4. Process Improvement: Utilize Understanding of Form Conversion of First-Generation Form IV Crystallization Process to Develop New Reslurry Process. The existing polymorph control process had multiple issues that second-generation research sought to address: use of xylenes, use of acetic acid, high solvent volumes, and distillation to control solvent composition. An initial evaluation was done to evaluate *n*-heptane as an alternative to xylenes for displacing acetic acid in the final polymorph conversion. Although this switch alleviates the need to complete the final reslurry and heptane wash to remove residual xylenes, the volume of antisolvent needed is increased due to less favorable distillation conditions between acetic acid and heptane. Although this process was able to displace the acetic acid with the heptane and arrive at Form IV without the use of xylenes, no further development work was undertaken due to the high solvent volume.

Additional development work focused on developing a process to avoid the dissolution in acetic acid and methanol and the subsequent distillation cycles. In order to avoid dissolution in acetic acid and methanol, the final recrystallization sequence was modified to move the speck-free operation to the previous purification step in which the API is dissolved in *n*-methyl pyrrolidone (NMP). The subsequent recrystallized API solids are then transferred under speck-free crystallization to a reactor for the polymorph control step. A second major change involved using a series of reslurry steps with various acetic acid ratios to allow for the transformation of axitinib to Form XIV and then on to Form IV without distillation. A study demonstrated that the penultimate form of the API could be converted to the acetic acid solvate (Form XIV) by stirring the API in 20 volumes of heptane and 1 volume of acetic acid at 60−70 °C for a few hours and then cooling to room temperature prior to filtration. Next, the material is slurried in heptane at 60−70 °C to convert from Form XIV to Form IV. After several hours of heating, the mixture is cooled to room temperature and filtered once PXRD analysis indicates conversion to the desired Form IV. This process avoided the use of xylenes, reduced the overall solvent consumption, and eliminated the use of distillation.

The most significant challenge with this new process was the variable extent of conversion of Form XIV to Form IV in the heptane slurry for a fixed reslurry time, which indicated a

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(15) Black, S. N.; Phillips, A.; Scott, C. I. *Org. Process Res. Dev.* **2009**, *13*, 78.

nonrobust process.[16] Therefore, a significant effort was focused on finding robust conditions for the conversion of Form XIV material to Form IV. A series of experiments was conducted at higher jacket temperatures during the heptane reslurry, but instead of converting to Form IV, these samples converted to a new acetic acid solvate (which was later shown to have a different solvate stoichiometry). A separate study identified the conditions for forming this new acetic acid solvate. Reslurrying axitinib in 11% acetic acid/heptane at 50 °C for 3−4 h resulted in the formation of Form XIV, while reslurry in 5.5% acetic acid/heptane under the same conditions resulted in the isolation of this new acetic acid solvate. Thermal characterization of this solid form indicated approximately 10.5% weight loss upon heating, which is roughly half the acetic acid content of Form XIV. Importantly, subsequent attempts to convert this form to Form IV to using the standard conditions of reslurrying in heptane at 70−80 °C resulted in no conversion to the desired Form IV.

In a subsequent attempt to convert to Form IV, a sample of this new acetic acid solvate form was reslurried in heptane and heated to 85 °C and allowed to stir overnight. The sample was filtered, and the solid form was analyzed by PXRD, which showed a previously unseen powder pattern. Attempts to convert this material to Form IV via a heptane reslurry at 90 °C left the solid form unchanged. Several subsequent lab-scale experiments probing the new process yielded the same new PXRD pattern. Thermal analysis also supported this material as a previously unknown anhydrous form, which led to rapid efforts to understand the relationship between the new form and Form IV. This new anhydrous form was designated Form XXV.

2.5. Characterization of Form XXV. Once discovered, it was determined that Form XXV was a more thermodynamically stable form than Form IV and the other known anhydrous forms. Specifically, DSC measurements showed that the melting point of Form IV was about 1 °C higher than that of Form XXV (218 °C versus 217 °C), but the heat of fusion of Form XXV was about 12 J/g higher than that of Form IV, indicating they are enantiotropically related and thus their relative stabilities are temperature dependent. It is generally expected that Form XXV, with the higher heat of fusion, should be the more stable of the two forms at temperatures below the transition point.[17]

As a further confirmation of their relative stabilities and to obtain an estimation of the transition temperature between these enantiotropic forms, a multitemperature solubility study at 5 °C, 20 °C, and 40 °C was performed. Form XXV demonstrated the lower solubility at each condition, indicating it is the more stable form at these temperatures, as displayed in Figure 3. Though only three temperatures were employed, good van't Hoff solubility[18] relationships ($r = 0.999$) were obtained for each form. A transition temperature of 75 °C can be estimated from these data; thus, Form XXV is expected to be the more stable form below this temperature.

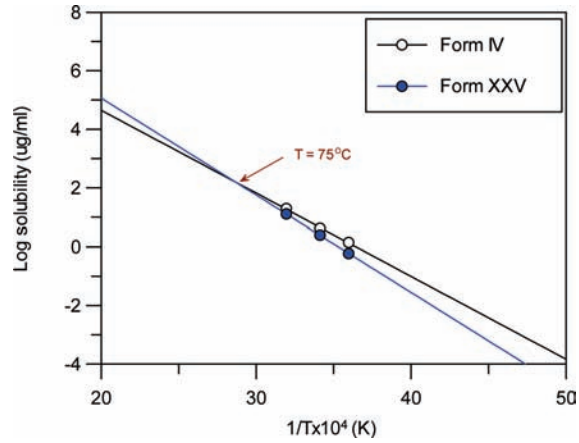

Figure 3. **van't Hoff solubility relationship of Form XXV and Form IV in 80:20 water/ethanol. Solubility measured at 5 °C, 20 °C, and 40 °C. The 75 °C transition temperature is indicated at the intersection of the two lines.**

This new form, Form XXV, was not observed in any of the aforementioned polymorph screens. Many factors (solvents, temperature, starting material, Pd, impurities, pathways) can influence crystallization and interconversion.[19] It is speculated that impurities, particularly palladium, may have played a part in inhibiting nucleation of Form XXV. Also, and as described in a later section, subsequent structural analysis would later show that the molecular conformation of essentially all of the solvate structures was very similar to that of Form IV. Thus, the fact that axitinib tends to form solvates and that the solvates would typically desolvate to Form IV helps explain the predominant appearance of Form IV. As discussed earlier, Form IV itself is a stable form and is extremely slow to cascade to more thermodynamically stable forms as would be typically expected on the basis of Ostwald's rule of stages.[20] Also, the crystal packing and molecular conformation of Form XXV, though related to Form IV, are different from those of Form IV (to be discussed in section 4.4). Unlike Form IV, the molecular arrangement of Form XXV was generally not achievable through desolvation; thus, it is believed the propensity of solvate formation significantly contributed to the lack of appearance of Form XXV in our polymorph screens.

2.6. Development of Enabled Process for Producing Form XXV. Once Form XXV was identified as the lowest-energy form, process development studies were initiated to enable the manufacture of a large-scale lab lot to supply needed API and drug product development studies of the new form. Using findings from the Form IV process development studies, the isopropanol solvate, Form XVI, was chosen a replacement for Form XIV (acetic acid solvate) as the intermediate form for converting into the final desired form. These earlier process development studies demonstrated that the isopropanol solvate was an easier to handle solid form and converted in a more robust manner to the final anhydrous forms as compared to Form XIV. The Form XVI material was then converted to Form XXV via a reslurry in heptane at 85 °C or via a 60 °C reslurry in 1% acetic acid/heptane. However, both of these processes

(16) This process could have been made more robust via the use of Form IV seed as it would avoid the effects of inconsistent generation of Form IV. For a review of seeding to control polymorphism, see: Beckman, W. *Org. Process Res. Dev.* **2000**, *4*, 372.
(17) Burger, A.; Ramberger, R. *Mikrochim. Acta II* **1979**, 259.
(18) James, K. C. *Solubility and Related Properties*; Marcel Dekker: New York and Basel, 1986.
(19) Mullin, J. W. *Crystallization*, 4th ed.; Butterworth-Heinemann: Oxford, 2001; Sect. 5.4, pp 205−206.
(20) Ostwald, W. Z. *Phys. Chem.* **1897**, *22*, 289.

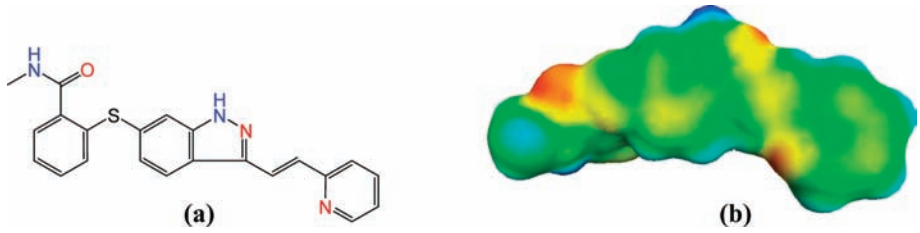

Figure 4. **(a) Molecular representation of axitinib, illustrating potential hydrogen-bond donors (in blue) and acceptors (in red) in the molecule. (b) Polarization surface charge density (σ-Surface) of the molecule,[24,27] reflecting the acceptor moiety (in red) and the donor moiety (in blue).**

Table 5. **Crystallographic data for Forms IV and XXV**

API form	space group	Z'	unit cell dimensions and volume	refinement R factor, %
IV	$P\bar{1}$	2	$a = 11.86$ Å, $b = 12.41$ Å, $c = 15.00$ Å $\alpha = 81.7°$, $\beta = 81.2°$, $\gamma = 66.0°$ $V = 1984.7$ Å^3	6.57
XXV	$P2_1/c$	1	$a = 4.54$ Å, $b = 11.75$ Å, $c = 34.83$ Å $\alpha = 90°$, $\beta = 92.13°$, $\gamma = 90°$ $V = 1858.1$ Å^3	6.25

were found to give inconsistent results with a wide range in the extent of conversion to Form XXV observed via PXRD results.[21] A set of experiments was run to examine the role of purity on the resulting isolated solid form that suggested that the nucleation of Form XXV was inhibited by either higher levels of organic impurities or higher residual Pd levels, as less pure samples showed only conversion to Form IV. Specifically, elevated heavy metal levels are known to inhibit the nucleation of forms.[19] Subsequent attempts to confirm these results with additional sets of experiments indicated no correlation of the final form with purity level, as Form XXV was observed in all cases. These later studies may have been impacted by the unintentional seeding of these reslurry experiments with Form XXV material akin to the well-known disappearing polymorph challenge.[22]

A large-scale lab lot of Form XXV was subsequently prepared by first forming the isopropanol solvate via a warm reslurry in isopropanol and subsequent vacuum drying. Utilizing a 1% acetic acid/heptane mixture, the Form XVI material was reslurried at 60 °C to provide a mixture of Form IV and Form XXV. On the basis of information from the previously described solid form bridging studies between Form IV and Form XXV, we knew that reslurring this mixture of forms in ethanol at elevated temperature would enable complete conversion to Form XXV. A reslurry process was developed (slurry in 5 volumes of ethanol at temperatures above 60 °C for more than one hour) and scaled up to allow for complete conversion to the desired Form XXV, which was isolated and dried.[23] This Form XXV material was subsequently used for additional process development studies as well as initial formulation development, particle size control, and stability studies needed to maintain the project development timeline.

In summary, the rapid development of axitinib along with the complex solid-form behavior has been a constant challenge during the development of this compound. The first-generation process for controlling the solid form delivered Form IV consistently but was not suitable for a commercial process due to the high solvent volumes, long cycle times, and use of distillation to control solvent composition. As work on a second-generation process for producing Form IV, which eliminated the significant issues with the first-generation process, was reaching a critical stage, Form XXV was discovered. Key findings from the solid-form bridging studies including the use of ethanol to convert to Form XXV were leveraged in order to quickly develop an enabled process for producing Form XXV.

2.7. Structural Aspects of Forms IV and XXV and Interrelationships. As previously mentioned, during the course of development of axitinib, numerous solvates were encountered during extensive polymorph screening, and there was no evidence for the existence of additional anhydrous forms. As part of screening activities and to further probe the recent appearance of Form XXV, significant efforts were made to grow and obtain the single-crystal structure of all the relevant forms and solvates, with the intent of understanding at the molecular level the interrelationships between the critical forms.

Axitinib has two hydrogen-bond donors and three hydrogen-bonding acceptors which can potentially form hydrogen-bonding interactions in the crystalline state (Figure 4a). Analysis of the relative strength of these acceptors and donors was performed on the basis of the molecular polarization charge density (σ-Surface),[24] as calculated by the Turbomole package[25] at the BP-TVZP level of theory[26] and visualized by COSMOTherm software[27] (Figure 4b). According to these calculations the strongest donor−acceptor pair for this molecule should be respectively the pyrazole amine and amide oxygen, independently of which conformation (Form XXV or IV) was adopted

(21) The addition of seed crystals of the desired form (Form XXV) would have resulted in a more robust process for completing this polymorph conversion.
(22) Dunitz, J.; Bernstein, J. *Acc. Chem. Res.* **1995**, *28*, 193.
(23) Subsequent solubility studies that incorporated on-line Raman spectroscopy to monitor the solid form indicated that Form XXV had a lower solubility than the ethanol solvate forms (Form XII or Form XV) of axitinib in ethanol at temperatures above 25 °C.
(24) Klamt, A. *COSMO-RS: From Quantum Chemistry to Fluid-Phase Thermodynamics and Drug Design*; Elsevier: Amsterdam, 2005.
(25) *TURBOMOLE*, Version 5.10; Program Package for ab Initio Electronic Structure Calculations; Cosmologic GmbH: Leverkusen, Germany, 2008.
(26) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822.
(27) Eckert, F.; Klamt, A. COSMOTherm, Version C2.1, Revision 01.07; COSMOLogic GmbH: Leverkusen, Germany, 2007.

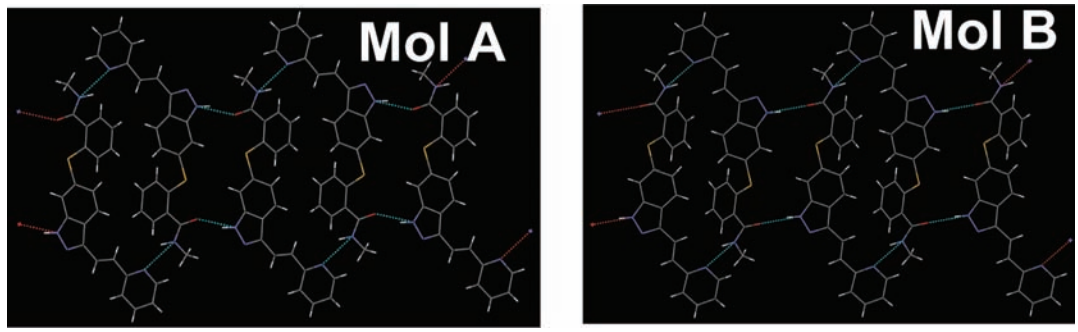

Figure 5. **Representation of the crystal packing for the individual components of the asymmetric unit for Form IV. Mol A and Mol B refer to first and second molecule of the asymmetric unit, respectively, of Form IV.**

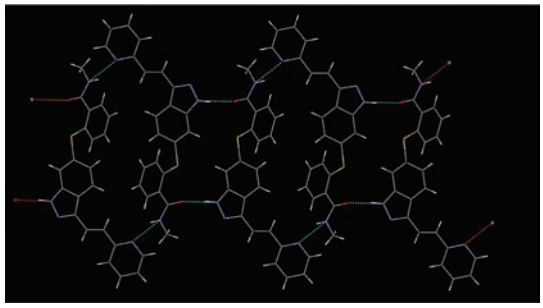

Figure 6. **Representation of the crystal packing for Form XXV.**

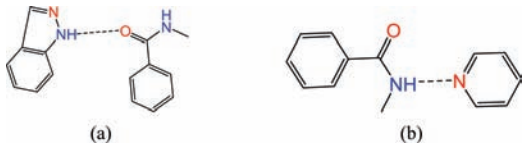

Figure 7. **Schematic illustrating the strong pyrazole−amide (a) and weaker amide−pyridine (b) hydrogen bonds observed in the crystal structures of the Forms IV and XXV.**

for the calculations. The rest of the donors and acceptors should display a noticeably weaker hydrogen-bonding propensity.

Crystallographic information is presented in Table 5 for Forms IV and XXV; Figures 5 and 6 give molecular perspectives of the packing associated with the different molecular conformations in the asymmetric unit in Forms IV and XXV.

Extensive hydrogen bonding is noted within the crystal structures of these two anhydrous API forms, which is depicted in Figure 7. In agreement with the hydrogen bond propensity analysis, the packing of both forms is dominated by the pyrazole−amide N−H···O hydrogen bond (Figure 7a), which leads to dimer formation within the crystal structures, a feature also noted within the crystal structures of numerous solvates. Those dimers are connected to each other by weaker hydrogen bonds formed between the amide donor and the pyridine acceptor (Figure 7b).

2.8. Relative Stability of Forms IV and XXV. The relative stability of the two anhydrous forms at ambient temperature, which is well below the transition point, can be estimated on the basis of relative conformational (internal) and intermolecular energies neglecting the entropic contributions. Two molecular conformations of Form IV are depicted in Figure 8 along with a molecular conformation of Form XXV. Form XXV displays two molecular conformations with the same energy that are related to each other by a mirror image operation with respect to the indazole ring plane. One of these conformations is similar to Mol A of Form IV. The conformational energies were calculated by the Turbomole software[25] at the BP-TZVP level of theory[26] at room temperature in liquid self-media, which mimics the solid-state environment ignoring long-range order contributions. The molecular conformation of Form XXV (and Mol A of Form IV) is less stable than Mol B of Form IV by approximately 0.3 kcal/mol. Normalizing to one axitinib molecule per anhydrous unit, the internal energy difference between Form XXV and Form IV is approximately 0.15 kcal/mol. We propose that this internal energy difference must be more than counterbalanced by stronger intermolecular interactions to explain the empirical relative stability at ambient temperature.

Given that a similar type of hydrogen bonding is observed in both polymorphs (thus assuming that hydrogen bond energy differences are not a dominant factor) coupled with close values of the molecular van der Waals volumes of the conformers ($V_{XXV}/V_{IV,molB} = 0.998$), the relative strength of the intermolecular interactions can be evaluated on the basis of the principles of Burger's density rule.[17,28] The true crystallographic density of Form XXV at room temperature, 1.38 g/cm^3, is significantly higher than that of Form IV, 1.29 g/cm^3. Thus, this density difference suggests stronger intermolecular interactions taking place in Form XXV, which supports our proposed explanation of the higher stability of this form at ambient temperature.

It was also noted that the conformation of the second molecule (Figure 5, Mol B) in the Form IV crystal structure is very similar to the conformation determined from the crystal structure of a number of the solvates studied. (The crystal packing of an MEK solvate, Form XIX, is depicted in Figure 9.) This important structural feature combined with the above consideration of the relative stability of Form IV and Form XXV could explain the high propensity to form solvates when Form IV was used as the starting material during solvent-mediated polymorphic transformations and other polymorph screening protocols. It is reasonable to assume that strongly bonded pyrazole−amide dimers observed in the crystal structure of Form IV and Form XXV are preserved in the saturated liquid state in a solvent. These dimers are then used as building blocks for assembling other forms, including solvates. Depending on molecular size and hydrogen-bonding features, the solvent can

(28) Burger, A.; Ramberger, R. *Mikrochim. Acta II* **1979**, 273.

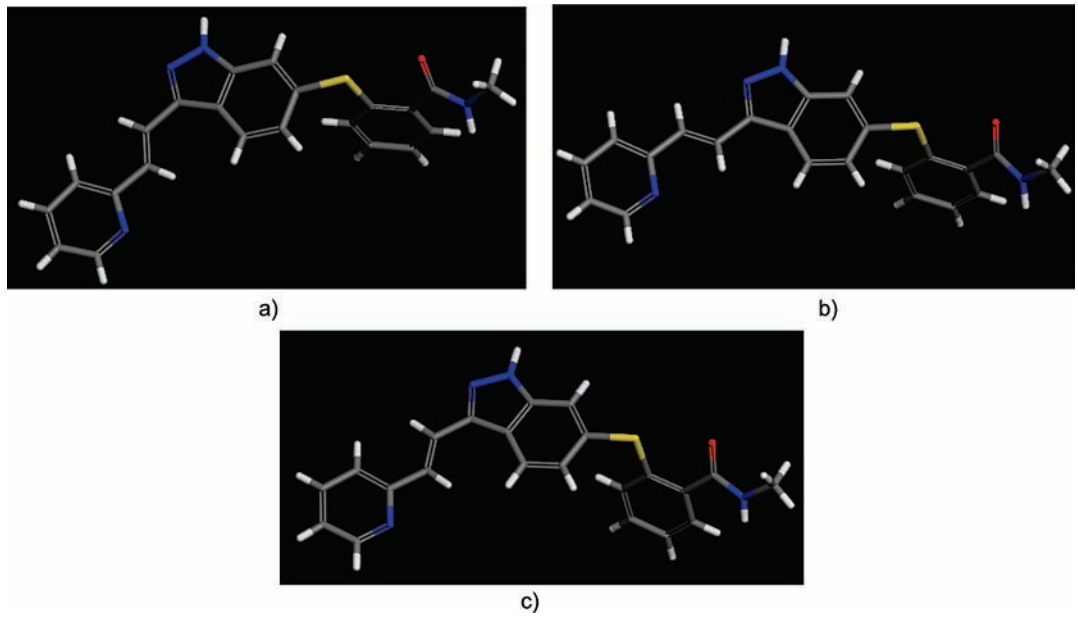

Figure 8. **Molecular conformations of Form IV: molecule A (a), molecule B (b), and Form XXV (c). Form XXV displays two molecular conformations, one of which (c) is similar to the molecule A of Form IV (a) and the other of which is a mirror image of (c) relative to the indazole ring plane.**

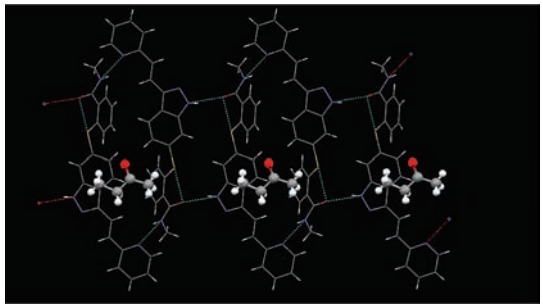

Figure 9. **Representation of the crystal structure of the MEK pocket solvate. Ball and stick rendering is adopted to display the MEK molecules.**

either occupy pockets between the dimers of the Mol B of Form IV forming pocket solvates or link these dimers together by hydrogen bonding with the pyridine or the pyrazole acceptor and the amide donor. While the pocket solvates were observed for acetonitrile, tetrahydrofuran, DMSO, IPA, and MEK solvates, the latter configuration took place for hydrate, methanol, and acetic acid solvates.

In summary, examination of the crystal structures provided an explanation of the propensity for Form IV to form solvates, and the subtle relationship between Form IV and Form XXV.

Conclusions

API crystallization process development can be a daunting challenge when the compound of interest has a complex polymorphic landscape. Described herein were the early efforts to develop an improved crystallization process for axitinib Form IV, the efforts to understand the solid form behavior of this compound, and the rapid characterization and scale-up of Form XXV once discovered. From a solid form and crystallization process development perspective, axitinib was atypical as it has both a propensity to form solvates while having poor solubility in most solvent systems. Crystallization process development of axitinib required an in-depth understanding of the phase space of the various forms in order to develop a robust process capable of avoiding solvates and delivering the desired form upon scale-up. Simple analysis of the intermediate solid forms isolated from the first-generation process gave insight into the local solid form landscape of axitinib and helped to define a thermodynamic transition point on the basis of solvent composition between the intermediate solvate form and the desired final form. With knowledge of how the first-generation process converted axitinib to the desired form, work on an improved process was directed at replicating the same solid form progression but in a more efficient manner by replacing distillation with sequential reslurry steps to change the solvent composition. Attempts to optimize this new polymorph control process generated a new lowest-energy form (Form XXV) by utilizing temperature and solvent conditions that were outside the standard polymorph screening protocol.

This compound was also atypical in that traditional polymorph screening techniques were not effective in elucidating the most stable forms due to the formation of stable solvates and very slow kinetics of conversion to nonsolvated forms. A new screening approach was subsequently rationalized and designed for this compound and will be described in a future paper. In addition, the development of axitinib has demonstrated that, by gaining an understanding of the solid-state packing of forms, an assessment can be made of the propensity to solvate and a rationale of the relative stability of one form versus another below the transition temperature on the basis of crystal packing and hydrogen-bonding considerations. These determinations were reinforced in more recent studies of this compound as subsequent development for the Form XXV crystallization process led to further challenges,[29] which will be the topic of a future publication.

4. Experimental Section

4.1. Solubility Experiments. For the data reported in Table 1, solvents with solubility listed as "less than" were made through visual observation based on microliter amounts of solvent required to dissolve approximately 1−2 mg of solid. Aliquots of solvent were continuously added to the solid, the slurry vortexed for several minutes, and the solid assessed for dissolution after each addition. For solvents with an absolute solubility value, a slurry of the solid in the given solvent was allowed to equilibrate with stirring for 4 h. The solids were separated through centrifugation, and the supernatant was quantitated using HPLC. All experiments were conducted at temperatures between 20−25 °C. Note that these data were generated at a very early developmental stage, designed to provide rapid initial estimation of the compound's solubility. Knowledge of the polymorphism of this compound did not exist at this time. As such, the identity of the solid form was not confirmed at the completion of these experiments.

For the data shown in Figure 3, slurries of approximately 25 mg of Form IV or Form XXV were allowed to equilibrate with stirring in 3 mL of 80:20 water/ethanol v/v at 5, 20 and 40 °C. After approximately 20 h, the slurries were filtered, and the filtrate was quantitated using HPLC. The identity of the solid form was verified with PXRD using the filtered solids at the completion of the experiments. In all cases, no polymorphic conversions had occurred.

4.2. Polymorph Screening Experiments. The first late-development high-throughput polymorph screen with Form IV was carried out using a Symyx Systems Workstation. The experimental design was implemented with the use of the Library Studio software package version 7.1.3.10. Approximately 8 mg of axitinib and 0.8 mL of an individual solvent or cosolvent (55 total) were added to each well of a 96-well master plate. The slurries were first equilibrated at 25 °C for 2 h, then subjected to a temperature cycle of 40 °C for 2 h, then 25 °C for 12 h. The cycle was repeated three additional times, with the total slurry time being approximately 2.5 days. Each well was filtered to remove the solid material. The filtrate from each well was daughtered to an evaporation plate and a 5 °C cooling plate to allow for additional solids recovery. Each well was analyzed in-line for crystallinity by microscopic birefringence and PXRD, and characterized by Raman spectroscopy.

The polymorph screen using Form IX (hydrate) as the in-going material was performed using a Bohdan (Mettler-Toledo) Automated Workstation. Approximately 40 mg of axitinib and 3 mL of an individual solvent (20 total) was added to an appropriate size minitube. The samples were allowed to slurry at 45 °C for 3 days. The contents of each tube were filtered, and the solids were characterized off-line by PXRD, DSC and TGA. The filtrate from each tube was allowed to slowly evaporate at room temperature. Any solids that were recovered were also characterized as above.

In some cases, solids obtained through evaporation of the isolated saturated solutions from the above experiments produced crystals large enough for single-crystal X-ray diffraction analysis. Other common techniques were used to obtain crystals for this purpose, which included vapor and liquid diffusion and antisolvent crystallization. The X-ray diffraction measurements were carried out at room temperature on either a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and sealed tube Cu radiation (1.54178 Å) source or a Bruker FR591 rotating anode with Motel Multilayer Optics, Cu radiation (1.54178 Å), equipped with an APEX II detector. All crystallographic calculations were facilitated by the SHELXTL software suite system. In general hydrogens bonded to hetero atoms were located by difference Fourier techniques. The remaining hydrogen atoms were placed in idealized positions. The hydrogen parameters were added to the structure factor calculations but were not refined.

4.3. Form IV Manufacturing. Acetic acid (334.5 L, 10 mL/g), methanol (134 L, 3 mL/g) and recrystallized axitinib (29.7 kg) were charged to a reactor. The batch was heated to 50 °C, and a clear yellow solution formed. The batch solution at 50 °C was transferred to a second reactor through a 1.2-μm polypropylene cartridge filter. The line was blown, and fresh acetic acid (33.5 L, 1 mL/g) and methanol (100.4 L, 3 mL/g) were charged to the first reactor and transferred to the second reactor as a line rinse. The acetic acid was distilled off and replaced with xylenes (4 × charges of 268 L, 8.0 mL/g) via vacuum distillation. These acetic acid distillations were not ideal since the level of vacuum needed to be adjusted in the early distillation cycles in order to minimize foaming, and the jacket temperature for the condenser had to be set to a warmer temperature than normal to avoid freezing the acetic acid in the condenser. A set of freezing point studies for various mixtures of acetic acid and xylenes indicated that the freezing point of 80% acetic acid:xylenes is 10 °C and decreases to −10 °C as the fraction of acetic acid decreases to 20%. On the basis of these measurements, the condenser temperature was set to 15 °C in the pilot plant to effectively condense the distillate while avoiding freezing the acetic acid.

After the final distillation to ∼10 mL/g final volume (∼335 L), the suspension was cooled to 25 °C at 1 °C/min. An in-process sample was taken for confirmation of polymorph conversion by PXRD. After it was confirmed that the batch was the correct form, the batch was filtered onto an agitated filter/dryer. The cake was rinsed with xylenes (150.5, 4.5 mL/g). The damp cake on the filter/dryer was reslurried in *n*-heptane (150.5 L, 4.5 mL/g) at 20 °C for 1 h, and the liquors were blown clear from the cake. A final wash of *n*-heptane (66.9 L, 2 mL/g) was completed, and the damp cake was blown with nitrogen for ∼2.5 h. The filter/dryer was placed under vacuum and heated to 50 °C, and the batch dried until confirmed dry

(29) Campeta, A. M.; Chekal, B. P.; McLaughlin, R. W.; Singer, R. A. (Pfizer Products Inc., U.S.A.). Novel Crystalline Forms of a VEGF-r Inhibitor PCT Int. Appl. WO 2008122858, 2008.

by in-process testing. A drier check sample pulled after 28 h indicated xylenes at 0.1% and *n*-heptane not detected. The batch was discharged to yield axitinib as a fine homogeneous off-white powder, with a total yield of 24.45 kg (83% yield, uncorrected).

4.4. Form XXV Manufacturing. To two parallel reactors were charged isopropanol (750 mL, 3 mL/g) and axitinib Form IV (125 g). For each reactor, the batch was heated to 60 °C, and the resulting slurry was stirred at this temperature for 3 h. The slurry was cooled to 20 °C and held at this temperature for an hour before filtering the batch. After filtering, each reactor and cake was washed with *n*-heptane (600 mL, 4.8 mL/g). PXRD analysis of both isolated API lot indicated the isopropanol solvate. Each lot of the isopropanol solvate was charged back to a reactor along with heptane (1250 mL, 10 mL/g) and acetic acid (12 mL, 0.1 mL/g). For each reactor, the resulting slurry was heated to 60 °C and stirred for 16 h. After cooling back to 20 °C, a sample of each batch was pulled and analyzed by PXRD, which indicated a mixture of Form IV and Form XXV for the first batch and predominantly Form IV for the second batch. Each batch was filtered and dried. The two lots were combined to give 255 g of API, which was charged to a reactor along with ethanol (1000 mL, 3.9 mL/g). The resulting slurry was heated to 70 °C and held for approximately 16 h. After cooling to room temperature, the batch was filtered and washed with *n*-heptane to yield 244 g of axitinib (97.6% yield). PXRD analysis of the isolated API indicated Form XXV.

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