

Exploiting Undesired Solvate for Continuous Crystallization of Nitrofurantoin with Solid Form Transformation Process

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ABSTRACT: Crystallization of active pharmaceutical ingredients (APIs) is sometimes constrained by solvent selection and undesired solvate formation with challenging solid-form control. This study presents a crystallization and solid-form transformation strategy that exploits, rather than avoids, a solvate intermediate to access the two commercially relevant forms of nitrofurantoin (NIFU), anhydrate β and monohydrate II, thereby extending the known form map for this API. Solubility screening across biobased and green solvents identified dimethyl sulfoxide (DMSO) as the only viable Class 3 solvent providing solubility ≥ 20 mg/mL while generating an undesired NIFU DMSO hemisolvate. Batch and continuous antisolvent crystallization processes in a DMSO–water system at 25 °C were studied with high yields ($\geq 92\%$) supported by process analytical technology. Thermal desolvation resulted in complete conversion to anhydrate β between 170 and 180 °C within ≤ 40 min without detectable degradation (HPLC). Slurry crystallization in water between 10 and 40 °C enabled solvent-mediated phase transformation (SMPT) to monohydrate II within ≤ 15 min. The semiempirical Avrami–Erofeev equation fits the TGA ($R^2 \geq 0.986$) and Raman ($R^2 \geq 0.947$) data well, allowing qualitative assessment of the temperature effect on the desolvation and SMPT processes. Both generated NIFU forms meet US Pharmacopeia critical quality attributes. Based on the NIFU-specific work, the showcased strategy may be relevant for APIs, exhibiting similarly solubility limitations and strong solvation propensity.

KEYWORDS: solvent-mediated phase transformation, desolvation, polymorphism, DMSO, Avrami, antisolvent crystallization

1. INTRODUCTION

The pharmaceutical industry generally prefers the thermodynamically most stable solid form of an API to avoid the risk of unwanted phase transformations during drug product manufacturing, transportation, and storage.^{1,2} Nevertheless, metastable forms might be desirable because of enhanced physicochemical and mechanical properties,^{3–5} besides circumventing intellectual property of a specific protected polymorph or solvate.⁶ Anhydrous forms are often chosen for their greater stability and ease of processing.⁷ However, hydrated forms may be more thermodynamically stable and preferred under conditions of sufficient water activity at a given temperature, particularly for API salts.^{8–10} In contrast, solvated forms are generally undesirable due to regulatory limits on residual solvents, desolvation risks (e.g., agglomeration, physical instability),¹¹ and the need for specific storage conditions.⁷ Nonetheless, there are various commercially available exceptions, e.g., trametinib (DMSO solvate) and others.^{12–14}

The selection of an appropriate solvent is the cornerstone of successful API crystallization development.¹⁵ The solvent system may influence solubility, nucleation and growth kinetics, crystal morphology, and impurity purging as well as polymorph control and solvation propensity. When an undesired solid form (polymorph, solvate) is encountered with a particular solvent system, the typical response is to avoid the solvent system and optimize the crystallization conditions to favor the nucleation and growth of the most stable form.¹⁵ The choice of

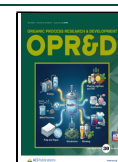
(anti)solvents as a means of solid-form control is further constrained by regulatory guidelines, which favor less toxic Class 3 solvents according to FDA/ICH guidelines,¹⁶ and by the need for sufficient solubility (typically ≥ 20 mg/mL) to allow for a viable window of effective crystallization with acceptable yield and productivity without excessive solvent usage.^{15,17,18} Yet, commercially undesired solid forms (solvates, polymorphs) may be used when APIs are difficult to crystallize in nonsolvated/polymorphic forms or when higher purity can be achieved through better impurity removal through the formation of a different solid form.^{19–21} Consequently, crystallization and purification constraints can sometimes inevitably result in the formation of undesired polymorphs or solvates demanding solid-form correction steps to generate the desired form. Common approaches to obtain the desired solid form are solvent-mediated phase transformation (SMPT) or thermal desolvation, while conventional pH-swing crystallization may sometimes be utilized assuming suitable pH-dependent solubility characteristics in acceptable solvents.^{2,6,15,22}

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Motivated by such challenges of a suitable solvent choice for the API nitrofurantoin (NIFU), the present study reports a crystallization and necessary solid-form transformation approach that begins with solubility screening, crystallization of an undesired solid form (solvate) followed by a conversion into the desired crystalline forms. NIFU is an essential medicine (antibacterial) recognized by the World Health Organization (WHO).²³ Moreover, NIFU exhibits numerous known solid forms: two anhydrides (α and β),²⁴ two monohydrates (I and II),²⁵ and several solvates, indicating a strong propensity for solvation in solvents such as methanol, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and dimethylacetamide (DMAC).^{26,27} The commercial NIFU drug product is made of the two forms, anhydrate β and monohydrate II.²⁸ Published studies on NIFU solid-form control and correction are fragmented, focusing only on individual steps rather than a comprehensive approach with a focus on manufacturing. For instance, solution crystallization of NIFU has been achieved in acetone/water mixtures, neat water, or aqueous solutions of weak acids (formic, acetic, propionic acid) for the preparation of anhydrate β or monohydrate II.^{29–32} However, these solvent systems exhibit unfavorable low solubility (<20 mg/mL) to be considered for a viable crystallization process.^{15,17,18} Also, dehydration of NIFU monohydrate II into anhydrate β has been investigated.^{33,34} Yet, these studies lack a cohesive process development strategy aimed at integrating API crystallization with the necessary solid-form correction steps. To the best of the authors' knowledge, articles reporting end-to-end API manufacturing strategies from crystallization through necessary solid-form correction steps are very limited.

This study successfully demonstrates an integrated crystallization and solid-form transformation process strategy by desolvation or SMPT for NIFU, utilizing experimental kinetics evaluation to confirm its feasibility. The work belongs to a series of the authors' efforts toward the integrated manufacturing of the API NIFU, starting with the synthesis³⁸ and the purification by crystallization to deliver NIFU in its commercial crystalline forms. To aid these efforts, this article reports the crystallization process development aimed at controlling the solid form of NIFU, a critical quality attribute for APIs. Regulatory authorities demand stringent control of the solid form throughout the pharmaceutical manufacturing process.³⁵ In this study, the quality attributes of the produced NIFU solid forms were compared to those reported in the US Pharmacopeia (USP) monograph,³⁶ including DSC, TGA, PXRD, water content, gas chromatography. In addition, Raman spectroscopy and image-derived total chord length distribution were utilized for *in situ* monitoring of the crystallization and SMPT processes.

Thus, this work might serve as a practical strategy for handling cases where solubility limitations may force crystallization through an undesired solid form (solvate, polymorph) and offers a pathway with solid-form control for APIs prone to solvation. Though this work is focused on commercial (already purified) NIFU, the reported strategy may also be utilized to overcome impurity purging challenges³⁷ by generating a commercially undesired solid form first.³⁸

2. EXPERIMENTAL SECTION

2.1. Materials

Nitrofurantoin (NIFU) anhydrate β (MW 238.16, assay 100.3%), acetone, acetic acid, acetonitrile (ACN), ethanol (EtOH), ethyl acetate, isopropanol (IPA), cyrene, dimethyl isosorbide (DMI), 2-methyltetrahydrofuran (2-MeTHF), methanol, dimethylacetamide (DMAC),

and dimethyl sulfoxide (DMSO) were obtained from Sigma-Aldrich. All solvents are from certified biorenewable sources, except acetic acid, ACN, DMAC, ethyl acetate, and methanol, which were petro-based in HPLC grade purity. Potassium phosphate monobasic (KH_2PO_4) was sourced from Macron Fine Chemicals. Details of the suppliers, CAS numbers, and purity are summarized in Table S1. Ultrapure water was obtained using a Barnstead MicroPure UV/UF purification system (Thermo Scientific). All materials were used "as received" without further purification.

2.2. Experiments and Setups

2.2.1. Solubility Measurements. To screen for viable crystallization solvents ($C_{\text{NIFU}} \geq 20$ mg/mL),^{15,17} the NIFU solubility was determined using the polythermal method, a proven and validated approach.^{39–43} Briefly, a suspension of a known concentration was heated at a constant rate using an automated multiple reactor system (Crystall16, Technobis Crystallization Systems). Suspensions were prepared by weighing NIFU crystals and the selected solvent or solvent mixture into 2 mL sealed glass vials (Agilent) using two analytical balances (XS104 and MS104S, Mettler Toledo, respectively) with a precision of ± 0.1 mg. The suspensions were agitated with a magnetic stir bar (rare earth, 8×3 mm, Fisherbrand) at 700 rpm while heating from 5 to 60 °C at a rate of 0.3 °C/min. The solubility measurements were conducted at the heating rate of 0.3 °C/min without claiming to be optimized in this study.^{39–43} The temperature range for each solvent and solvent mixture was adjusted based on their freezing and boiling points.⁴⁴ For instance, the temperature range for DMSO was modified from 20 to 60 °C due to its freezing point of 18.5 °C.⁴⁴ Acetone has a boiling of 56 °C,⁴⁶ therefore, the temperature range was changed from 5 to 50 °C. For water and aqueous acetic acid, the temperature range was extended from 5 to 80 °C, with the upper limit aligning with a NIFU crystallization procedure reported in the literature (no solubility data shown).³² Assuming negligible dissolution kinetics, the saturated temperature was defined as the point during heating when the solution became clear and free of crystals, indicating complete dissolution.⁴⁵ This clear point was monitored by light transmission using the Crystallization Systems software (version 2.0.3.2860).⁴⁶ The uncertainty of the saturation temperature measurements is ± 0.1 K.^{41–43} After heating and subsequent cooling, the formed crystals were collected using a polyethylene-frit filter funnel (pore size 10 μm , Chemglass Life Sciences), and dried employing a 60 °C oven at ambient pressure (ADP31, Yamato Scientific) for ≤ 2 days. The solid-state characterization by powder X-ray diffraction (PXRD) was conducted after drying.

2.2.2. Crystallization Setup. Antisolvent crystallization experiments were performed in both batch and continuous modes using an EasyMax 102 Basic Plus Synthesis Workstation (Mettler Toledo) equipped with a PTFE cover and an overhead 4-pitched-blade impeller (45° downward pumping, 38 mm outer diameter (OD), Alloy C-22) at 300 rpm. A BlazePlatform Micro probe (Blaze900 Gen 2, Blaze Metrics) and a Raman spectroscopy probe (Tornado HyperFlux PRO Plus 785) were separately inserted for *in situ* monitoring of, e.g., particle counts, particle size, turbidity, solid form, solution concentration.^{47–49} Programmable peristaltic pumps (Masterflex L/S Easy-Load II, Thermo Scientific) were used to add the feed solution and antisolvent as well as suspension removal. The peristaltic pumps for the feed and antisolvent addition were equipped with 1/32" inner diameter (ID) $\times$ 3/32" OD tubing (Masterflex Chem-Durance Bio, L/S size 13). The 60 mL working volume in the continuous crystallizer was controlled by the position of the outlet dip tube (1/8" ID $\times$ 1/4" OD, Masterflex Chem-Durance® Bio, L/S size 16) employing an intermittent withdrawal method.⁵⁰ Prior to each crystallization experiment, all peristaltic pumps were calibrated for precise control of the feeding rates.

2.2.3. Batch Antisolvent Crystallization. To prepare a NIFU solution of 20 mg/mL, 800 mg of "as-received" NIFU and 40 mL of DMSO were added to a 100 mL glass vessel, temperature-controlled at 25 °C with a stirring rate of 300 rpm. Upon complete dissolution, confirmed by particle counts using the Blaze probe,⁴⁹ 20 mL of water (antisolvent) was added at 0.25 mL/min using a peristaltic pump (detailed above). The progress of the 2 h crystallization (desupersatu-

ration) was monitored by tracing both solid and liquid phases using *in situ* Blaze and Raman probes detailed above.^{51,52} Specifically, the Blaze probe allowed monitoring particle counts and image-derived chord length distribution based on ~580 images captured every 10 s during the crystallization.⁵³ The Raman probe with settings of 500 ms/exposure for 5 exposures collected every 20 s enabled both tracking the onset of solid form generation and its transformation as well as the solution concentration utilizing univariate data analysis.⁵⁴ In addition to *in situ* PAT monitoring, every 3–15 min aliquots (~0.2–0.5 mL) were withdrawn utilizing a syringe and immediately filtered through a PTFE (hydrophilic) syringe filter (pore size 0.2 μ m, diameter 13 mm, Thermo Scientific). The filtrate was diluted to a target concentration and analyzed employing a USP HPLC method to measure the NIFU concentration in the mother liquor.³⁶ To satisfy the material demand for offline solid phase characterization used in this study, additional slurry samples of ~1.5 mL were drawn at similar intervals and filtered using a polyethylene-frit filter funnel (pore size 10 μ m, Chemglass Life Sciences). The recovered crystals (unwashed) were dried at 60 °C under ambient pressure at least overnight before solid-state characterization was conducted. Upon reaching equilibrium (after ~2 h) the batch crystallization was stopped and the entire slurry was transferred (~50 mL) and filtered under reduced pressure (Büchner funnel: diameter 90 mm; filter paper: pore size 5 μ m, grade 413, VWR). Thereafter, the crystals were washed with ethanol (30 mL at ambient temperature ~22 $\pm$ 1 °C, about three times the cake volume^{55,56}) and dried at 60 °C (detailed above) before conducting solid-state characterization. The NIFU yield loss due to washing was estimated to be negligible (<4%) based on the low solubility of NIFU in ethanol of <1 mg/mL at ambient temperature (~22 $\pm$ 1 °C) measured in this study (Table S2).

2.2.4. Continuous Antisolvent Crystallization. The startup phase began with a batch antisolvent crystallization at 25 °C as detailed above. Thereafter, the crystallization was held for ~10 min before initiating the continuous operation by starting the peristaltic pumps for the feed (0.5 mL/min), antisolvent (0.25 mL/min), and intermittent slurry withdrawal^{57,58} (every 8 min) resulting in a residence time of 80 min. A manually operated Büchner funnel (detailed above) was used to continuously collect the withdrawn slurry.^{18,59} The filter cake was washed every residence time with 30 mL of ethanol to remove residual mother liquor. The washed crystals were then dried at 60 °C for $\geq$ 1 day before further solid-state characterization. The filter paper was replaced after every residence time.¹⁸

2.2.5. Thermal Desolvation. The thermal desolvation was studied utilizing a thermogravimetric analysis (TGA Q5000, TA Instruments). The method was adapted from the literature reporting the dehydration of NIFU monohydrate II.^{17,60} Briefly, about 15 mg of NIFU DMSO hemisolvate solids (obtained by the above-mentioned antisolvent crystallization) were placed in a platinum pan. The samples (ambient temperature) were heated at 10 °C/min from 30 °C (without equilibration time) to the targeted set temperatures ranging from 120 to 200 °C and then held for 2 h under a nitrogen purge of 25 mL/min. Upon completing the 2 h holding time, the samples were swiftly cooled to ambient temperature within ~30 min and collected for further solid-state characterization. In addition, preliminary experiments were conducted in an oven under reduced pressure, detailed in Section S6.

2.2.6. Solvent-Mediated Phase Transformation (SMPT). Batch SMPT crystallization experiments were conducted in the crystallizer setup detailed above. Briefly, a total of 80 mL of water was added to a 100 mL EasyMax glass vessel and heated under agitation at 300 rpm to the preset temperatures studied (10, 25, 40 °C). Once the water reached the set temperature (measured inside the crystallizer), 2 g of NIFU DMSO hemisolvate solids (obtained by the above-detailed antisolvent crystallization) were added yielding a slurry concentration of 25 mg/mL. The SMPT crystallization process was monitored using *in situ* (Blaze and Raman probes) and offline (HPLC, PXRD) techniques. Slurry sampling was conducted every 3–15 min as detailed above. After 1 h of SMPT crystallization, the entire crystallizer content was filtered. The retained crystals were washed and dried as detailed above prior to the solid-state characterization. As a side note, a higher working volume of 80 mL was used for the SMPT crystallization

compared to the 60 mL used in batch and continuous antisolvent crystallization. This approach ensured the collection of sufficient amounts of NIFU crystals needed for the offline solid-state analysis during the frequent slurry sampling.

2.2.7. Transformation Kinetics. The experimental kinetic data of the desolvation and SMPT processes were correlated using the semiempirical Avrami–Erofeev equation (eq 1)^{9,61–64} by utilizing the data of the TGA and normalized Raman intensity, respectively:

$$\alpha = 1 - \exp(-kt^n) \quad (1)$$

where α is the extent of transformation, k the rate constant (min^{-1}), t the time (min), and n the Avrami exponent referring to the dimensionality of crystal growth.^{61–63}

2.3. Characterizations

2.3.1. Powder X-ray Diffraction (PXRD). PXRD was conducted using a PANalytical X'Pert Pro MPD diffractometer equipped with a CuK α radiation source (λ = 1.5419 Å) and a nickel filter. The instrument was operated at 45 kV and 20 mA, utilizing an X'Celerator RTMS detector in a scanning mode. Samples of ~10–15 mg were required for the diffractometer configuration employed in this study to ensure adequate sample thickness. Diffractograms were collected over a 2θ range of 4–41° with a step size of 0.0167° and a scan rate of 59.69 s/step at ambient conditions.

2.3.2. Thermogravimetric Analysis (TGA). Thermographs were recorded employing a TGA Q5000 (TA Instruments) calibrated with calcium oxalate monohydrate standard. Samples of ~5–10 mg were placed in a platinum pan and heated from 30 to 240 °C at a rate of 10 °C/min under a nitrogen purge of 25 mL/min. For as-received NIFU, the temperature was extended from 30 to 300 °C to validate the decomposition temperature reported in the literature.²⁴ The data, measured in duplicate, were analyzed with TA Universal Analysis software (version 4.5A).

2.3.3. Differential Scanning Calorimetry (DSC). DSC thermograms were determined using a DSC Q2000 (TA Instruments) equipped with an autosampler and an RC40 single-stage refrigeration unit. The instrument was calibrated with an indium standard (T_m = 429.62 K and ΔH_{fus} = 28.8 J/g). An analytical balance (XS104, Mettler Toledo) with a precision of $\pm$ 0.1 mg was employed to weigh samples (~5 mg) into hermetically sealed aluminum pans (Tzero, TA Instruments) with a pinhole, which is the preferred method when studying solvates.^{40,65–67} The samples were heated to 240 °C at a rate of 10 °C/min (temperature accuracy $\pm$ 0.1 °C) under a nitrogen purge of 50 mL/min. Similar to TGA, the temperature range for as-received NIFU was adjusted from 30 to 300 °C to validate the decomposition.²⁴ DSC measurements were performed as single runs and analyzed using the TA Universal Analysis 2000 software (version 4.5A) to determine the melting point, T_m (peak value), and decomposition temperature (peak value).

2.3.4. High-Performance Liquid Chromatography (HPLC). An Agilent 1260 Infinity HPLC system equipped with a photodiode array (PDA) detector was used to determine the NIFU concentration in solution and the purity of NIFU crystals after desolvation. In this study, the column type, mobile phase, and wavelength of analysis were selected to match those reported in the USP monograph for NIFU.³⁶ Briefly, a Pursuit C18 column (300 $\times$ 3.9 mm, particle size 10 μ m, Agilent) was used. The mobile phase consisted of an aqueous potassium phosphate buffer and acetonitrile (88/12 v/v) for isocratic elution at a flow rate of 1.4 mL/min at ambient temperature (~22 $\pm$ 1 °C) for 20 min. The buffer solution was prepared by dissolving 6.8 g of monobasic potassium phosphate in 500 mL of water and adding ~30 mL of 1 N sodium hydroxide (aq.) to adjust to a pH of 7 before diluting with water to 1 L. The injection volume was 5 μ L and the UV detector wavelength was set to 254 nm.³⁶ No other USP-related tests were conducted on the samples nor suitability tests or comparisons with USP standards. The success criterion for purity was solely based on meeting the USP assay specification for commercial (purified) NIFU and individual impurities were not considered.^{17,18,36}

2.3.5. Particle Size Analysis. A particle size analyzer (Mastersizer 2000, Malvern Panalytical) equipped with a Hydro 2000 μ P dispersion

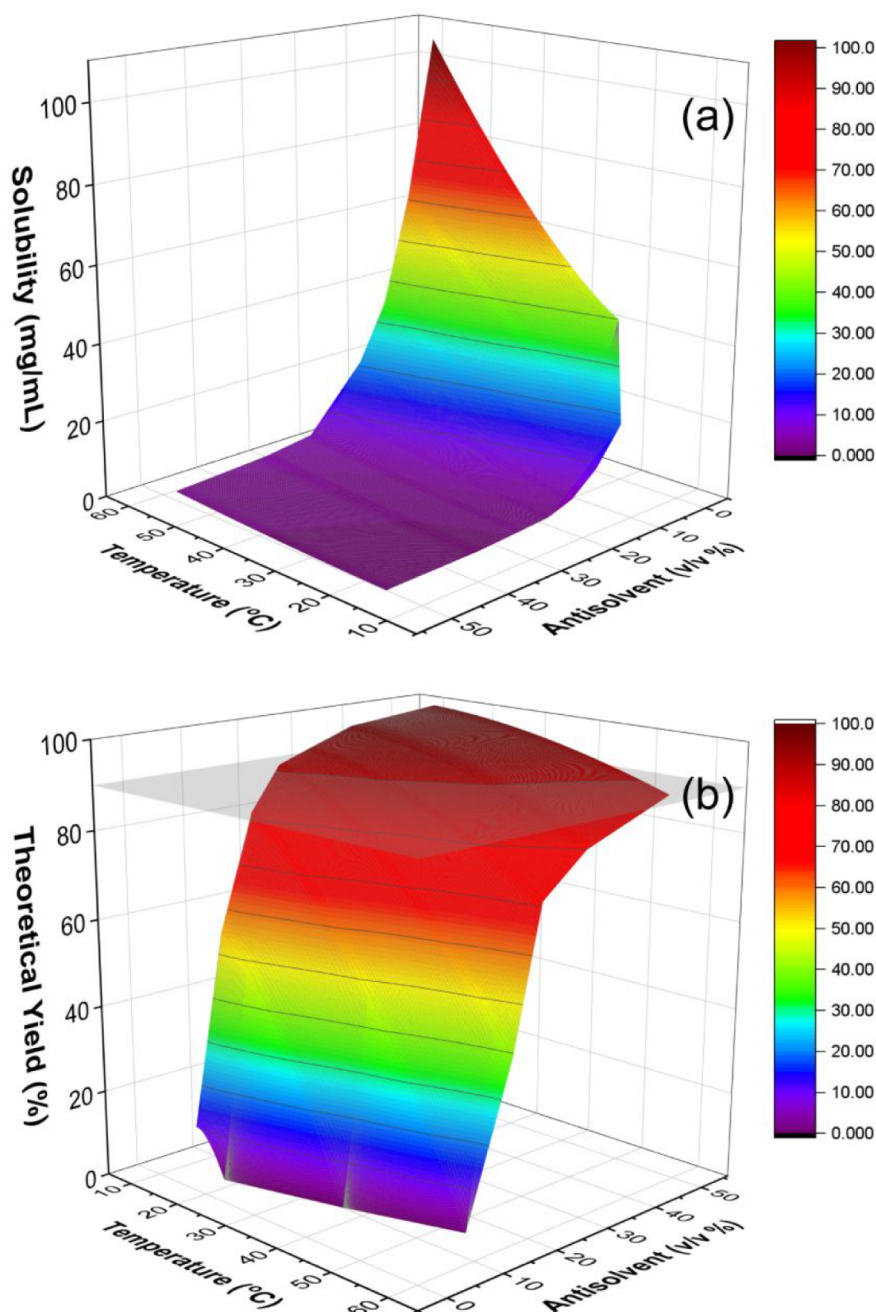


Figure 1. Surface plots of (a) the solubility of NIFU DMSO hemisolvate in the binary solvent system (DMSO + water) correlated utilizing the modified Apelblat equation^{39,41,43} and (b) the theoretical yield $[(c - c^*)/c] \times 100\%$ ⁷⁶ for an antisolvent crystallization process (feed concentration $c = 20$ mg/mL) as a function of temperature and antisolvent (water) content. Gray shaded horizontal plane represents 90% yield.

unit was employed to measure offline the volume-weighted particle size distribution (PSD) of the collected crystals. Briefly, ~10 mg of dried NIFU crystals were dispensed in neat IPA, an antisolvent that does not cause polymorphic phase transformation or yield solvate formation as determined in this work (Figure S1). The dispersions were measured with a laser obscuration between 10 and 20% achieved by a pump speed of 2500 rpm and an ultrasonics level of 20% set in the Mastersizer 2000 software (version 5.60). The PSD results were averaged in triplicate with a 10 s delay between each measurement.

2.3.6. Gas Chromatography (GC). An Agilent 7890A GC system equipped with an autosampler (Model 7693, Agilent), a flame ionization detector (FID), and a HP-SMS column (30 m $\times$ 250 μ m $\times$ 0.25 μ m, Agilent) was used to determine the residual content of DMSO. The GC method was adopted from the literature.⁶⁸ Prior to the injection, ~2 mg of NIFU solid samples ("as-received", as well as

DMSO hemisolvate, monohydrate II, and anhydrate β prepared in this study) were visually dissolved in 1 mL of acetone at room temperature, followed by a polish filtration¹⁵ using PTFE syringe filters (pore size 0.2 μ m, diameter 13 mm, Thermo Scientific) to remove possible solids (≥ 0.2 μ m) prior to injection.¹⁵ For the GC analysis, 1 μ L of the filtered solution was injected with a split ratio of 10:1.⁶⁸ Briefly, the ratio means that for every 11 parts of the sample entering the injector, 10 parts are vented, and only 1 part goes into the GC column for analysis. The inlet temperature for the injection port was temperature-controlled at 280 °C to ensure the sample is rapidly vaporized and enters the GC column in the gas phase.⁶⁹ The oven temperature housing the column was programmed to increase from 50 to 280 °C at 10 °C/min, followed by a 6 min hold at 280 °C, with a total run time of 29 min. This gradual increase in the oven temperature helps to separate the various components of the sample.⁶⁹

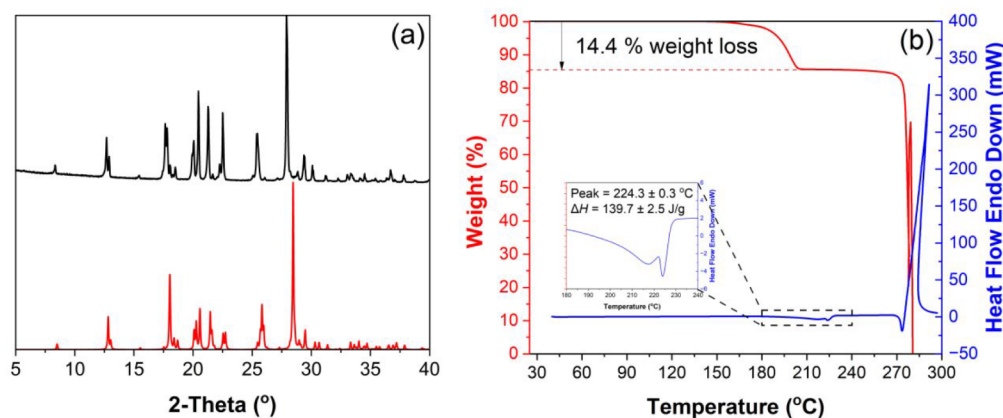


Figure 2. (a) Powder X-ray diffractogram of NIFU recrystallized from DMSO in this study (top, black, measured at ambient temperature 22 ± 1 °C) and the simulated diffractogram of NIFU DMSO hemisolvate (bottom, red, measured at -24 °C, refcode: AKEMEJ)²⁷ obtained from the Cambridge Structural Database.⁷⁷ (b) TGA and DSC thermograms of NIFU DMSO hemisolvate prepared in this study.

3. RESULTS AND DISCUSSION

3.1. Solvent Screening

The solubility measurements were conducted to identify a suitable solvent or solvent mixture possessing NIFU solubility ≥ 20 mg/mL for a viable crystallization process,^{15,17} aiding the development of an integrated advanced API manufacturing platform.^{18,38} Based on the screening experiments conducted in this study, NIFU anhydrate β (as-received) exhibited limited solubility (≤ 14.1 mg/mL at 72 °C; ≤ 2.1 mg/mL at 30 °C) in various Class 3 solvents, recommended for NIFU crystallization processes,^{26,31,70} including acetone, cyrene, dimethyl isosorbide, ethanol, ethyl acetate, isopropanol, methanol, 2-methyltetrahydrofuran, water, and aqueous acetic acid. Details for the solubility data are provided in Section S3. Briefly, from all solvents published and tested in this study, only DMAc and DMSO exhibited a target solubility of ≥ 20 mg/mL (Figure S3a). Though DMAc offers relatively high solubility (≥ 30 mg/mL at 25 °C), it is a less favorable Class 2 solvent for API crystallization⁷¹ due to a residual concentration limit of ≤ 1090 ppm¹⁶ while also forming an undesired NIFU DMAc solvate (Figure S5).²⁶ Therefore, DMSO was selected as the crystallization solvent because it is a Class 3 solvent⁷² offering a viable solubility of 46.5 mg/mL at 25 °C (Figure S3a). However, DMSO also yielded an undesired NIFU DMSO hemisolvate (Figure S5),²⁷ necessitating additional solid-form correction steps¹⁵ to obtain one of the two commercial crystal forms (anhydrate β and monohydrate II). Since NIFU anhydrate β is the metastable solid form in DMSO, it exhibited an apparent solubility of ~ 112 mg/mL at 20 °C, measured employing the polythermal method.⁴¹ This value is significantly higher than the solubility for the stable form in DMSO, NIFU DMSO hemisolvate.²⁷ Noticeably, upon adding NIFU anhydrate β to DMSO at 25 °C, the solids visually dissolved in vials with known suspension concentration of ≥ 70 mg/mL within ~ 5 min. Once the solids visually dissolved, the yielding solution concentration exceeded the solubility of NIFU DMSO hemisolvate (46.5 mg/mL measured in this study, Figure 1a). As a result, yellowish NIFU DMSO hemisolvate crystallized quickly within 30 min via the solvent-mediated phase transformation mechanism: dissolution of the metastable form, followed by nucleation and growth of the stable form.^{73–75}

A known challenge in employing neat DMSO is its relatively high freezing point of 18.5 °C,⁴⁶ typically resulting in

unfavorable low yield ($\leq 90\%$) when sole cooling crystallization is applied¹⁸ due to the API's remaining solubility close to DMSO's freezing point. For NIFU the remaining solubility is ~ 41 mg/mL at 20 °C (Figure S3a). To overcome the remaining solubility, antisolvent (water) crystallization was employed.¹⁵ The data for solubility and theoretical yield are illustrated in Figure 1. To the authors' knowledge, no solubility data of NIFU DMSO hemisolvate in the binary DMSO-water solvent system has been reported to date.

Figure 1a exhibits a decreasing solubility of NIFU DMSO hemisolvate with increasing antisolvent content and decreasing temperature without freezing the binary DMSO/water solvent mixture below 18.5 °C,⁴⁴ allowing to obtain a theoretical yield of $>90\%$ (Figure 1b) across a broad temperature range. At low antisolvent content (<20 v/v%), the NIFU DMSO hemisolvate solubility shows strong temperature dependence. Above 20 v/v %, the solubility becomes predominantly governed by the antisolvent content (Figure 1a).

3.2. Solid Form Characterization of NIFU DMSO Hemisolvate

The NIFU solid form obtained through recrystallization from DMSO in this study was characterized by PXRD, TGA, and DSC (Figure 2).

The PXRD diffractogram confirmed the formation of the known NIFU DMSO hemisolvate (Figure 2a).²⁷ The slight shift of the experimental data compared to the simulated diffractogram (refcode: AKEMEJ)²⁷ can be explained by the difference in the temperatures at which the diffractograms were recorded ($\sim 22 \pm 1$ °C versus -24 °C).^{27,78} In addition, the absence of PXRD peaks other than those matching the simulated diffractogram of the DMSO hemisolvate²⁷ (Figures 2a and S5c) suggests that within the detection limit of the employed PXRD instrument, only NIFU DMSO hemisolvate crystals were obtained.⁶⁵ It needs to be stated that the focus in this work was limited to phase identification and qualitative structural comparison. A comprehensive crystal structure analysis of NIFU and the transformation pathways reported below was beyond the scope of this study.

The DSC thermogram (Figure 2b) revealed a splitting endothermic peak between 210 and 230 °C, suggesting a complex desolvation mechanism reported in the literature,⁷⁹ confirmed by TGA data (Figure 2b). The weight loss of 14.1% at 200 °C aligns well with the theoretical value of 14.1% for the desolvation of a DMSO hemisolvate based on the NIFU and

DMSO molecular weights (238.16 and 78.13 g/mol, respectively).⁷⁹ Upon further heating, the thermal events at peak temperatures of 271 and 288 °C correspond to the melting and subsequent complete decomposition (TGA) of NIFU anhydrate β , respectively, as characterized in this study (Figure S2) and reported in the literature.⁷⁹

3.3. Batch Antisolvent Crystallization

Based on preliminary screening experiments (Section S4), it was opted for an isothermal antisolvent crystallization operated at 25 °C because of the low temperature sensitivity at increasing antisolvent content (Figure 1). In addition, the isothermal operation will lower the carbon footprint of the process by eliminating the need for energy-intensive heating followed by cooling to below ambient temperature.^{80,81} The environmental benefits of using DMSO as the solvent and water as an antisolvent are also significant, as they are considered green solvents.^{15,76,82,83} Without claiming an optimized process, a desupersaturation curve of NIFU DMSO hemisolvate antisolvent crystallization using the water addition rate of 0.25 mL/min was studied to estimate the residence time needed for the continuous antisolvent crystallization (Figure 3).

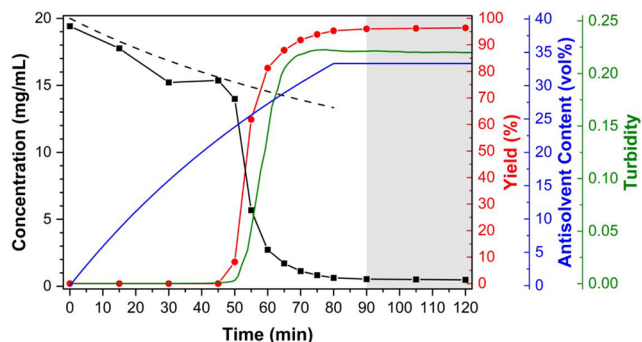


Figure 3. Results of batch antisolvent crystallization of NIFU DMSO hemisolvate: HPLC measured NIFU mother liquor concentration (black squares), experimentally determined yield (red circles), calculated antisolvent (water) volume fraction based on 0.25 mL/min feed rate (blue line), and slurry turbidity measured *in situ* using the Blaze probe (green line). Dashed black line represents the calculated theoretical NIFU solution concentration without crystallization, assuming dilution caused by antisolvent addition.^{84,85} Gray area indicates when equilibrium was reached ($c^* \sim 0.8$ mg/mL, Figure 1).

Upon antisolvent (water) addition, the NIFU concentration slowly decreases with increasing water content up to ~ 30 v/v% (Figure 3).^{84,85} In this study, supersaturation was defined as the concentration ratio $\frac{c}{c^*}$, where c is the concentration of the solution and c^* is the concentration at saturation (Figure 1a).⁸⁶ When reaching ~ 15 mg/mL at ~ 30 v/v% water content, NIFU DMSO hemisolvate nucleated from the supersaturated solution ($S = \frac{c}{c^*} \sim 8.1$),¹⁵ causing a sudden concentration drop starting at ~ 45 min. This nucleation event was also detected by an increase in the solution turbidity (Blaze Metrics probe). The mother liquor concentration desupersaturated and approached equilibrium at ~ 0.8 mg/mL after ~ 90 min (Figure 3) with an experimentally determined yield of 95% that matched the solubility and theoretical value of 96%, respectively (Figure 1). This assessment is supported by the plateaued turbidity (Figure 3), indicating the end point of the batch crystallization process.^{87,88}

3.4. Continuous Antisolvent Crystallization

After determining viable crystallization conditions for NIFU DMSO hemisolvate (detailed above), a proof-of-concept continuous antisolvent crystallization with 80 min residence time was conducted, utilizing the batch process as the startup phase.^{89,90} The key process metrics (NIFU concentration, yield, median chord length [d50], chord length distribution) stabilized after about three residence times, indicating the process reached steady state quickly (Figure 4). At steady state, the d50 for the well-defined prismatic NIFU DMSO hemisolvate crystals with a unimodal cube-weighted chord length distribution was 208 ± 2.6 μm achieved with a yield of $92 \pm 0.4\%$ averaged over four residence times. The mother liquor concentration of 0.9 ± 0.1 mg/mL is very close to the solubility (Figure 1). Offline PXRD diffractograms of crystals collected at steady state confirmed the formation of NIFU DMSO hemisolvate (Figure S7). Notably, the continuous antisolvent crystallization maintained the crystal quality and process stability over an extended operation of 6 residence times without fouling and clogging of the crystallizer walls and transfer lines.

3.5. Solid-Form Correction Processes

Since NIFU DMSO hemisolvate is not one of the two commercial forms used for drug formulation (anhydrate β and monohydrate II),²⁸ two possible solid-form correction steps were explored for feasibility: (1) temperature-induced phase transformation⁹¹ into NIFU anhydrate β via desolvation and (2)

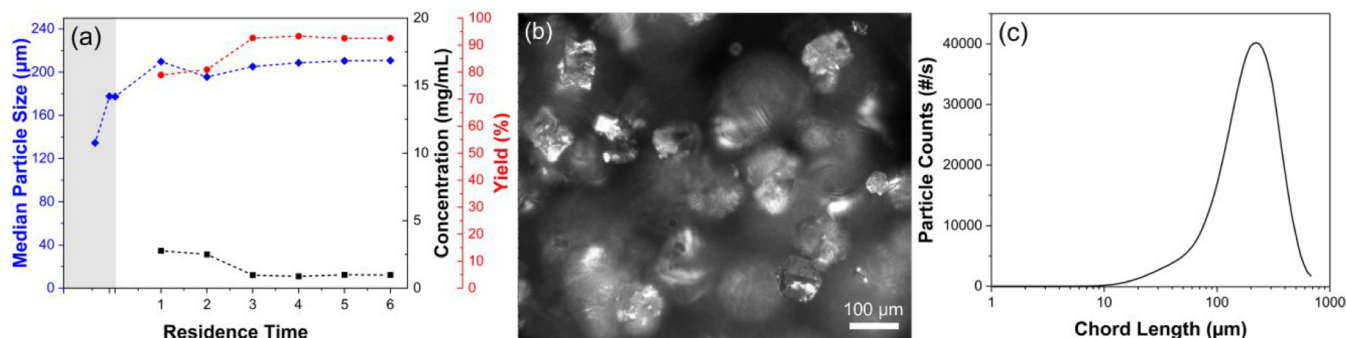


Figure 4. Experimental results of continuous antisolvent crystallization of NIFU DMSO hemisolvate: (a) Evolution of cube-weighted median chord length [d50] (blue, left y-axis), solute concentration (black, right y-axis; monitored after one residence time), and yield (red, right y-axis). Gray area represents the startup phase (90 min) of the continuous experiment. (b) Representative *in situ* microscopy image of NIFU DMSO hemisolvate crystals at steady state. (c) Image-derived cube-weighted chord length distribution at steady state (after 6 residence times, thus, 570 min).

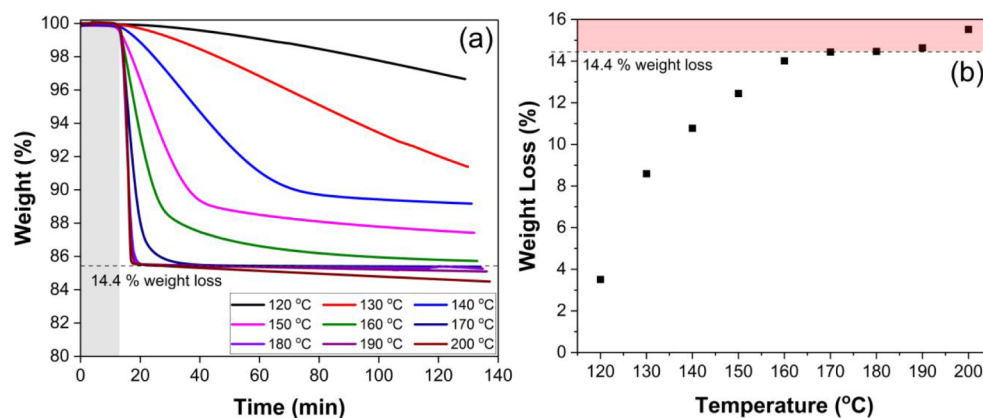


Figure 5. (a) Isothermal TGA thermograms of NIFU DMSO hemisolvate at temperatures ranging from 120 to 200 °C. Gray area represents the heating period of ≤ 17 min from 30 °C to the target temperatures at a heating rate of 10 °C/min. Dashed horizontal line corresponds to an experimental weight loss of 14.4% by desolvation, which is close to the theoretical value of 14.1%.⁷⁹ (b) Weight loss as a function of desolvation temperature. Red area indicates decomposition, as it exceeds the experimental desolvation weight loss of 14.4% for NIFU DMSO hemisolvate.

solvent-mediated phase transformation (SMPT)²² into NIFU monohydrate II via slurry crystallization in water.

3.5.1. Desolvation by Heating. It is a common practice in the pharmaceutical industry to achieve a desired solid form by dehydration or desolvation through heating in a drying process.^{55,91} Traditionally such drying operations are conducted in large-scale batch equipment under vacuum at moderate temperatures (e.g., 50–60 °C).^{11,91} Employing the Clausius–Clapeyron relation (eqs S1 and S2), the reduced pressure required to remove DMSO at e.g., 50 °C suggested a reduced pressure of ~ 0.3 bar to generate the commercial NIFU anhydrate β by desolvation of NIFU DMSO hemisolvate. Though the setup available for this study was unable to achieve this low pressure, preliminary experiments at ~ 0.55 bar and 80 °C yielded an incomplete desolvation after 20 h. Further details are provided in S6.2 in the [Supporting Information](#).

Yet, motivated by these promising results the feasibility of NIFU DMSO hemisolvate desolvation was evaluated at elevated temperatures. The thermal analysis conducted in this work (Figures 2b and S2) suggests the possibility of desolvation because of NIFU's relatively high melting point (271 °C) and thermal stability. Therefore, desolvation studies of NIFU DMSO hemisolvate were conducted by heating samples to different temperatures (120–200 °C) and held for 2 h using a TGA (Figure 5a).

Based on Figure 5, complete desolvation of NIFU DMSO hemisolvate (weight loss of 14.4%) was achieved between 170 and 180 °C within 40 min without signs of decomposition. Using the USP assay method,³⁶ HPLC data of the sample desolvated at 180 °C confirmed the absence of decomposition products (Figure S10). In Figure 5b for $T \geq 190$ °C, the weight loss continued to increase beyond 14.4% at 130 min, suggesting the onset of thermal decomposition. Below 170 °C, the transformation was significantly slower and incomplete within the time of 130 min studied in this work (Figure 5a). However, PXRD diffractograms confirmed that at least all samples treated at ≥ 160 °C were completely desolvated into the commercial NIFU anhydrate β ²⁴ (Figure S11). While the sample at $T = 160$ °C revealed a weight loss of only 14% (Figure 5b), slightly less than the experimental and theoretical values of 14.4% and 14.1%,⁷⁹ respectively, in combination with the PXRD results (Figure S11) it was considered desolvated. Moreover, Figure 5 indicates that the recrystallization process already starts at 120

°C, as indicated by the weight loss and the appearance of characteristic peaks of NIFU anhydrate β (Figure S11), suggesting that complete transformation might be achievable for $T < 160$ °C with desolvation times > 120 min.

One might argue that upon solvent removal (e.g., by desolvation of a solvate), the crystal structure may collapse yielding an amorphous solid¹ due to changes in the molecular conformation and lattice constants.⁷⁹ The PXRD diffractograms (Figure S11) demonstrated that the desolvated NIFU DMSO hemisolvate samples remained crystalline similar to “as-received” NIFU anhydrate β even without the DMSO molecule (0.5 mol) in the crystal structure. This assessment is made within the detection limit of the PXRD instrument used in this study and supported by the known transformation mechanism.⁷⁹ For mere visualization purposes in this study, the crystal structures documented in the literature have been regenerated (Figure S12).⁹² Conversion of the NIFU DMSO hemisolvate²⁷ to the anhydrate β form²⁴ involves removal of solvent-filled channels (Figure S13) and a conformational change in NIFU, evidenced by a different torsion angle between the heterocyclic rings (Figure S12). This supports a reconstructive transformation rather than a simple packing rearrangement (Figure S14).⁷⁹ Details are provided in Section S6.1.

To further quantify the measured desolvation level, the extent of transformation, α , was calculated from the observed weight loss (ΔW) relative to the total experimental weight loss ($\Delta W_t = 14.4\%$) based on the TGA weight-loss data (Figure 5a) using eq 2:⁹³

$$\alpha = \Delta W / \Delta W_t \quad (2)$$

where ΔW is the observed weight loss (%) at a given time, and ΔW_t the experimental total weight loss for complete desolvation (14.4%, Figure 5). The data are illustrated in Figure 6, revealing a logarithmic characteristic of the desolvation process. The Avrami–Erofeev equation (eq 1)^{9,61–64} has been recommended for such desolvation/dehydration behavior. Correlating the experimental kinetic data using the Avrami–Erofeev equation allows to interpolate the extent of transformation within the selected time range impacted by the desolvation temperature.^{61–64,94,95} The Avrami–Erofeev equation (Figure 6, $R^2 \geq 0.986$) yielded rate constants (k) of 0.120, 0.059, and 0.040 min^{-1} and Avrami exponents (n) of 0.84, 1.66, and 2.56 at 160,

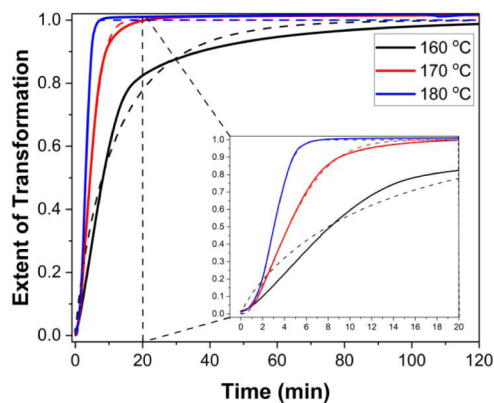


Figure 6. Desolvation kinetics of NIFU DMSO hemisolvate into anhydrate β at 160 °C (black), 170 °C (red), and 180 °C (blue). Solid lines were calculated from the experimental TGA data (Figure 5). Dashed lines represent the fitted curves using the Avrami–Erofeev equation (eq 1)^{9,61–64} with $R^2 \geq 0.986$.

170, and 180 °C, respectively. These values are summarized in Table S5.

Typically, $n \sim 1$ corresponds to one-dimensional (needlelike) growth or interface-controlled processes; $n \sim 2$ indicates two-dimensional plate-like growth; and $n \sim 3$ suggests three-dimensional, diffusion-controlled crystallite growth.^{93,96} The increase of n with temperature (Table S5) is consistent with a

transition from lower-dimensional to more three-dimensional, diffusion-controlled growth ($n > 2.5$) at 180 °C.^{93,96} This trend suggests that mass transfer effects (diffusion or solvent removal) become increasingly relevant with rising temperature.^{93,96}

Consequently, these results suggest that desolvating the NIFU DMSO hemisolvate during a potential drying step following a continuous crystallization process is experimentally feasible for the preparation of the desired crystalline NIFU anhydrate β .²⁸ Due to the absence of a solvent and thus solubility losses, the yield is assumed to be 100% (excluding the removed DMSO fraction).⁹¹

3.5.2. Solvent-Mediated Phase Transformation by Slurry Crystallization. Another common practice to obtain a desired solid form is solvent-mediated phase transformation (SMPT).^{15,22} In this study, slurry crystallization of NIFU DMSO hemisolvate in water was conducted. The use of Blaze and Raman probes (separately immersed) enabled the *in situ* monitoring of the SMPT from prismatic-shaped NIFU DMSO hemisolvate to needle-shaped NIFU monohydrate II⁷⁹ (Figures 7 and S17). In this work it was found that the Raman bands at 270 and 840 cm^{-1} correspond to the disappearing hemisolvate and the forming monohydrate II, respectively (Figure S19), as confirmed by offline PXRD (Figure S18). Further details are provided in Section S7.1.

The *in situ* Raman spectra (Figures 7 and S20–21) revealed a rapid transformation within ≤ 15 min for all three temperatures, suggesting that offline PXRD was not viable to track the fast

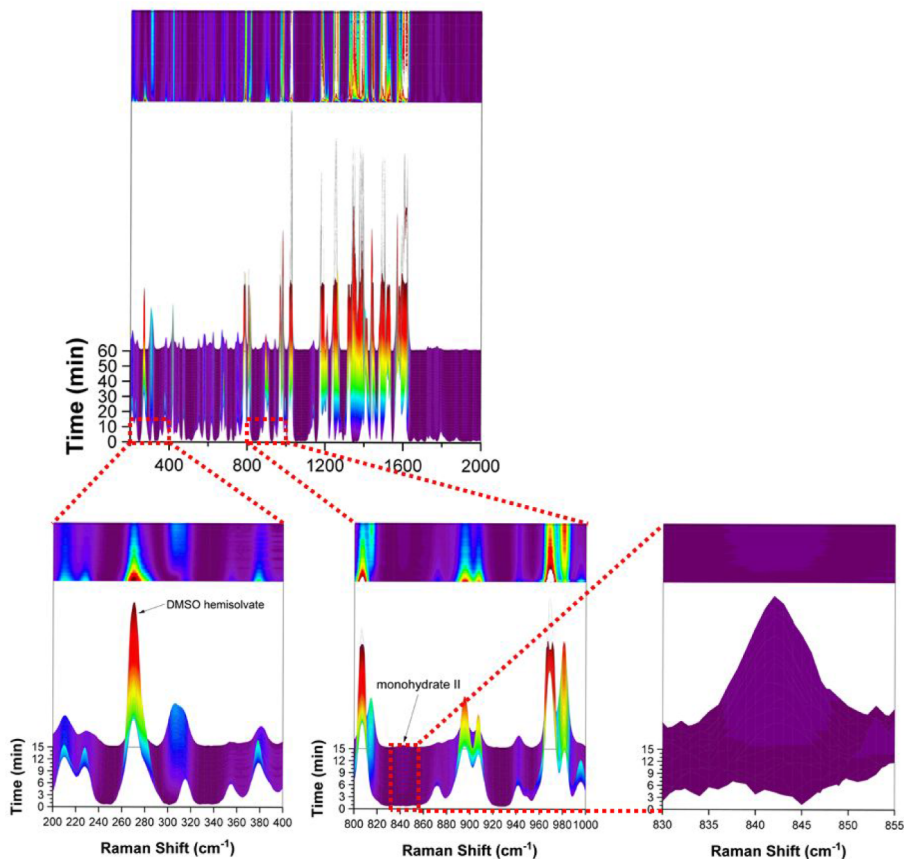


Figure 7. Representative *in situ* Raman spectra of the SMPT of NIFU DMSO hemisolvate to monohydrate II during slurry crystallization in water at 10 °C. The insets present zoom-in views of the spectral regions of 200–400, 800–1000, and 830–855 cm^{-1} . The intensity for the Raman shifts at 270 and 840 cm^{-1} represent the disappearance of NIFU DMSO hemisolvate and the formation of monohydrate II, respectively. *In situ* Raman spectra for 25 and 40 °C are provided in Figures S20 and S21.

SMPT progress considering its time-consuming sampling and sample preparation requirements.⁹⁷ To further assess the SMPT process, these Raman spectra (Figure S21) were utilized to extract the SMPT kinetics (Figure 8) revealing a logarithmic characteristic.^{14,75,98} Details are provided in Section S7.2.

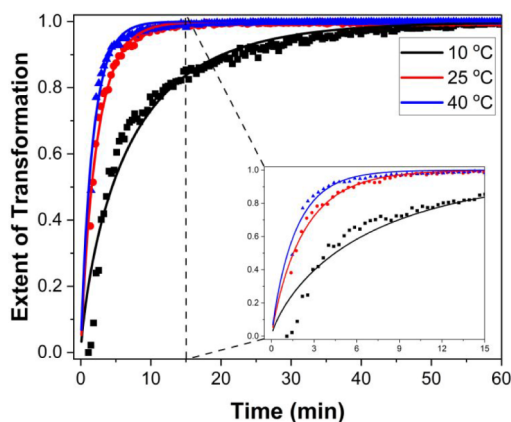


Figure 8. SMPT kinetics of NIFU DMSO hemisolvate into monohydrate II fitted using the Avrami–Erofeev equation (eq 1)^{61–64} Data points (Figure S22a) indicate normalized Raman intensity at 270 cm^{-1} corresponding to the disappearance of NIFU DMSO hemisolvate during slurry crystallization at 10 (black), 25 (red), and 40 $^{\circ}\text{C}$ (blue). Solid lines represent the fitted curves with $R^2 \geq 0.947$.

Generally, it can be stated that both the induction time and total time for the SMPT decrease with increasing temperature (Figure S22b). It is known that increasing the temperature lowers the solid–liquid interfacial tension and enhances

solubility, thereby promoting faster dissolution of the metastable form and, thus, facilitating the nucleation of the stable form.^{74,99} Figure 8 illustrates the fitting of the Avrami–Erofeev equation (eq 1) to the Raman data (Figures 7 and S20–S21) of the SMPT process^{100,101} yielding $k = 0.21, 0.46$, and 0.61 min^{-1} at 10, 25, and 40 $^{\circ}\text{C}$, respectively. The relatively low Avrami exponents ($n < 1$, Table S5) indicate that the SMPT process proceeds via a one-dimensional, interface-controlled growth mechanism with swift nucleation of the needlelike monohydrate II crystals (Figure S17).^{93,96} Consequently, the SMPT process of NIFU DMSO hemisolvate is a fast and viable approach with a yield of $\geq 92\%$ of NIFU monohydrate II due to the low solubility of NIFU between 10 and 40 $^{\circ}\text{C}$ of $\leq 0.75 \text{ mg/mL}$ (Figure S3b).

3.6. Form Map, Quality Attributes, and Process Performance

Figure 9 summarizes the reported transformation pathways of different NIFU anhydrous, hydrated, and solvated forms extracted from the literature (black arrows) and in this study (red arrows).^{24,26,27,102–104} Particularly, to the authors’ knowledge, the transformation of NIFU DMSO hemisolvate to either anhydrate β by thermal desolvation or monohydrate II by slurry crystallization in water is detailed for the first time.

GC analysis verified that both NIFU anhydrate β and monohydrate II generated under the desolvation and slurry crystallization conditions employed in this study did not contain residual DMSO within the detection limit of the GC instrument ($<0.5\%$, Figure S23). Table 1 summarizes the yield of each process and the key product quality attributes for each solid form generation and transformation pathway in comparison with the USP acceptance criteria for the API NIFU.³⁶ Commercially purified (as-received) NIFU was used as the starting material,

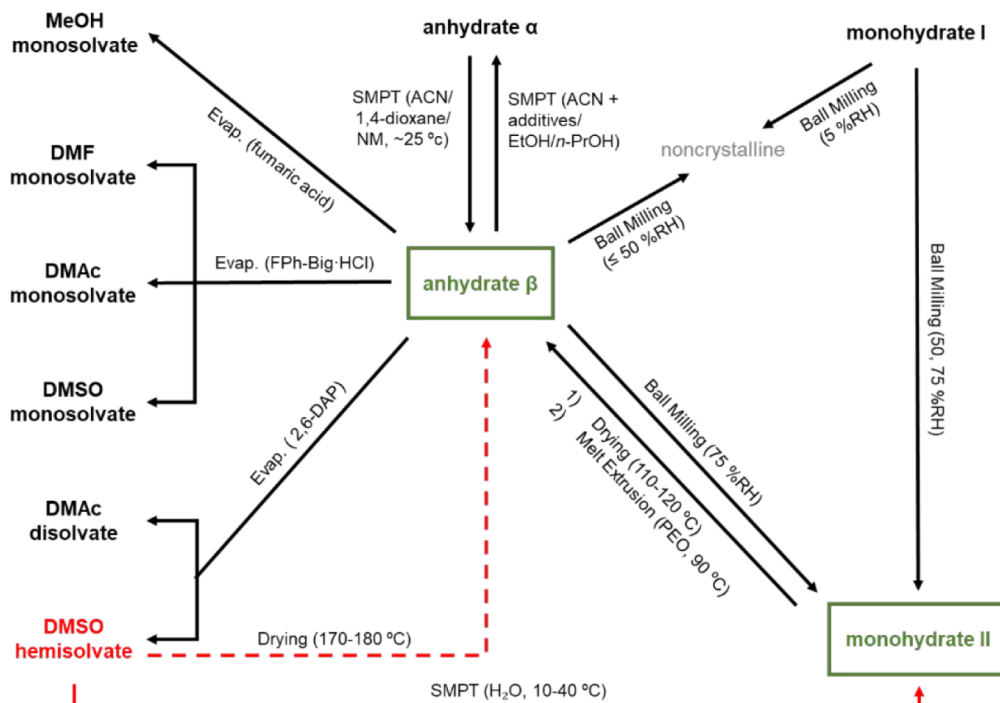


Figure 9. Form map of NIFU anhydrous, hydrated, and solvated forms. The transformation pathways (arrows) of the different solid forms are extracted from the literature (black)^{24,26,27,102–104} and reported in this study (red). For the drying (desolvation) pathway (red dashed arrow), this study reports for the first time detailed temperature conditions and kinetic information, yielding a possible process with no detection of decomposition products (HPLC³⁶). FPh-Big-HCl = 1-(4-fluorophenyl)biguanide HCl, 2,6-DAP = 2,6-diaminopyridine, NM = nitromethane, additives = BIS-TRIS, PVC, PAN, PEO = poly(ethylene oxide).

Table 1. Yield and Quality Attributes of NIFU DMSO Hemisolvate, Anhydrate β , and Monohydrate II Obtained by Crystallization and Solid-Form Correction Steps Reported in This Study

API quality attributes	Acceptance criteria (USP monograph)	Antisolvent crystallization	Drying ^a	Slurry crystallization
Solid form	Anhydrate β Monohydrate II	DMSO hemisolvate	Anhydrate β	Monohydrate II
Water content	<1.0% (anhydrous) 6.5%–7.5% (hydrous)	NA	<0.4%	7.0%
Residual solvent	<0.5% by GC (for Class 3 solvents)	14.4% by TGA	Nondetected ^b	Nondetected ^b
Yield		95% (batch), 92% (continuous)	~100%	92%

^aNo impurity was detected for the desolvated sample at 180 °C using the USP assay HPLC method³⁶ (Figure S10). ^bResidual solvent content must be below the detection limit of the GC instrument (<0.5%) employed in this study.

and the analytical deliverable of this study was defined as meeting the USP specifications using USP-certified standards. Comprehensive impurity profiling, including targeted screening for possible trace genotoxic impurities, was beyond the scope of this work. Such analysis should be conducted in future efforts, should the proposed strategy be considered for implementation.

Without claiming optimized crystallization and solid-form correction processes, the approach reported in this study using as-received (purified) NIFU met the required solid form and residual-solvent specifications. The achieved material yields (batch antisolvent crystallization ~ 95%, continuous antisolvent crystallization ~ 92%, desolvation assumed ~ 100%, and SMPT ~ 92%) were obtained while maintaining stable process operation and crystal quality.

4. CONCLUSIONS

While most API crystallization studies focus on avoiding the formation of undesired solvates, this work demonstrates how such a solvate may be deliberately exploited to achieve a favorable crystallization platform for NIFU. Two solid-form correction operations provided access to the commercial crystalline forms under laboratory conditions: anhydrate β and monohydrate II via thermal desolvation and slurry crystallization in water, respectively. Pending further research, both processes could be considered for postcrystallization treatment steps: filtration, washing, and drying. In addition to the relatively high product yields of these steps ($\geq 92\%$), both the anhydrate β and monohydrate II forms meet the USP acceptance criteria for NIFU.

The experimental data of the transformation processes fitted the semiempirical Avrami–Erofeev model providing a qualitative assessment of the temperature-dependent kinetics (≤ 15 min). In the slurry crystallization for SMPT, the use of PAT for *in situ* monitoring enabled robust process tracing supporting further implementation studies.

Ultimately, this study presents a workflow for NIFU with possible relevance to other APIs exhibiting solubility and purity purging limitations or upstream process conditions not favoring the generation of the desired crystalline solid form. This proof-of-concept study might be used as a rationale for further investigations. For instance, determining the critical water activity and composition of the desolvation and SMPT processes, desolvation in continuous drying equipment, impact of solid-form correction processes on formulation properties of NIFU and technoeconomic analysis to evaluate the feasibility, economic and environmental impact of the presented approaches.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.5c00513>.

Solubility screening results, batch and continuous antisolvent crystallization data, desolvation studies (ambient and reduced pressure), solvent-mediated phase transformation studies (including *in situ* Blaze and Raman monitoring), PXRD, DSC, TGA characterizations of NIFU forms, HPLC of desolvated product, GC of obtained products, and crystal structure visualization (PDF)

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Notes

Any additional relevant notes should be placed here.
The authors declare no competing financial interest.

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REFERENCES

- (1) *Polymorphism in the Pharmaceutical Industry: solid Form and Drug Development*, Hilfiker, R.; von Raumer, M., Eds.; Wiley: Weinheim, 2019.
- (2) Lee, A. Y.; Erdemir, D.; Myerson, A. S. Crystal polymorphism in chemical process development. *Annu. Rev. Chem. Biomol. Eng.* **2011**, *2*, 259–280.
- (3) Di Martino, P.; Guyot-Hermann, A. M.; Conflant, P.; Drache, M.; Guyot, J. C. A new pure paracetamol for direct compression: the orthorhombic form. *Int. J. Pharm.* **1996**, *128*, 1–8.
- (4) Nicoud, L.; Licordari, F.; Myerson, A. S. Estimation of the solubility of metastable polymorphs: a critical review. *Cryst. Growth Des.* **2018**, *18*, 7228–7237.
- (5) Lee, T.; Yang, C. L.; Lee, H. L. Saving energy upon water removal in drying by making the α -polymorph of L-glutamic acid. *Sep. Sci. Technol.* **2022**, *57*, 1948–1965.
- (6) Bernstein, J. Polymorphism – A perspective. *Cryst. Growth Des.* **2011**, *11*, 632–650.
- (7) Samas, B.; Seadeek, C.; Campeta, A. M.; Chekal, B. P. A thermodynamic-based approach to analyzing a highly solvating polymorphic system: The desolvation window method. *J. Pharm. Sci.* **2011**, *100*, 186–194.
- (8) Tian, F.; Qu, H.; Zimmermann, A.; Munk, T.; Jørgensen, A. C.; Rantanen, J. Factors affecting crystallization of hydrates. *J. Pharm. Pharmacol.* **2010**, *62*, 1534–1546.
- (9) Byrn, S. R. *Solid-State Chemistry of Drugs*; Academic Press: New York, 1982.
- (10) Dette, S. S.; Stelzer, T.; Jones, M. J.; Ulrich, J. Dehydration behaviour of hydrates. *Cryst. Res. Technol.* **2010**, *45*, 697–702.
- (11) Adamson, J.; Faiber, N.; Gottlieb, A.; Hamsmith, L.; Hicks, F.; Mitchell, C.; Mittal, B.; Mukai, K.; Papageorgiou, C. D. Development of suitable plant-scale drying conditions that prevent API agglomeration and dehydration. *Org. Process Res. Dev.* **2016**, *20*, 51–58.
- (12) Brittain, H. G. Paroxetine hydrochloride: Polymorphs and solvatomorphs. *Profiles Drug Subst. Excip. Relat. Methodol.* **2013**, *38*, 407–421.
- (13) Legendre, A. O.; Silva, L. R.; Silva, D. M.; Rosa, I. M.; Azarias, L. C.; de Abreu, P. J.; de Araújo, M. B.; Neves, P. P.; Torres, C.; Martins, F. T.; et al. Solid state chemistry of the antibiotic doxycycline: structure of the neutral monohydrate and insights into its poor water solubility. *CrystEngcomm* **2012**, *14*, 2532–2540.
- (14) Zheng, Z.; Hou, B.; Cheng, X.; Liu, W.; Huang, X.; Bao, Y.; Wang, T.; Wang, Z.; Hao, H. The mechanism of solvent-mediated desolvation transformation of levatinib mesylate from dimethyl sulfoxide solvate to form D. *Acta Crystallogr.* **2020**, *B76*, 343–352.
- (15) Myerson, A. S.; Erdemir, D.; Lee, A. Y.. *Handbook of Industrial Crystallization*; Cambridge University Press: Cambridge, 2019.
- (16) FDA. Q3C(R8) Impurities: Guidance for Residual Solvents Guidance for Industry 2021 <https://www.fda.gov/vaccines-bloodbiologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>.
- (17) Rogers, L.; Briggs, N.; Achermann, R.; Adamo, A.; Azad, M.; Brancazio, D.; Capellades, G.; Hammersmith, G.; Hart, T.; Imbrogno, J.; Kelly, L. P.; Liang, G.; Neurohr, C.; Rapp, K.; Russell, M. G.; Salz, C.; Thomas, D. A.; Weimann, L.; Jamison, T. F.; Myerson, A. S.; Jensen, K. F. Continuous production of five active pharmaceutical ingredients in flexible plug-and-play modules: A demonstration campaign. *Org. Process Res. Dev.* **2020**, *24*, 2183–2196.
- (18) Silva-Brenes, D. V.; Agrawal, S.; López-Mejías, V.; Duconge, J.; Vlaar, C. P.; Monbaliu, J. C. M.; Stelzer, T. Continuous flow synthesis and crystallization of modafinil: a novel approach for integrated manufacturing. *React. Chem. Eng.* **2024**, *9*, 2728–2739.
- (19) Wirth, D. D.; Stephenson, G. A. Purification of dirithromycin. Impurity reduction and polymorph manipulation. *Org. Process Res. Dev.* **1997**, *1*, 55–60.
- (20) Black, S. N.; Cuthbert, M. W.; Roberts, R. J.; Stensland, B. Increased chemical purity using a hydrate. *Cryst. Growth Des.* **2004**, *4*, 539–544.
- (21) Maini, L.; Braga, D.; Farinella, F.; Melotto, E.; Verzini, M.; Brescello, R.; Michieletto, I.; Munari, I. Crystal forms of enzalutamide and a crystal engineering route to drug purification. *Cryst. Growth Des.* **2018**, *18*, 3774–3780.
- (22) Chekal, B. P.; Campeta, A. M.; Abramov, Y. A.; Feeder, N.; Glynn, P. P.; McLaughlin, R. W.; Meenan, P. A.; Singer, R. A. The challenges of developing an API crystallization process for a complex polymorphic and highly solvating system. Part I. *Org. Process Res. Dev.* **2009**, *13*, 1327–1337.
- (23) World Health Organization. WHO Model List of Essential Medicines - 22nd list, 2021. <https://iris.who.int/server/api/core/bitstreams/285bb318-3177-4ed6-8fc9-Sd1106220fa4/content> (accessed 3 March, 2026).
- (24) Pienaar, E. W.; Caira, M. R.; Lötter, A. P. Polymorphs of nitrofurantoin. 2. Preparation and X-ray crystal structures of two anhydrous forms of nitrofurantoin. *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 785–790.
- (25) Pienaar, E. W.; Caira, M. R.; Lötter, A. Polymorphs of nitrofurantoin. I. Preparation and X-ray crystal structures of two monohydrated forms of nitrofurantoin. *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 739–744.
- (26) Vangala, V. R.; Chow, P. S.; Tan, R. B. Nitrofurantoin methanol monosolvate. *Acta Crystallogr.* **2011**, *E67*, o550–o551.
- (27) Tutughamiasro, M.; Bolte, M.; Wagner, G.; Egert, E. Five pseudopolymorphs and a cocrystal of nitrofurantoin. *Acta Crystallogr.* **2011**, *C67*, o18–o25.
- (28) MACROBID Macrobid (nitrofurantoin monohydrate/macrocrystals). Procter and Gamble Pharmaceuticals, Inc.: Cincinnati, OH, 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020064s019lbl.pdf (accessed 11 March, 2025).

- (29) Tian, F.; Qu, H.; Louhi-Kultanen, M.; Rantanen, J. Insight into crystallization mechanisms of polymorphic hydrate systems. *Chem. Eng. Technol.* **2010**, *33*, 833–838.
- (30) Wang, X.; Ji, X.; Cai, T.; Guo, M. Mechanistic insight of polymer effects on the kinetic of solution-mediated phase transformation of nitrofurantoin anhydrate to monohydrate. *Pharm. Res.* **2023**, *40*, 1587–1598.
- (31) US Patent. JPH 0,212,156 A1. 2023
- (32) India Patent IN. 3941/CHE/2011.
- (33) Koradia, V.; de Diego, H. L.; Elema, M. R.; Rantanen, J. Integrated approach to study the dehydration kinetics of nitrofurantoin monohydrate. *J. Pharm. Sci.* **2010**, *99*, 3966–3976.
- (34) Crawford, D. E.; Porcheddu, A.; McCalmont, A. S.; Delogu, F.; James, S. L.; Colacino, E. Solvent-free, continuous synthesis of hydrazone-based active pharmaceutical ingredients by twin-screw extrusion. *ACS Sustainable Chem. Eng.* **2020**, *8*, 12230–12238.
- (35) Yu, L. X.; Amidon, G.; Khan, M. A.; Hoag, S. W.; Polli, J.; Raju, G. K.; Woodcock, J. Understanding pharmaceutical quality by design. *AAPS J.* **2014**, *16*, 771–783.
- (36) United States Pharmacopeia. *Nitrofurantoin*; United States Pharmacopeia, 2020. DOI: .
- (37) Scott, D.; Briggs, N. E.; Formosa, A.; Burnett, A.; Desai, B.; Hammersmith, G.; Rapp, K.; Capellades, G.; Myerson, A. S.; Roper, T. D. Impurity purging through systematic process development of a continuous two-stage crystallization. *Org. Process Res. Dev.* **2023**, *27*, 148–158.
- (38) Hellwig, H.; Bovy, L.; Van Hecke, K.; Vlaar, C. P.; Románach, R. J.; Noor-E-Alam, M.; Myerson, A. S.; Stelzer, T. M.; Jean-Christophe, M. Continuous Flow Synthesis of Nitrofurantoin Pharmaceuticals Using Acetyl Nitrate. *Angew. Chem., Int. Ed.* **2025**, *64*, No. e202501660.
- (39) Zorrilla-Veloz, R. I.; Stelzer, T.; López-Mejías, V. Measurement and Correlation of the Solubility of 5-Fluorouracil in Pure and Binary Solvents. *J. Chem. Eng. Data* **2018**, *63*, 3809–3817.
- (40) George De La Rosa, M. V.; Santiago, R.; Malavé Romero, J.; Duconge, J.; Monbaliu, J. C.; López-Mejías, V.; Stelzer, T. Solubility Determination and Correlation of Warfarin Sodium 2-Propanol Solvate in Pure, Binary, and Ternary Solvent Mixtures. *J. Chem. Eng. Data* **2019**, *64*, 1399–1413.
- (41) Vázquez Marrero, V. R.; Piñero Berriós, C.; De Dios Rodríguez, L.; Stelzer, T.; López-Mejías, V. In the context of polymorphism: Accurate measurement, and validation of solubility data. *Cryst. Growth Des.* **2019**, *19*, 4101–4108.
- (42) Jiménez Cruz, J. M.; Vlaar, C. P.; López-Mejías, V.; Stelzer, T. Solubility measurements and correlation of mbq-167 in neat and binary solvent mixtures. *J. Chem. Eng. Data* **2021**, *66*, 832–839.
- (43) Zimmermann, L.; Lee, H. L.; Koishybay, A.; Vlaar, C. P.; Monbaliu, J. C. M.; Románach, R. J.; Noor-E-Alam, M.; Myerson, A. S.; Stelzer, T. Measurements and correlation of timolol maleate solubility in biobased neat and binary solvent mixtures. *J. Chem. Eng. Data* **2024**, *69*, 2369–2379.
- (44) Smallwood, I. M. *Handbook of Organic Solvent Properties*; Elsevier: Arnold, 1996.
- (45) Vellema, J.; Hunfeld, N. G. M.; Van Den Akker, H. E. A.; Ter Horst, J. H. Avoiding Crystallization of lorazepam during infusion. *Eur. J. Pharm. Sci.* **2011**, *44*, 621–626.
- (46) Reus, M. A.; Van Der Heijden, A. E. D. M.; Ter Horst, J. H. Solubility determination from clear points upon solvent addition. *Org. Process Res. Dev.* **2015**, *19*, 1004–1011.
- (47) Aprile, G.; Pandit, A. V.; Albertazzi, J.; Eren, A.; Capellades, G.; Thorat, A. A.; Gamekanda, J.; Vetter, T.; Skovby, T.; Sin, G.; Wu, H.; Dam-Johansen, K.; Myerson, A. S. Loop-configuration for plug flow crystallization process development. *Cryst. Growth Des.* **2023**, *23*, 8052–8064.
- (48) Aprile, G.; Pandit, A. V.; Albertazzi, J.; Vetter, T.; Viano, R.; Milani, L.; Adamo, A.; Myerson, A. S.; Stelzer, T. Residence time distribution characterization and proof-of-concept of a novel stacked 7-stage continuous crystallizer cascade with diaphragm-driven slurry transfer. *Ind. Eng. Chem. Res.* **2024**, *63*, 18199–18211.
- (49) Pal, K.; Radocea, A. Gravity as a Knob for Tuning Particle Size Distributions of Small Molecules. *Cryst. Growth Des.* **2024**, *24*, 2370–2383.
- (50) Stelzer, T.; Lakerveld, R.; Myerson, A. S. Process Intensification in Continuous Crystallization. In *Handbook of Continuous Crystallization*; RSC Publishing: Cambridge, 2020; pp. 266–299.
- (51) Li, J.; Lai, T. T. C.; Trout, B. L.; Myerson, A. S. Continuous crystallization of cyclosporine: Effect of operating conditions on yield and purity. *Cryst. Growth Des.* **2017**, *17*, 1000–1007.
- (52) Mo, Y.; Jensen, K. F. A miniature CSTR Cascade for continuous flow of reactions containing solids. *React. Chem. Eng.* **2016**, *1*, 501–507.
- (53) Blaze Metrics, LLC. *Gen 1 through Gen 2.5 BlazeBasic and BlazePlatform Manual: blaze UI and Office Software 148.03.10*; Quil Ceda Village: WA, USA 2023.
- (54) Pataki, H.; Markovits, I.; Vajna, B.; Nagy, Z. K.; Marosi, G. In-line monitoring of carvedilol crystallization using Raman spectroscopy. *Cryst. Growth Des.* **2012**, *12*, S621–S628.
- (55) Beckmann, W. *Crystallization: basic Concepts and Industrial Applications*; John Wiley & Sons: Hoboken, NJ, 2013.
- (56) Ottoboni, S.; Simurda, M.; Wilson, S.; Irvine, A.; Ramsay, F.; Price, C. J. Understanding effect of filtration and washing on dried product: paracetamol case study. *Powder Technol.* **2020**, *366*, 305–323.
- (57) Wong, S. Y.; Tatusko, A. P.; Trout, B. L.; Myerson, A. S. Development of continuous crystallization processes using a single-stage mixed-suspension, mixed-product removal crystallizer with recycle. *Cryst. Growth Des.* **2012**, *12*, S701–S707.
- (58) Li, J.; Trout, B. L.; Myerson, A. S. Multistage continuous mixed-suspension, mixed-product removal (MSMPR) crystallization with solids recycle. *Org. Process Res. Dev.* **2016**, *20*, S10–S16.
- (59) Cole, K. P.; Campbell, B. M.; Forst, M. B.; McClary Groh, J.; Hess, M.; Johnson, M. D.; Miller, R. D.; Mitchell, D.; Polster, C. S.; Reizman, B. J.; Rosemeyer, M. An automated intermittent flow approach to continuous Suzuki coupling. *Org. Process Res. Dev.* **2016**, *20*, 820–830.
- (60) Remoto, P. I. J.; Bērziņš, K.; Fraser-Miller, S. J.; Korter, T. M.; Rades, T.; Rantanen, J.; Gordon, K. C. Elucidating the dehydration mechanism of nitrofurantoin monohydrate II using low-frequency raman spectroscopy. *Cryst. Growth Des.* **2022**, *22*, 2733–2741.
- (61) Avrami, M. Kinetics of phase change. I. General theory. *J. Chem. Phys.* **1939**, *7*, 1103–1112.
- (62) Avrami, M. Kinetics of phase change. II. Transformation-time relations for random distribution of nuclei. *J. Chem. Phys.* **1940**, *8*, 212–224.
- (63) Avrami, M. Granulation, phase change, and microstructure kinetics of phase change. III. *J. Chem. Phys.* **1941**, *9*, 177–184.
- (64) Joshi, V.; Stowell, J. G.; Byrn, S. R. Solid-state stability of indomethacin solvates. *Mol. Cryst. Liq. Cryst. Sci. Technol. A* **1998**, *313*, 265–270.
- (65) Brittain, H. G. *Polymorphism in Pharmaceutical Solids*; Informa Healthcare: USA, Inc., 2009.
- (66) Ahuja, S.; Scypinski, S. *Handbook of Modern Pharmaceutical Analysis*; Academic Press: Amsterdam, 2011.
- (67) Giron, D. Thermal Analysis and Calorimetric Methods in the Characterisation of Polymorphs and Solvates. *Thermochim. Acta* **1995**, *248*, 1–59.
- (68) Stone, M. L.; Webber, M. S.; Mounfield, W. P.; Bell, D. C.; Christensen, E.; Morais, A. R.; Li, Y.; Anderson, E. M.; Heyne, J. S.; Beckham, G. T.; Román-Leshkov, Y. Continuous Hydrodeoxygenation of lignin to jet-range aromatic hydrocarbons. *Joule* **2022**, *6*, 2324–2337.
- (69) McNair, H. M.; Miller, J. M. *Basic Gas Chromatography*; John Wiley & Sons, Inc.: Hoboken, NJ, 2009.
- (70) Yaseen, G.; Ahmad, M.; Zafar, M.; Akram, A.; Sultana, S.; Kilic, O.; Sonmez, G. D. Current status of solvents used in the pharmaceutical industry. *Green Sustainable Process for Chemical and Environmental Engineering and Science*; Elsevier: Amsterdam. 2021, pp. 195–219.
- (71) Duereh, A.; Sato, Y.; Smith, R. L., Jr; Inomata, H. Methodology for replacing dipolar aprotic solvents used in API processing with safe hydrogen-bond donor and acceptor solvent-pair mixtures. *Org. Process Res. Dev.* **2017**, *21*, 114–124.

- (72) FDA. *Guidance for Industry. Q3C - Tables and List*; 2017. <https://www.fda.gov/downloads/drugs/guidances/ucm073395.pdf> (accessed 3 March 2026).
- (73) Cardew, P. T.; Davey, R. J. The kinetics of solvent-mediated phase transformations. *Proc. R. Soc. London A Math. Phys. Sci.* **1815**, 398, 415–428.
- (74) O'Mahony, M. A.; Maher, A.; Croker, D. M.; Rasmuson, Å. C.; Hodnett, B. K. Examining solution and solid state composition for the solution-mediated polymorphic transformation of carbamazepine and piracetam. *Cryst. Growth Des.* **2012**, 12, 1925–1932.
- (75) Hernández Espinell, J. R.; Toro, V.; Yao, X.; Yu, L.; López-Mejías, V.; Stelzer, T. Solvent-mediated polymorphic transformations in molten polymers: The account of acetaminophen. *Mol. Pharmaceutics* **2022**, 19, 2183–2190.
- (76) American Chemical Society Crystallisation, 4th Edition By J. W. Mullin. 2001. Butterworth Heinemann: Oxford, UK. 600 pp. £75.00. ISBN 075-064-833-3. *Org. Proc. Res. Dev.*, **2002**, 6, 201–202.
- (77) Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. The Cambridge structural database. *Acta Crystallogr.* **2016**, B72, 171–179.
- (78) Cullity, B. D.; Stock, S. R. *Elements of X-Ray Diffraction*, 3rd ed.; Pearson Prentice Hall: Upper Saddle River, NJ, 2001.
- (79) Caira, M. R.; Pienaar, E. W.; Lötter, A. P. Polymorphism and pseudopolymorphism of the antibacterial nitrofurantoin. *Mol. Cryst. Liq. Cryst. Sci. Technol. A* **1996**, 279, 241–264.
- (80) Nagy, Z. K.; Fujiwara, M.; Braatz, R. D. Modelling and control of combined cooling and antisolvent crystallization processes. *J. Process Contr.* **2008**, 18, 856–864.
- (81) Bueno, A.; Viar, N.; Barredo, A.; Gandarias, I.; Requies, J. M. Integrated process for 2,5-furandicarboxylic acid production from fructose via NaCl-promoted dehydration and Au/HT-catalyzed oxidation. *J. Ind. Eng. Chem.* **2025**, 147, 696–704.
- (82) Sheldon, R. A. The E factor: fifteen years on. *Green Chem.* **2007**, 9, 1273–1283.
- (83) Xie, W.; Li, T.; Chen, C.; Wu, H.; Liang, S.; Chang, H.; Liu, B.; Drioli, E.; Wang, Q.; Crittenden, J. C. Using the green solvent dimethyl sulfoxide to replace traditional solvents partly and fabricating PVC/PVC-g-PEGMA blended ultrafiltration membranes with high permeability and rejection. *Ind. Eng. Chem. Res.* **2019**, 58, 6413–6423.
- (84) O'Grady, D.; Barrett, M.; Casey, E.; Glennon, B. The effect of mixing on the metastable zone width and nucleation kinetics in the anti-solvent crystallization of benzoic acid. *Chem. Eng. Res. Des.* **2007**, 85, 945–952.
- (85) Yu, Z. Q.; Tan, R. B. H.; Chow, P. S. Effects of operating conditions on agglomeration and habit of paracetamol crystals in anti-solvent crystallization. *J. Cryst. Growth* **2005**, 279, 477–488.
- (86) O'Mahony, M.; Ferguson, S.; Stelzer, T.; Myerson, A. Separation and Purification in the Continuous Synthesis of Fine Chemicals and Pharmaceuticals. In *Science of Synthesis: Flow Chemistry in Organic Synthesis*; Thieme, 2018, pp. 51–102.
- (87) Yu, X. Y.; Lionberger, R. A.; Raw, A. S.; D'Costa, R.; Wu, H.; Hussain, A. S. Applications of process analytical technology to crystallization processes. *Adv. Drug Delivery Rev.* **2004**, 56, 349–369.
- (88) Feng Báez, J. P.; Soto-Bibiloni, A.; Stelzer, T. Real-Time Monitoring of Crystallization Processes Using a Novel Compact Composite Sensor Array. *Org. Process Res. Dev.* **2023**, 27, 2174–2182.
- (89) Liu, J.; Benyahia, B. Optimal start-up strategies of a combined cooling and antisolvent multistage continuous crystallization process. *Comput. Chem. Eng.* **2022**, 159, 107671.
- (90) Yang, Y.; Nagy, Z. K. Combined cooling and antisolvent crystallization in continuous mixed suspension, mixed product removal cascade crystallizers: Steady-state and startup optimization. *Ind. Eng. Chem. Res.* **2015**, 54, S673–S682.
- (91) Dufour, F.; Stichel, B.; Grayson, J. I. Control of crystal modification and crystal shape by control of solid–solid transitions during crystallization and drying: Two industrial case studies. *Org. Process Res. Dev.* **2013**, 17, S68–S77.
- (92) Cambridge Crystallographic Data Centre. *New Functionality for the Geometry Optimization of Crystal and Molecular Structures*. <https://www.ccdc.cam.ac.uk/discover/blog/new-functionality-for-the-geometry-optimization-of-crystal-and-molecular-structures/> (accessed 26 February 2026).
- (93) Joshi, V.; Morris, K. R.; Byrn, S. R.; Carvajal, M. T. Evaluation of the use of E_a (activation energy) as a quantitative indicator of physical stability of indomethacin solvates: Methanolate and tertiary butyl alcohol solvate. *Cryst. Growth Des.* **2009**, 9, 3359–3366.
- (94) Nordhoff, S.; Ulrich, J. Solvent-induced phase transformations of hydrates. *J. Thermal Anal. Calorim.* **1999**, 57, 181–192.
- (95) Bechtloff, B.; Nordhoff, S.; Ulrich, J. Pseudopolymorphs in industrial use. *Cryst. Res. Technol.* **2001**, 36, 1315–1328.
- (96) Shirzad, K.; Viney, C. A critical review on applications of the Avrami equation beyond materials science. *J. R. Soc. Interface* **2023**, 20, 20230242.
- (97) Chanda, A.; Daly, A. M.; Foley, D. A.; La Pack, M. A.; Mukherjee, S.; Orr, J. D.; Reid, G. L.; Thompson, D. R.; Ward, H. W. Industry perspectives on process analytical technology: tools and applications in API development. *Org. Process Res. Dev.* **2015**, 19, 63–83.
- (98) Hu, Y.; Liang, J. K.; Myerson, A. S.; Taylor, L. S. Crystallization monitoring by Raman spectroscopy: simultaneous measurement of desupersaturation profile and polymorphic form in flufenamic acid systems. *Ind. Eng. Chem. Res.* **2005**, 44, 1233–1240.
- (99) Wang, Y.; Sun, P.; Xu, S.; Du, S.; Zhang, T.; Yu, B.; Zhang, S.; Wang, Y.; Wang, Y.; Gong, J. Solution-mediated phase transformation of argatroban: ternary phase diagram, rate-determining step, and transformation kinetics. *Ind. Eng. Chem. Res.* **2017**, 56, 4539–4548.
- (100) Nguyen, D. L. T.; Kim, K. J. Solvent-mediated polymorphic transformation of α -taltirelin by seeded crystallization. *Chem. Eng. Technol.* **2016**, 39, 1281–1288.
- (101) Pan, B.; Wei, H.; Jiang, J.; Zong, S.; Lv, P.; Dang, L. Solution-mediated polymorphic transformation of CL-20: An approach to prepare purified form ϵ particles. *J. Mol. Liq.* **2018**, 265, 216–225.
- (102) Otsuka, M.; Matsuda, Y. Effect of environmental humidity on the transformation pathway of nitrofurantoin modifications during grinding and the physicochemical properties of ground products. *J. Pharm. Pharmacol.* **1993**, 45, 406–413.
- (103) Rajjada, D.; Arnfast, L.; Bond, A. D.; Aho, J.; Bøtker, J.; Sandler, N.; Rantanen, J. Dehydration of nitrofurantoin monohydrate during melt extrusion. *Cryst. Growth Des.* **2017**, 17, 3707–3715.
- (104) Berzins, A.; Trimdale-Deksne, A.; Belyakov, S.; Ter Horst, J. H. Switching nitrofurantoin polymorphic outcome in solvent-mediated phase transformation and crystallization using solvent and additives. *Cryst. Growth Des.* **2023**, 23, S469–S476.