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A Robust, Streamlined Approach to Bosutinib Monohydrate

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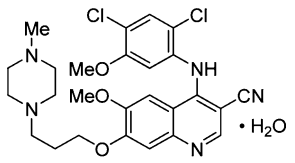
ABSTRACT: This article describes a systematic approach used to streamline the process for the isolation of bosutinib monohydrate, a promiscuous solvate former. A thorough understanding of the complex solid form landscape was garnered, and this knowledge was used to develop a process that routinely delivered the correct solid form and excellent purity at the end of the last bond-formation step, without the need for additional recrystallization and/or solid form conversion steps.

INTRODUCTION

Bosutinib monohydrate (**1·H$_2$O**) is a potent competitive dual inhibitor of Src and Abl kinases that inhibits cell growth, metastasis, and osteoclast activity and has been developed as a treatment for chronic myelogenous leukemia (CML). Several synthetic approaches to this compound were evaluated,[1−4] and the synthesis depicted in Scheme 1 was selected for the manufacture of late-stage clinical supplies.[5]



1·H$_2$O

Alkyl chloride **2** was treated with *N*-methylpiperazine **3** to furnish adduct **4**, which was reduced to provide aniline **5**. A three-component coupling reaction of **5** with cyanoacetamide **6** and triethyl orthoformate led to **7** as a mixture of cis/trans isomers. Cyclization of **7** using $POCl_3$ in sulfolane provided the core structure of bosutinib (**1**). Basification of the reaction mixture with aqueous KOH led to precipitation of the hexahydrate, **1·6H$_2$O**. Recrystallization of the hexahydrate from aqueous *iso*-propyl alcohol upgraded purity by removing organic impurities and furnished the dihydrate-*iso*-propyl alcohol solvate (**1·2H$_2$O·*i*-PrOH**). This compound was converted to the desired monohydrate solid form (**1·H$_2$O**) by treatment with hot water.

The sequence of synthetic transformations works very well and produces acceptable quality active pharmaceutical ingredient (API). The two additional steps after the final bond-formation step were incorporated in order to achieve the desired purity and solid form. Not surprisingly, an evaluation of processing costs indicated that these steps contributed significantly to the overall cost of API manufacture. In addition, the solid form conversion step (step 6) was carried out as a slurry-to-slurry transformation in water and produced the product as a wide distribution of fine particles prone to agglomeration, suggesting that filtration on large-scale would likely be problematic, depending on the choice of equipment. For these reasons, there was a huge impetus to eliminate the last two steps, and strive to attain the desired purity and solid form at the end of the last synthetic step via a controlled crystallization. This paper describes our efforts that culminated in a robust, streamlined isolation process for bosutinib monohydrate from **7**.

RESULTS AND DISCUSSION

While the desired solid form, the monohydrate (**1·H$_2$O**), exists as a single polymorph, bosutinib is known to be a promiscuous solvate former, and exhibits a propensity to form solvate/hydrates, solvates, and higher-order hydrates under a variety of conditions.[6] Therefore, it was important to gain a full understanding of the complex solid form landscape in order to develop a process that would routinely deliver bosutinib monohydrate (of acceptable purity) at the end of the last bond-forming step.

Solid form screening was initiated on bosutinib using a variety of single organic solvents, and binary systems with water. In this screen, approximately 20 mg of **1·H$_2$O** was weighed into 1.5 mL HPLC vials, and diluted with ∼300 μL of the appropriate solvent or binary solvent/water mixture. More **1·H$_2$O** was added to ensure saturation, and the samples were allowed to stir for 10 days at room temperature. The resulting slurries were filtered using a 0.45 μm nylon centrifuge filter, and the filtrates were gravimetrically analyzed for solubility. The isolated solids were analyzed via PXRD, DSC, and TGA to determine the solid form recovered, and the key findings are summarized in Table 1.

A large number of screened solvent systems generated undesirable solvated solid forms (column 3, Table 1). The esters and ketones screened were a notable exception, where the monohydrate was recovered. Similarly, hydrocarbon solvents such as toluene, *n*-heptane, and xylene provided the monohydrate, although the solubility of **1·H$_2$O** was too low to warrant further investigation of these solvents (Table 2). Most of the alcohol solvents resulted in the corresponding solvates, and binary systems containing water and alcohols provided solvate/hydrates.

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Scheme 1

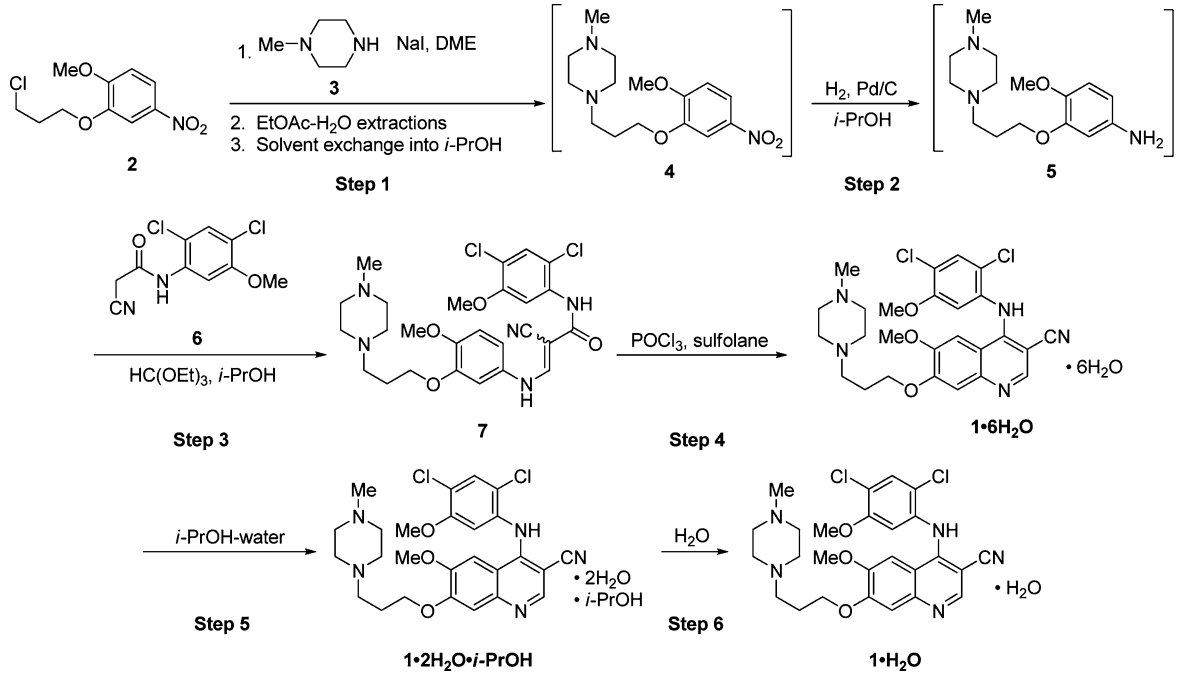

Table 1. Solvent screen for bosutinib solid forms

solvents that provide **1·H$_2$O**[a]	solvents that provide **1·6H$_2$O**[a]	solvents that provide other solvates or solvate/hydrates[a]
EtOAc	80:20 acetone/H_2O	MeOH
i-PrOAc	20:80 acetone/H_2O	EtOH
n-PrOAc	90:10 MEK/H_2O	*n*-PrOH
n-BuOAc	80:20 CH_3CN/H_2O	*n*-BuOH
acetone	20:80 CH_3CN/H_2O	*i*-BuOH
MEK	20:80 MeOH/H_2O	80:20 *i*-PrOH/H_2O
MIBK	20:80 EtOH/H_2O	50:50 *i*-PrOH/H_2O
MIBK/H_2O[b]	20:80 *n*-PrOH/H_2O	80:20 MeOH/H_2O
Toluene	20:80 *i*-PrOH/H_2O	50:50 MeOH/H_2O
n-Heptane	EtOAc/H_2O[b]	THF
Xylene	*i*-PrOAc/H_2O[b]	CH_3CN
		$CHCl_3$
		CH_2Cl_2
		1,4-dioxane
		tert-amyl alcohol
		2-methoxyethanol

[a]All solvent ratios are on a volumetric basis. [b]Saturated with water.

As the water content is increased in the binary systems (increasing water activity), the hexahydrate becomes increasingly favored at ambient conditions (column 2, Table 1). This trend was observed in alcohols, ketones, and esters. In order to further understand the system, the critical water activity between the monohydrate and hexahydrate was determined as a function of temperature, as described in the Experimental Section. The critical water activity was found to be ~0.8 near room temperature and increases slightly with temperature, such that above ~40 °C the hexahydrate (**1·6H$_2$O**) is no longer favored—even in pure water (Figure 1).

Table 2. Solubility of bosutinib monohydrate in various solvent systems at 20 °C

solvent	solubility of **1·H$_2$O** (mg/mL)
EtOAc	12.4
i-PrOAc	2.5
n-PrOAc	5.2
n-BuOAc	4.0
acetone	33.2
MEK	28.1
MIBK	9.6
MIBK/water	1.1
toluene	<1
n-heptane	<1
xylene	<1

On the basis of the solvent screen and critical water activity data, solvents that routinely provided the monohydrate were chosen for further evaluation (column 1, Table 1). Specifically, the goal was to determine which of these solvents could be used for an extractive workup and direct isolation of **1·H$_2$O** after the last bond-forming reaction (cyclization of **7** with $POCl_3$ in sulfolane). In addition to providing the correct solid form, the ideal workup solvent should be an ICH class 3 solvent, allow for phase separation when mixed with sulfolane/water, maintain a high solubility of **1** at reasonable temperatures, adequately reject sulfolane and other impurities during the extraction and/or the crystallization, and provide the product in high yield and purity upon isolation.

Examination of the room temperature solubility of **1·H$_2$O** in the preferred solvents revealed that it was relatively soluble in acetone and MEK, while the solubility was lower in MIBK and the ester solvents (Table 2). Since the workup of the $POCl_3$ reaction involved a basic quench, it was felt that ester hydrolysis was a concern, especially at elevated temperatures. Acetone and MEK are not ideal for an extractive workup due to their miscibility with water. For these reasons, MIBK appeared to be the best choice for the extractive workup and isolation.

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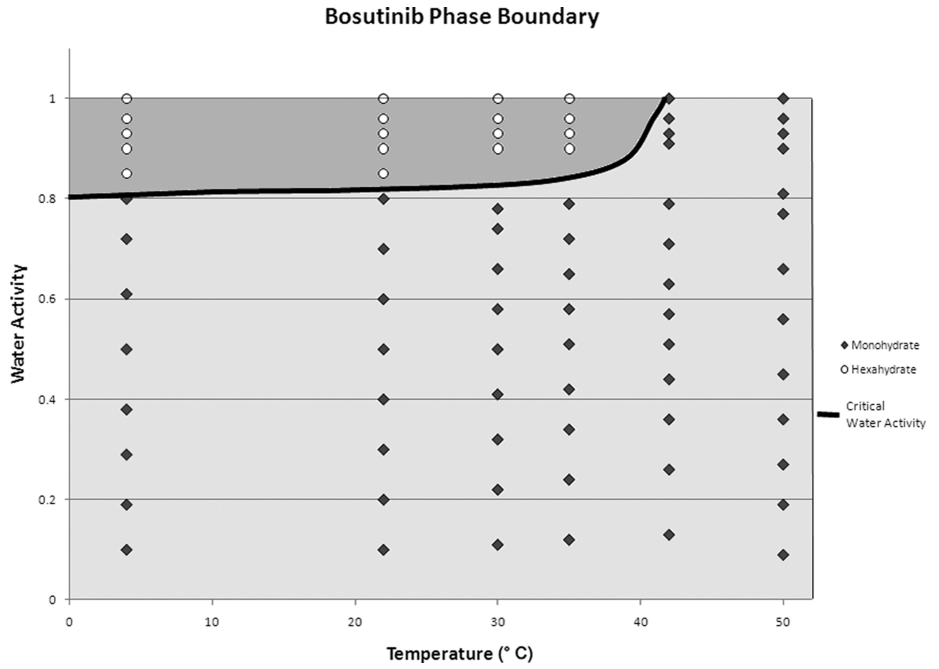

Figure 1. Critical water activity for conversion between monohydrate and hexahydrate forms of bosutinib determined in acetone/water.

Once the MIBK/water system was chosen out of this screen, temperature-solubility curves for bosutinib monohydrate were determined in MIBK with various amounts of added water (Figure 2).[7] The data indicated that **1·H$_2$O** was fairly soluble in

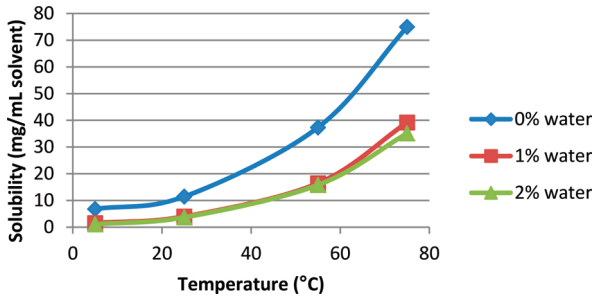

Figure 2. Temperature–solubility curves for bosutinib monohydrate in MIBK with added water.

MIBK at 80 °C (~75 mg/mL), and could be isolated from this solvent via a cooling crystallization, and/or by the addition of small amounts of water. The substantially higher solubility of **1·H$_2$O** in MIBK at higher temperatures also suggested that the extractive workup might be carried out at an elevated temperature in order to improve throughput. Additionally, the poor miscibility of MIBK with water and its high boiling point rendered it an attractive option for the extractive workup.

Designing the Extractive Workup. After completion of the $POCl_3$-mediated cyclization in sulfolane, the reaction mixture needed to be basified prior to an extractive workup. However, adding the extraction solvent (MIBK) immediately after reaction completion (at pH $\ll$ 1) led to spontaneous precipitation of the HCl salt of **1**.[8] This uncontrolled precipitation had the potential to cause agitation issues upon scale-up. Additionally, these solids did not readily dissolve in MIBK-water even upon basification to pH 10.

It was found that adjusting the pH of the reaction mixture to pH 3–5 with aqueous KOH at 75–80 °C, followed by addition of MIBK (~15 L/kg of **7**) maintained a biphasic mixture with **1** dissolved in the aqueous layer. This allowed for MIBK washes of the product-containing aqueous layer (at pH 3–5), which proved to be an effective method for sulfolane removal. More importantly, this set of conditions ensured that **1** remained in solution throughout the pH adjustment from pH 3 to pH 10. A layer separation at pH 10, followed by aqueous washes of the product-containing organic layer (at 75–80 °C) removed most of the residual sulfolane.

Crystallization and Isolation of 1·H$_2$O. The initial solid form screening exercise and critical water activity determination revealed that water levels up to 2% in MIBK would allow for crystallization of the desired solid form (**1·H$_2$O**), but the presence of additional water in the system could lead to mixtures of **1·H$_2$O** and **1·6H$_2$O**. In order to consistently control the water content during the crystallization and to ensure ultimate isolation of the correct solid form, the variability in water content of the **1**/MIBK layer at the end of the extractive work up needed to be eliminated. Following the extractive workup, the MIBK layer was concentrated to 4 L/kg of **7**. This typically reduced the water level to less than 0.3%. At such low water levels, **1** could not crystallize as the monohydrate, and was soluble in as little as 3 L/kg MIBK at ambient temperature. This provided us with a convenient operating window for unit operations, including a speck-free filtration, prior to crystallization and isolation of the API.

Distillative removal of the water, followed by an accurate water charge (between 1 and 2% v/v based on the volume of the **1**/MIBK solution prior to crystallization) and seeding, led to crystallization of **1·H$_2$O**. After further experimentation, the temperature for the water charge and seeding operation was established at 60–65 °C. This temperature range ensured the mixture was supersaturated (thus preventing the seed from dissolving). Although the system was significantly supersaturated at this temperature and composition, a controlled, growth-dominated crystallization with very little secondary nucleation was observed.[9] In addition, as mentioned previously, by initiating the crystallization at an elevated temperature

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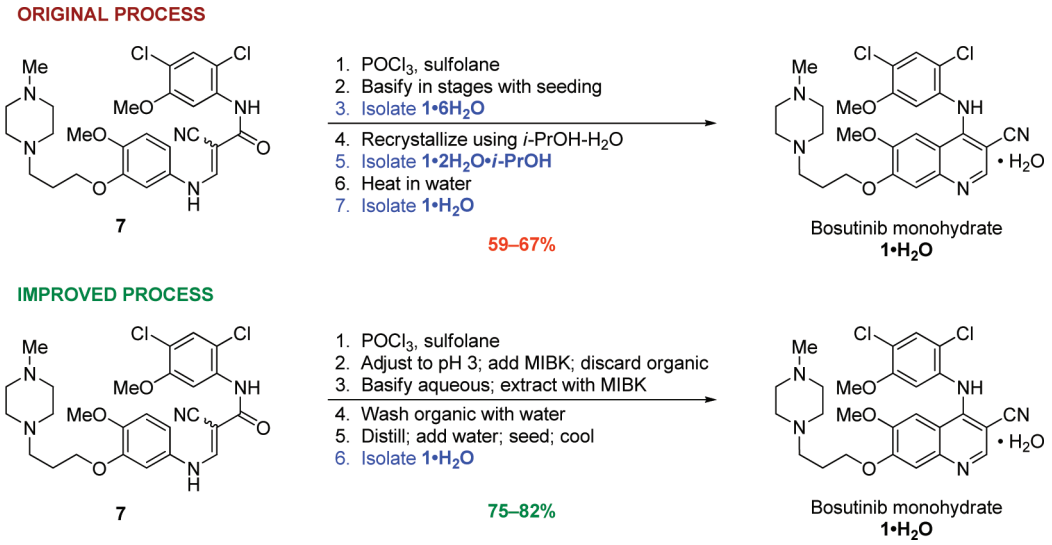
Scheme 2



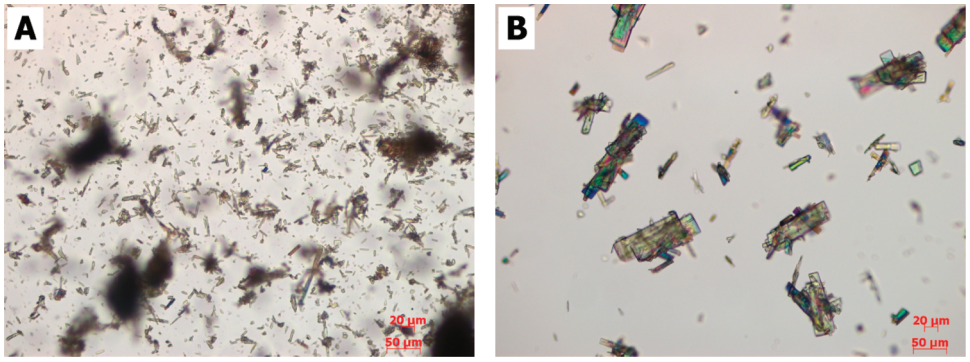


Figure 3. Optical micrographs of bosutinib monohydrate isolated from: A) water, and B) MIBK/water.

(above ~40 °C), the crystallization occurs in a phase space where the hexahydrate is not favored.

This process produced bosutinib monohydrate in 75−82% yield, and >99.5 area % purity in a single step from **7**, which compares favorably to the 59−67% cumulative yield over three steps for the process described in Scheme 1 (see Scheme 2 for a comparison of the two processes).

Optical micrographs of the material isolated from the original and the improved processes are provided in Figure 3. The particles isolated from the reslurry in water (original process, Figure 3A) were generally smaller, with a tendency to form dense agglomerates. In contrast, **1·H$_2$O** from MIBK/water (Figure 3B) was consistently larger, had defined facets, was only loosely agglomerated, and filtered significantly faster.

CONCLUSION

In summary, a robust, streamlined process for the isolation of bosutinib monohydrate (**1·H$_2$O**) was developed. A systematic exploration of the solid form landscape led to the identification of solvents that would exclusively provide the desired monohydrate. This list was further narrowed down to solvents that were amenable to an extractive workup at high temperature and across a wide pH range. MIBK was ultimately chosen for the extractive workup, and the final crystallization was designed to furnish API quality material at the end of the last synthetic step in high yield. The improved process significantly reduces processing costs by eliminating two processing steps, and by increasing the overall yield.

EXPERIMENTAL SECTION

Determination of the Critical Water Activity between Bosutinib Monohydrate (1·H$_2$O) and Bosutinib Hexahydrate (1·6H$_2$O). An acetone/water system was chosen for the determination of the critical water activity between the monohydrate and the hexahydrate. Acetone/water exhibits a more gradual increase in water activity as the solution composition is varied, in contrast with MIBK/water, where the water activity rises sharply with composition. A series of acetone/water binary mixtures of varying water content was prepared and saturated with bosutinib monohydrate (**1·H$_2$O**). A small amount of the hexahydrate (**1·6H$_2$O**) was added to each. The saturated solutions were allowed to stir at various temperatures between 5 and 50 °C for 10 days, the solids were isolated, and the solid form characterized by PXRD. The water activity of the binary mixtures was calculated using an NRTL (nonrandom two-liquid) model of VLE (vapor liquid equilibrium) data.

Synthesis and Isolation of Bosutinib Monohydrate (1·H$_2$O). Sulfolane (100 mL) and **7** (30 g) were charged to a flask fitted with a mechanical stirrer, and heated to 80−90 °C. $POCl_3$ (10.9 g, 1.3 equiv) was added slowly, and the resulting mixture was maintained at 105 °C for 16 h. Once the reaction was deemed complete, the mixture was cooled to 75−80 °C,

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and the pH was adjusted to ~pH 3 with 5% w/w aqueous KOH solution (85 mL required). MIBK (225 mL) and water (90 mL) were added, maintaining the temperature at 70−75 °C. The phases were separated at this temperature, and the organic layer was discarded. MIBK (450 mL) was added to the aqueous phase (at 70−75 °C), and the pH was adjusted to pH 10.8 with 5% w/w aqueous KOH solution (182 mL required). The layers were separated, and the aqueous layer was discarded. The organic layer was washed with water (2 × 300 mL) maintaining the temperature at 70−75 °C, and concentrated in vacuo to a final volume of 250 mL. MIBK (~150 mL) was added, the solution was concentrated in vacuo to a final volume of 240 mL. The solution was diluted with MIBK to a total volume of 300 mL, and warmed to 60−65 °C. Water (3 mL) was added to the filtrate (~1 mL of water per 100 mL of MIBK/product solution), followed by 300 mg of **1·H$_2$O** as seed. The mixture was maintained at 60−65 °C for 1 h, gradually cooled to room temperature, and allowed to crystallize with agitation overnight. The resulting slurry was filtered, and the filter cake was washed with MIBK (30 mL) and dried in a vacuum oven at 50−55 °C overnight to provide 21.8 g of **1·H$_2$O** (76% yield) in 99.90 area % purity by UPLC.

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Notes

The authors declare no competing financial interest.

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(7) We believe that this two-step workflow (initial solvent screening followed by determination of process-relevant solubility) is a robust way to design a crystallization process, and as such, high temperature solubility data in all solvent systems is not necessary for the design.

(8) The incompatibility of $POCl_3$ with acetone has been documented in the literature: Brenek, S. J.; am Ende, D. J.; Clifford, P. J. *Org. Process Res. Dev.* **2000**, *4*, 585. We did not observe a similar exotherm with MIBK and $POCl_3$; however, *due caution must be exercised while mixing $POCl_3$ and MIBK prior to an aqueous quench.*

(9) Our experiments indicated that both seeded and unseeded batches produced material of identical quality. However, we chose to incorporate seeding in the process in order to provide a consistent nucleation point.