

Article



Polymorphism and Purification Mechanism of Nicosulfuron

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Abstract: The purification of nicosulfuron from phenol-rich mother liquors is challenged by strong solute-impurity co-solvency, which hinders targeted impurity rejection and stable polymorph control. To address this, empirical solubility correlation (modified Apelblat equation), ternary thermodynamic modeling (NRTL), and molecular dynamics (MD) simulations were integrated with solid-liquid equilibrium and slurry purification studies. Solubility measurements and MD simulations revealed that phenol acts as a potent co-solvent by associating with the nicosulfuron urea bridge via strong hydrogen bonding. Comparative solvent-mediated slurry purifications were conducted to disrupt these interactions. Methanol functioned as a lattice filler, co-crystallizing with the solute to form a metastable hemi-solvate (Form S1) that entrapped residual phenol and transformed into the undesired Form IV during drying. Conversely, ethanol successfully decoupled impurity rejection from phase selection. Energy analysis revealed that ethanol displaced phenol from solute clusters in the liquid phase. Experimental results confirmed the thermodynamic dominance of the anhydrous phase under slurry conditions, inherently preventing impurity-trapping solvate formation. This thermodynamically driven phase-selection mechanism enabled the direct isolation of stable anhydrous Form Ia (>99% purity), establishing a robust strategy for impurity rejection and solid-form manipulation of sulfonylurea herbicides in highly non-ideal industrial systems.

Keywords: nicosulfuron; solubility; thermodynamics; crystallization; molecular dynamics

1. Introduction

Sulfonylurea herbicides (SU), characterized by their specific inhibition of acetolactate synthase (ALS) and low mammalian toxicity, have significantly advanced weed management since their introduction [1–4]. Within this family, nicosulfuron [2-(4,6-dimethoxypyrimidin-2-ylcarbamoylsulfamoyl)-N,N-dimethylnicotinamide] (NS, Figure 1) dominates the post-emergence maize herbicide market, with manufacturing scales escalating to meet the demands of food security and bioethanol production. While nicosulfuron is a cornerstone of global maize protection, its industrial synthesis via the phenyl carbamate route inevitably generates a phenol-rich mother liquor [5]. This creates a challenging thermodynamic environment where strong solute-impurity interactions (i.e., co-solvency) and the molecule's conformational flexibility hinder the nucleation of the thermodynamically stable anhydrous



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form (Form Ia) [6–8]. For advanced formulations like oil-based dispersions (OD), strict specifications on chemical purity (>98%) and phase stability are critical to prevent Ostwald ripening and sedimentation [9–11]. Consequently, the central scientific challenge lies in achieving the simultaneous control of high purity and the stable polymorphic form in such impurity-dominated systems.

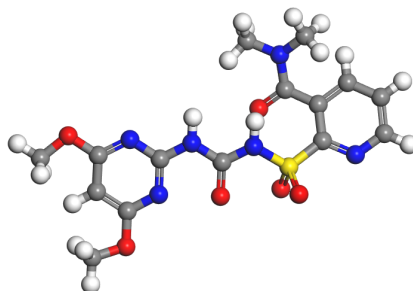


Figure 1. Nicosulfuron molecular structural formula. Atom colors: C (gray), H (white), N (blue), O (red), and S (yellow). Adapted from PubChem.

Industrial crystallization processes often require careful process design to balance product quality, yield, and robustness under kinetic uncertainties [12]. Current industrial processes typically recover crude nicosulfuron via evaporative crystallization, followed by methanol washing to exploit the high solubility of phenol. However, this approach is limited by specific solvent-solute interactions. The strong affinity of methanol for nicosulfuron thermodynamically favors the formation of a methanol hemi-solvate (Form S1) [13], preventing the nucleation of the desired anhydrous Form Ia. This solvated phase represents a critical processing bottleneck with a twofold disadvantage. First, structurally, the rapid formation of the methanol solvate induces severe crystal agglomeration, facilitating the physical entrapment of residual phenol-rich mother liquor at the mesoscopic level, rather than direct lattice incorporation. Second, thermodynamically, this solvate is prone to uncontrolled desolvation into the structurally defective Form IV during downstream drying, which further encapsulates the residual impurities. Industrial processes typically rely on a multi-step isolation strategy, in which a crude product is first isolated and subsequently recrystallized. However, a more sustainable approach would ideally combine impurity rejection and direct formation of the stable polymorph (Form Ia) within a single purification step. The conventional methanol washing strategy fails to meet either of these operational objectives efficiently.

During solution crystallization, impurities can be retained in the final solid product through several well-established theoretical mechanisms, primarily including surface adsorption, mother liquor entrapment (liquid inclusions), and direct incorporation into the crystal lattice to form solid solutions [14,15]. To address these retention challenges, leveraging specific crystal forms—such as polymorphs or solvates—to selectively purge structure-related organic impurities has become a routine and highly effective approach in industrial crystallization [16]. Furthermore, the intricate relationship between polymorphism and impurity incorporation, particularly how the formation of solid solutions or solvate channels shifts polymorphic thermodynamic stability and alters final purity, has been extensively documented in recent literature [17–19].

While previous studies have extensively documented the structural characteristics of nicosulfuron polymorphs and the solid-state desolvation pathways of isolated solvates [8,13], a critical research gap remains regarding the dynamic interplay between strong liquid-phase solute-impurity interactions and solid-state polymorphic selection in highly non-ideal industrial environments. Prior investigations primarily focused on pure solvent systems or isolated phase transitions, largely overlooking the potent anchoring effect of interacting impurities like phenol. The novelty of this work lies in shifting the focus from conventional polymorphic characterization to a dynamic, mechanism-based disruption strategy. By integrating macroscopic thermodynamic modeling with microscopic molecular dynamics, we systematically elucidate how specific solvent choices can competitively decouple strong solute-impurity associations in the liquid phase, thereby actively manipulating the thermodynamic phase-selection pathway to achieve simultaneous deep purification and stable polymorph control.

However, for complex sulfonyleurea herbicides characterized by strong solute-impurity co-solvency (such as the nicosulfuron-phenol system), the molecular mechanisms dictating how specific solvent choices can actively disrupt these interactions remain challenging. Specifically, while macroscopic purification strategies exist, the microscopic mechanism governing how solvent steric exclusion synergizes with phase selection to circumvent specific impurity entrapment within solvate channels has not been systematically elucidated.

Here, we address this limitation by integrating thermodynamic modeling and molecular dynamics (MD) simulations to establish a mechanism-based crystallization strategy. By moving beyond macroscopic solubility

considerations, we reveal a competitive mechanism where ethanol acts as a competitive displacer for phenol in the liquid phase. Based on these molecular mechanisms, we demonstrate an ethanol-mediated slurry purification process that bypasses metastable solvate formation via strict thermodynamic control, enabling the direct crystallization of high-purity stable Form Ia.

2. Experimental Section

2.1. Materials

High-purity nicosulfuron standard (mass fraction purity 99.9%) was obtained from Tanmo Quality Inspection-Reference Materials Center (Changzhou, China) and used exclusively for High-Performance Liquid Chromatography (HPLC) calibration. Technical-grade nicosulfuron used for crystallization experiments was synthesized in-house via the condensation of phenyl carbamate and 2-amino-4,6-dimethoxypyrimidine. Quantitative HPLC analysis indicated a purity of approximately 95 wt%, with phenol identified as the dominant impurity alongside minor organic byproducts. Analytical grade solvents, including dichloromethane (DCM, >99.5%), methanol (>99.7%), and ethanol (>99.7%), as well as phenol (>98.0%), were purchased from Aladdin Reagents (Shanghai, China). All chemicals were used as received without further purification.

2.2. Solubility Measurement

The solubility of nicosulfuron in binary (DCM + phenol) systems was determined using the isothermal saturation method over the temperature range from 293.15 to 313.15 K under atmospheric pressure.

Experiments were conducted in a 100 mL jacketed glass vessel equipped with a magnetic stirrer and connected to a high-precision thermostatic bath (Huber, Germany), which controlled the temperature with a standard uncertainty of $u(T) = 0.05$ K. In a typical run, an excess amount of nicosulfuron was added to the prepared solvent mixture and agitated at 400 rpm for 12 h to ensure that the system reached solid-liquid thermodynamic equilibrium. Then the agitation was stopped, and the suspension was allowed to settle for 4 h under isothermal conditions to ensure the complete sedimentation of fine particles. The supernatant was then withdrawn using a PTFE syringe filter (0.22 μ m pore size) that was preheated to approximately 5–10 K above the experimental temperature. This preheating step was strictly implemented to prevent premature precipitation caused by local cooling during sampling. The filtrate was immediately weighed, diluted with mobile phase, and the solute concentration was quantified by HPLC (analysis details in Section 2.4). To ensure high analytical precision, each solubility sample was analyzed via triplicate HPLC injections. The solubility values reported in this study represent the calculated averages of these analytical replicates, with the relative standard deviation (RSD) controlled within 5% across all temperature and solvent conditions.

2.3. Crystallization and Purification Procedures

The crystallization experiments utilized the nicosulfuron reaction mixture synthesized in dichloromethane (DCM) at 50 °C. The mixture was first concentrated under reduced pressure to obtain a phenol-rich mother liquor, which corresponds to a saturated solution of nicosulfuron at 50 °C. Subsequently, the mother liquor was evaporated to dryness via evaporative crystallization to isolate the crude nicosulfuron solid.

To comprehensively investigate the impurity rejection mechanism and decouple the thermodynamic solvent effects from kinetic crystallization factors, the isolated crude solid was subjected to two distinct process pathways. The primary approach utilized a thermodynamically controlled slurry process. The crude solid was slurried with either methanol (representing the conventional industrial washing protocol) or ethanol at a constant liquid-to-solid ratio of 3:1 (w/w). Both processes were conducted strictly at ambient temperature under constant agitation for 1 h to ensure sufficient time for thermodynamic phase equilibration and structural rearrangement. For comparison, a kinetically driven anti-solvent crystallization was performed as a control group. In this setup, methanol or ethanol was rapidly added as an anti-solvent directly to the concentrated phenol-rich mother liquor at ambient temperature to intentionally generate a high initial supersaturation and induce rapid precipitation.

Following these treatments, the final wet solids from all processes were collected by vacuum filtration. To precisely track solvent entrapment, desolvation behavior, and phase stability, the recovered wet cakes were subjected to stepwise vacuum drying at 40 °C and 80 °C. Samples were systematically withdrawn at these thermal stages for subsequent thermogravimetric and solid-state phase analyses. Separately, product recovery was evaluated in pilot-scale trials, yielding approximately 88.8% for the conventional methanol washing process and approximately 85.3% for the ethanol-mediated slurry process.

2.4. Analytical Methods

Solid-state characterization and chemical purity analyses were performed to monitor the crystallization process. The polymorphic forms were identified by Powder X-ray Diffraction (PXRD) using a Rigaku SmartLab 9 kW diffractometer (Rigaku, Tokyo, Japan) with Cu K α radiation ($\lambda = 1.5406 \text{ \AA}$) over a 2θ range of 5° to 40° at a scanning speed of $8^\circ/\text{min}$. Thermal behavior was analyzed using a Mettler Toledo TGA/DSC1 system (Switzerland): samples (3–5 mg) were heated from 30 to 200°C at $10^\circ\text{C}/\text{min}$ under a nitrogen purge ($50 \text{ mL}/\text{min}$). Crystal morphology was examined using a JEOL JSM-7001F Scanning Electron Microscope (JEOL, Tokyo, Japan) at an accelerating voltage of 5 kV, with samples sputter-coated with gold prior to imaging. The chemical purity of the nicosulfuron product was determined by HPLC using a Shimadzu LC-20A system equipped with a ShimNex CS C18 column. The quantitative analysis was conducted in accordance with established standard testing methods for the nicosulfuron active ingredient. The analysis employed isocratic elution with acetonitrile: water (60:40 v/v, pH 3.0 adjusted with acetic acid) at a flow rate of $1.0 \text{ mL}/\text{min}$ and detection at 240 nm. Linearity was verified over 100–1000 mg/L ($R^2 > 0.999$).

3. Theoretical and Computational Framework

3.1. Thermodynamic Modeling of Solubility

To quantitatively evaluate the specific thermodynamic interactions induced by the phenol impurity and provide a robust mathematical basis for process design, the solid-liquid equilibrium (SLE) data were systematically correlated.

First, the semi-empirical modified Apelblat equation was employed to rigorously evaluate the macroscopic temperature-dependent solubility. The model is expressed as:

$$\ln x_1 = A + \frac{B}{T} + C \ln T \quad (1)$$

where x_1 represents the mole fraction solubility of nicosulfuron, T is the absolute temperature, and A , B , and C are the empirical model parameters obtained by non-linear regression.

While the modified Apelblat equation offers excellent mathematical correlation for industrial application, it inherently lacks the capacity to elucidate microscopic solvation mechanisms. Therefore, the local composition-based Non-Random Two-Liquid (NRTL) activity coefficient model was subsequently applied to provide fundamental insights into the specific molecular interactions (Δg_{ij}) within the multi-component environment. The general solid-liquid equilibrium (SLE) relates the solubility to the fugacity ratio, which includes the heat capacity difference (ΔC_p) between the supercooled melt and the solid phase [20]. By assuming the heat capacity difference (ΔC_p) is negligible over the relatively narrow temperature window investigated (293.15 to 313.15 K), the practical SLE equation used within the NRTL framework is expressed as:

$$\ln x_i = \frac{\Delta_{fus}H}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) - \ln \gamma_i \quad (2)$$

where $\Delta_{fus}H$ and T_m are the enthalpy of fusion and melting temperature of nicosulfuron, respectively (determined in this work by DSC as $\Delta_{fus}H = 28.73 \text{ kJ}/\text{mol}$ and $T_m = 460.15 \text{ K}$), and R is the universal gas constant. By rigorously treating the system as a ternary mixture (solute + solvent + co-solvent impurity), the activity coefficient γ_i is defined by the multi-component NRTL equations:

$$\ln \gamma_i = \frac{\sum_j \tau_{ji} G_{ji} x_j}{\sum_k G_{ki} x_k} + \sum_j \frac{G_{ij} x_j}{\sum_k G_{kj} x_k} \left(\tau_{ij} - \frac{\sum_l \tau_{lj} G_{lj} x_l}{\sum_k G_{kj} x_k} \right) \quad (3)$$

$$G_{ij} = \exp(-\alpha_{ij} \tau_{ij}) \quad (4)$$

$$\tau_{ij} = \frac{g_{ij} - g_{jj}}{RT} = \frac{\Delta g_{ij}}{RT} \quad (5)$$

$$\alpha_{ij} = \alpha_{ji} \quad i, j = 1, 2, 3 \quad (6)$$

The goodness of fit for the model was evaluated using the relative average deviation (*RAD*) and root-mean-square deviation (*RMSD*). These statistical metrics ensure the reliability of the regressed parameters for process design:

$$RAD = \frac{1}{N} \sum_{i=1}^N \left| \frac{x_{1,exp} - x_{1,cal}}{x_{1,exp}} \right| \quad (7)$$

$$RMSD = \sqrt{\frac{1}{N} \sum_{i=1}^N (x_{1,exp} - x_{1,cal})^2} \quad (8)$$

where N is the number of experimental data points, and $x_{1,exp}$ and $x_{1,cal}$ refer to the experimental and calculated mole fraction solubility, respectively.

3.2. Molecular Dynamics Simulation

Microscopic solvation environments and competitive interactions were investigated using molecular dynamics simulations. The COMPASS force field [21], previously applied to related molecular systems [22,23], was used in cubic simulation boxes under periodic boundary conditions. Each system contained 10 nicosulfuron molecules, 10 phenol molecules, and 200 solvent molecules (dichloromethane, methanol, or ethanol). This composition enabled sampling of finite-concentration solute–impurity associations. Initial box densities were set according to the experimental bulk densities of the corresponding solvent systems. After energy minimization, the DCM and methanol systems were equilibrated in the NPT ensemble at 298.15 K and 1.0 bar for 2.0 ns, whereas the ethanol system was equilibrated for 1.0 ns. Temperature and pressure were controlled using the Nosé–Hoover thermostat and Berendsen barostat, respectively. Each system then underwent a 5.0 ns NVT production run with a 1.0 fs time step. Stable density and potential-energy profiles (Figure 2) supported subsequent RDF and interaction-energy analyses. Electrostatic interactions were treated using Ewald summation, with a 12.5 Å cutoff for van der Waals interactions. RDFs and interaction energies (E_{int}) were averaged over the production trajectory. The interaction energy was defined as:

$$E_{int}^{A-B} = E_{A+B} - (E_A + E_B) \quad (9)$$

where A and B denote the selected component pair (solute-phenol or solvent-phenol), E_{A+B} is the potential energy of the combined pair, and E_A and E_B are the potential energies of the isolated components in the same configuration. Accordingly, the absolute values of interaction energies are not intended to represent individual hydrogen bond strengths but are used comparatively to evaluate competitive association tendencies across different solvent environments.

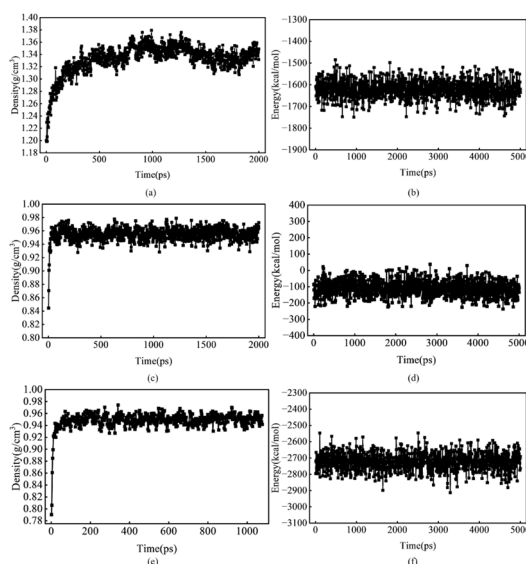


Figure 2. Convergence profiles during molecular dynamics simulations of the ternary systems (nicosulfuron + phenol + solvent): density evolution during the NPT equilibration phase for (a) DCM (2.0 ns), (c) methanol (2.0 ns), and (e) ethanol (1.0 ns), and potential-energy fluctuations during the 5.0 ns NVT production phase for (b) DCM, (d) methanol, and (f) ethanol. The density profiles reached stable plateaus during the equilibration stage, while the potential energies fluctuated around stable mean values without systematic drift during the production runs, supporting the use of the trajectories for subsequent RDF and interaction-energy analyses.

4. Results and Discussion

4.1. Solubility Analysis and Thermodynamic Modeling

4.1.1. Solubility and Model Correlation

The solubility of nicosulfuron was systematically measured in the binary (dichloromethane + phenol) system using the isothermal saturation method. The experiments were conducted over a temperature range from 293.15 to 313.15 K. The detailed experimental solubility data, expressed as mole fraction (x_1), are presented for phenol mass fractions of 0%, 5%, 10%, and 15%.

As shown in Table 1, the solubility of nicosulfuron exhibits a positive correlation with temperature in both pure dichloromethane and phenol-doped solutions. Furthermore, a significant co-solvency effect is observed: at any given temperature, the solubility increases drastically with the rising phenol concentration. For instance, increasing the phenol mass fraction from 0% to 15% results in a nearly 3-fold increase in nicosulfuron solubility at 298.15 K. Thermodynamically, this pronounced solubility enhancement indicates strong non-ideal intermolecular interactions between the solute and the phenol impurity in the liquid phase. We hypothesize that phenol acts as a strong co-solvent by deeply participating in the solute's primary solvation shell; this microstructural hypothesis will be explicitly validated at the molecular level using molecular dynamics simulations in Section 4.2. Consequently, the observed solubility enhancement is considered strictly a liquid-phase co-solvency phenomenon.

Table 1. Experimental mole fraction solubility (x_1) of nicosulfuron in binary (dichloromethane + phenol) solvent mixtures at varying temperatures (T) under atmospheric pressure ($p = 0.1$ MPa).

Phenol Content/%	T/K	$10^3 x_1^{\text{exp}}$	$10^3 x_1^{\text{APELBLAT}}$	$10^3 x_1^{\text{NRTL}}$
0	293.15	13.64	13.63	11.14
	298.15	14.16	14.19	11.85
	303.15	15.18	15.15	13.88
	308.15	16.53	16.54	17.05
	313.15	18.46	18.46	22.4
5	293.15	31.64	31.69	26.72
	298.15	33.88	33.81	30.48
	303.15	36.74	36.67	35.09
	308.15	40.22	40.37	40.72
	313.15	45.12	45.06	48.1
10	293.15	35.21	35.29	33.27
	298.15	37.93	37.84	37.33
	303.15	41.36	41.19	41.98
	308.15	45.20	45.49	47.25
	313.15	51.01	50.9	53.63
15	293.15	38.66	38.74	39.24
	298.15	43.18	43.09	43.72
	303.15	48.36	48.24	48.66
	308.15	54.09	54.32	54.13
	313.15	61.59	61.5	60.17

Notes: x_1^{exp} denotes the mean experimental mole-fraction solubility obtained from triplicate HPLC injections of each equilibrated sample ($\text{RSD} \leq 5\%$; see Section 2.2). x_1^{APELBLAT} and x_1^{NRTL} denote values calculated using the modified Apelblat and NRTL models, respectively. Phenol content refers to the mass fraction of phenol in the DCM + phenol mixture before solute addition; temperature standard uncertainty $u(T) = 0.05$ K.

As illustrated in Figure 3, the solubility profiles exhibit a pronounced exponential dependence on temperature across all solvent compositions. The excellent agreement between the experimental data points (symbols) and the continuous Apelblat model curves (solid lines) visually confirms the exceptional accuracy of the empirical correlation. Crucially, the curves do not intersect at any point within the studied temperature range, demonstrating a consistent thermodynamic co-solvency effect where the incorporation of phenol monotonically enhances the solubility capacity of the bulk solution without inducing complex solvent-solute phase transitions.

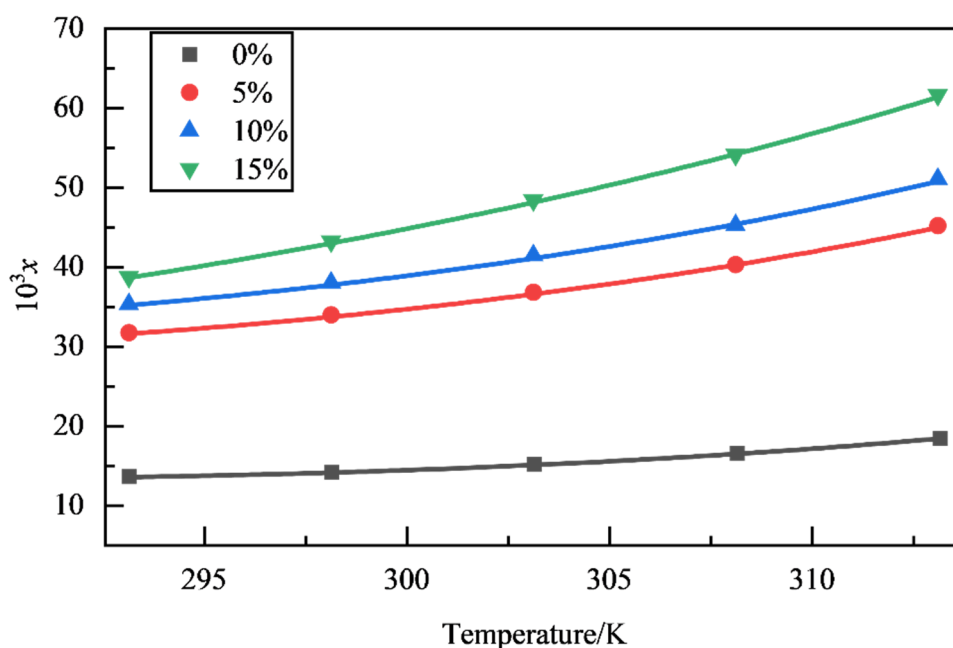


Figure 3. Mole fraction solubility (10^3x) of nicosulfuron in (dichloromethane + phenol) mixtures. The symbols represent the experimental measurements, and the solid lines represent the values calculated by the modified Apelblat equation. Error bars representing the standard deviation of the analytical replicates are omitted because they are smaller than the symbol size. The pronounced increase in solubility with increasing phenol content indicates a strong liquid-phase co-solvency effect.

To provide a robust mathematical basis for industrial crystallization design, the experimental solubility data were initially correlated using the empirical modified Apelblat equation. As summarized in Table 2, this model delivered an exceptional mathematical fit across all evaluated temperatures and concentrations. The regressed parameters (A , B , C) exhibited a smooth, monotonic dependency on the phenol concentration, yielding highly accurate correlation curves (plotted as solid lines in Figure 3) with a maximum relative average deviation (RAD) of merely 0.34%. Concurrently, to move beyond empirical fitting and extract physically meaningful insights into the co-solvency effect, the macroscopic thermodynamics were further evaluated using the NRTL model. The regressed ternary NRTL binary interaction parameters are summarized in Table 3, while the corresponding model deviations at different phenol contents are reported in Table 4.

Table 2. Regressed empirical parameters (A , B , C) of the modified Apelblat equation and corresponding statistical deviations (RAD, RMSD) for nicosulfuron solubility in (dichloromethane + phenol) mixtures.

Phenol Content/%	A	B	C	RAD/%	10^5 RMSD
0%	−629.99	27,052.64	93.90	0.12	2.19
5%	−440.64	18,357.77	65.94	0.21	8.51
10%	−423.80	17,547.94	63.48	0.34	16.58
15%	−236.20	8714.76	35.77	0.25	13.36

Notes: A , B , and C are the fitted parameters of the modified Apelblat equation, $\ln x_1 = A + B/T + C \ln T$. RAD is the relative average deviation and RMSD is the root-mean-square deviation, calculated according to Equations (7) and (8). $N = 5$ for each solvent composition.

Table 3. Regressed ternary NRTL binary interaction parameters (Δg_{ij}) for the nicosulfuron (1) + dichloromethane (2) + phenol (3) ternary system.

Interaction Pair (i–j)	Parameter	Value/(J·mol ^{−1})
Solute (1)—DCM (2)	Δg_{12}	−3627.74
	Δg_{21}	38,380.60
Solute (1)—Phenol (3)	Δg_{13}	21,797.61
	Δg_{31}	133.85
DCM (2)—Phenol (3)	Δg_{23}	48,741.30
	Δg_{32}	13,220.06

Notes: The non-randomness parameter α was fixed at 0.3.

Table 4. Relative average deviation (RAD) and root-mean-square deviation (RMSD) for the ternary NRTL model correlation of nicosulfuron solubility across varying phenol mass fractions.

Phenol Content/%	RAD/%	10 ³ RMSD
0%	13.52	2.41
5%	7.58	3.09
10%	3.65	1.76
15%	1.15	0.74

Notes: RAD and RMSD quantify deviations between experimental and NRTL-calculated mole-fraction solubilities. The metrics are defined by Equations (7) and (8). Values are reported separately for each nominal phenol mass fraction to show the composition dependence of model performance.

The ternary NRTL model captures the overall composition-dependent solubility trend, although its quantitative accuracy varies among the solvent compositions. The deviations decrease markedly with increasing phenol content, from a RAD of 13.52% in phenol-free DCM to 1.15% at 15 wt% phenol. Accordingly, the NRTL results are used primarily to describe the non-ideal composition dependence of the liquid phase rather than as a uniformly high-accuracy correlation across all subsystems. The modified Apelblat equation remains the more accurate empirical correlation for the individual temperature-dependent solubility curves.

4.1.2. Thermodynamic Limitations of Cooling Crystallization

The observed co-solvency behavior imposes a strict limitation on the efficiency of the conventional cooling crystallization process. As indicated by the solubility data, the phenol-induced enhancement of nicosulfuron solubility maintains a relatively high dissolved concentration of nicosulfuron even at lower temperatures. Here, the 4 wt% phenol condition in the DCM/phenol solvent mixture was estimated by linear interpolation between the 0 and 5 wt% data in Table 1. This interpolation gave $x_1 = 0.03979$ at 313.15 K and $x_1 = 0.02804$ at 293.15 K. The solute mass was calculated using $n_1 = [x_1 / (1 - x_1)] n_{\text{solv}}$ and $m_1 = n_1 M_1$, where $n_{\text{solv}} = m_{\text{solv}} (0.96/M_{\text{DCM}} + 0.04/M_{\text{phenol}})$. Here, n_{solv} and m_{solv} denote the amount and mass of the solvent mixture, respectively, while M_{DCM} and M_{phenol} denote the molar masses of DCM and phenol. Using 1.000 kg of saturated solution at 313.15 K as the initial basis, the solution contained 166.3 g of nicosulfuron and 833.7 g of the DCM/phenol solvent mixture. Assuming no solvent loss during cooling, the solvent mass remained fixed at 833.7 g. At 293.15 K, $x_1 = 0.02804$ therefore corresponded to 115.8 g of nicosulfuron remaining in solution. Consequently, 50.5 g of nicosulfuron could theoretically crystallize, giving a maximum theoretical recovery of $(166.3 - 115.8)/166.3 \times 100\% = 30.4\%$. Therefore, cooling crystallization is not a feasible strategy for high-yield recovery in this system. While anti-solvent crystallization could theoretically serve as an alternative to force precipitation and overcome this co-solvency effect, introducing a third solvent into this highly interacting solute-impurity environment often triggers intense and uncontrollable kinetic driving forces. For instance, as detailed later in Section 4.3.2, rapid supersaturation generated by anti-solvent addition (e.g., using ethanol) kinetically traps the solute into a metastable solvated phase (Form S2) rather than the desired stable polymorph.

To achieve a high product yield and eliminate the interference of complex phase-selection kinetics, evaporative crystallization was selected as the most robust baseline method to quantitatively isolate the crude solid. This decoupled two-step strategy allows the subsequent solvent-mediated slurry purification to proceed under near-equilibrium conditions that favor thermodynamically controlled phase transformation.

4.2. Molecular Mechanism of Impurity Rejection

4.2.1. The Anchoring Effect of Phenol in Reaction Solvent

To unravel the microscopic origin of impurity retention and solvent-impurity competition, molecular dynamics simulations were performed to quantify the intermolecular interactions in the ternary systems.

The specific solute-impurity association sites and their retention mechanisms were quantified via RDF analysis. In the DCM-based system, the RDF between the carbonyl oxygen of nicosulfuron and the hydroxyl hydrogen of phenol (Figure 4) exhibits a sharp, intense peak at $r = 1.73 \text{ \AA}$ with a remarkable intensity of $g(r) \approx 33.6$, providing direct structural evidence for the strong solute-impurity association proposed in the thermodynamic modeling. This specific interaction is stabilized by a cumulative interaction energy of -112.9 kcal/mol . It is important to note that this value represents the total interaction energy of the 10-molecule impurity ensemble. This corresponds to an average driving force of approximately -11.3 kcal/mol per phenol molecule, which is consistent with the formation of strong, directional hydrogen bonds ($\text{O}_{\text{urea}} \cdots \text{H}_{\text{phenol}}$) as indicated by the RDF analysis. This

strong “anchoring” effect effectively masks the polar urea bridge of nicosulfuron, increasing its solubility in the hydrophobic DCM significantly and inhibiting the nucleation of the pure phase.

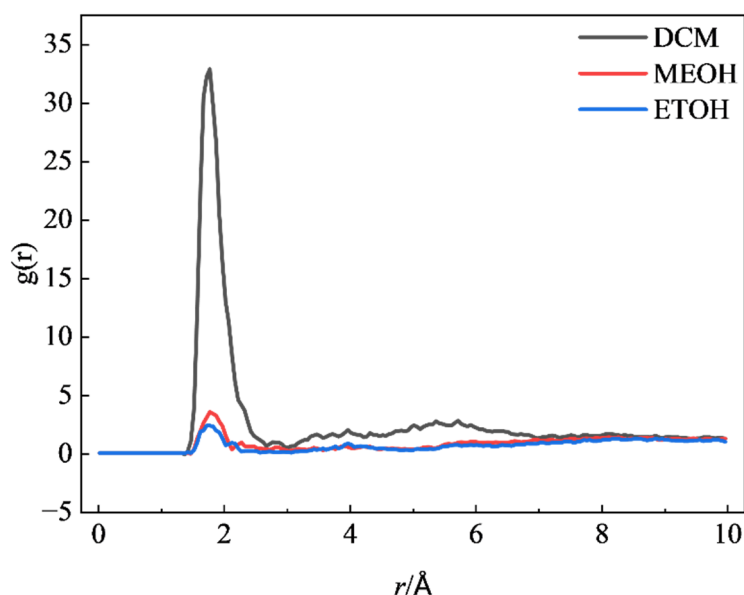


Figure 4. RDF plot of the carbonyl oxygen on the sulfonylurea bridge and the hydroxyl hydrogen on the phenol. The pronounced RDF peak in DCM indicates strong solute–phenol association, whereas the substantially reduced peak intensity in methanol and ethanol indicates weakened association in protic solvents.

4.2.2. Competitive Displacement by Alcohols

Upon the introduction of alcoholic solvents, the solvation landscape undergoes a fundamental shift. As evidenced in Figure 4, the characteristic solute–impurity peak intensity drops precipitously from 33.6 (in DCM) to 3.5 in methanol and 3.2 in ethanol. This distinct order-of-magnitude reduction strongly suggests that the phenol molecules can be effectively “stripped” from the nicosulfuron surface by the protic solvents. As further confirmation, the RDF plots for the solvent–phenol systems (Figure 5) exhibit sharp peaks corresponding to strong hydrogen bonding between the alcohol hydroxyl group and the phenol oxygen.

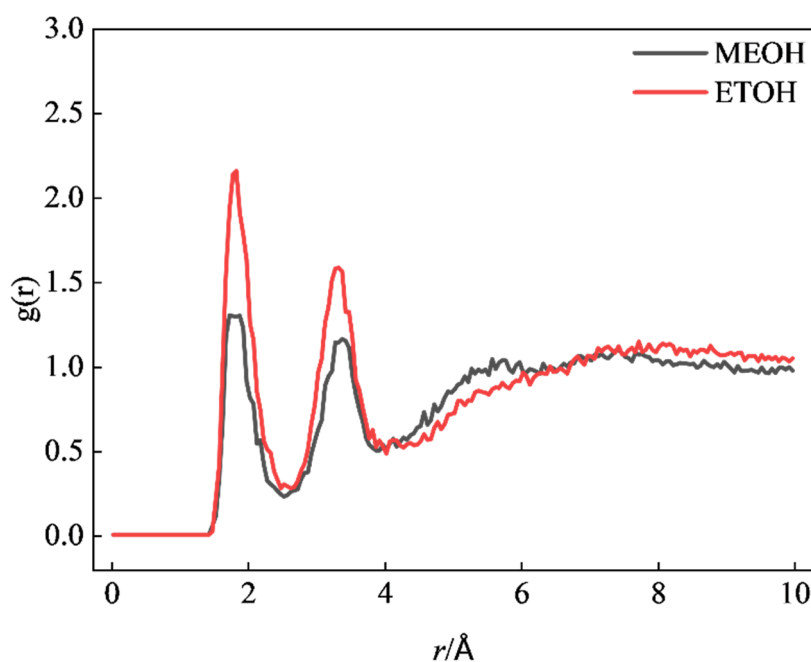


Figure 5. RDF plot of the oxygen on the phenol and the hydroxyl hydrogen on the alcohol. The pronounced RDF peaks indicate strong association between phenol and both alcohol solvents, supporting their potential role in disrupting solute–phenol interactions.

Energy analysis reveals the thermodynamic driving force behind this displacement. The interaction energy between the solvent and impurity ($E_{\text{solvent-phenol}}$) was calculated to be -185.0 kcal/mol for methanol and -188.6 kcal/mol for ethanol. These values indicate that, at the cluster level, alcohol–phenol associations are thermodynamically favored over solute–phenol associations ($E_{\text{solute-phenol}} = -112.9$ kcal/mol). This implies that the strong interaction between alcohol solvents and phenol is energetically favored over its association with the nicosulfuron solute.

Crucially, while both alcohols exhibit similar thermodynamic “stripping” capabilities (with E_{int} values of -185.0 vs. -188.6 kcal/mol), their impact on crystal growth differs fundamentally. This divergence in the final solid-state outcome is not governed merely by static steric exclusion. Instead, it is strongly influenced by the macroscopic thermodynamic phase-selection mechanisms specific to each solvent environment. These mechanisms are systematically discussed in the following section.

4.2.3. Thermodynamic Phase Selection vs. Kinetic Solvation Control

While the MD simulations confirm that both methanol and ethanol can successfully disrupt solute–impurity associations in the liquid phase, the ultimate phase purity is governed by the interplay between thermodynamic phase selection and kinetic control during solid-state reorganization.

As will be validated by the subsequent experimental results, methanol molecules act as “guest molecules”. They easily intercalate into the growing lattice to stabilize a solvated phase (Form S1) via host–guest hydrogen bonding. The rapid formation of this metastable solvate creates a deep kinetic trap at the mesoscopic level: it induces severe crystal agglomeration and structural defects, which exacerbate the retention of residual phenol and solvent within the crystal boundaries and surface crevices.

In contrast, the ethanol-mediated process operates under a distinctly different phase-selection mechanism. While an ethanol solvate (Form S2) can theoretically be induced under extreme kinetic driving forces (e.g., rapid anti-solvent addition), the mild, thermodynamically controlled conditions of the slurry process allow the system to bypass this kinetically trapped intermediate. Consequently, the ethanol-mediated process operates through a synergistic purification mechanism: ethanol disrupts phenol–solute associations in the liquid phase, as supported by the MD results, while the slurry conditions favor structural reorganization toward the thermodynamically stable anhydrous Form Ia. This combined effect promotes the exclusion of phenol and ethanol from the solid phase and their retention in the mother liquor, thereby favoring the formation of high-purity Form Ia under the tested conditions.

4.3. Experimental Validation of Purification

4.3.1. Purification Efficiency and Impurity Rejection

The purification efficiency of the two post-crystallization treatments was quantified by HPLC. Starting from the crude solid (initial purity of approximately 95.0 wt%), the experimental results revealed that the choice of solvent had a decisive impact on the final product purity.

The conventional methanol washing failed to achieve deep purification, with the product purity plateauing at merely $96.3\% \pm 0.1\%$ ($n = 3$). This limitation aligns with the structural insights: methanol molecules act as guest molecules that stabilize the channel solvate (Form S1). Consequently, instead of effectively purging impurities, the methanol-mediated transition into the solvated phase (Form S1) exacerbates impurity retention. As supported by the subsequent morphological analysis, the resulting crystals exhibit an irregular, agglomerate habit with numerous grain boundaries and structural defects. These mesoscopic features facilitate the retention of residual phenol through liquid inclusions and surface entrapment, consistent with the mesoscopic trapping mechanism established in Section 4.2.

Conversely, the ethanol-mediated slurry purification successfully broke this bottleneck, directly yielding highly pure nicosulfuron crystals with a final purity of $99.1\% \pm 0.1\%$ ($n = 3$). We note that the ethanol-mediated process affords a modestly lower product recovery (85.3%) than the conventional methanol process (88.8%), accompanied by a substantial improvement in product purity from 96.3% to 99.1%. An independent two-sample t-test confirmed that this purity enhancement is statistically significant ($p < 0.01$). This significant macroscopic enhancement is highly consistent with the proposed thermodynamic phase selection mechanism. By strictly operating under thermodynamic equilibrium, the ethanol-mediated process circumvents the formation of an impurity-trapping solvate structure. By circumventing the solvate-mediated mesoscopic entrapment, the process thermodynamically drives the crystallization pathway towards the stable anhydrous Form Ia.

4.3.2. Polymorphic Identification and Stability Analysis

Figure 6 presents the experimental PXRD patterns of the solid products obtained from the different purification protocols. Phase assignments were made by comparing the experimental diffractograms with reference PXRD patterns reported in the literature for nicosulfuron polymorphs and solvates [8,13]. The diffractogram of the solid obtained via conventional methanol washing exhibits characteristic reflections matching the standard pattern of the methanol hemi-solvate (Form S1) [13]. In stark contrast, the solid prepared via the thermodynamically controlled ethanol-mediated slurry displays a diffraction pattern consistent with the thermodynamically stable anhydrous Form Ia. Additionally, the metastable phase obtained upon thermal desolvation of the methanol solvate is assigned as Form IV, as its diffraction pattern is consistent with the desolvated phase previously reported in the literature [8].

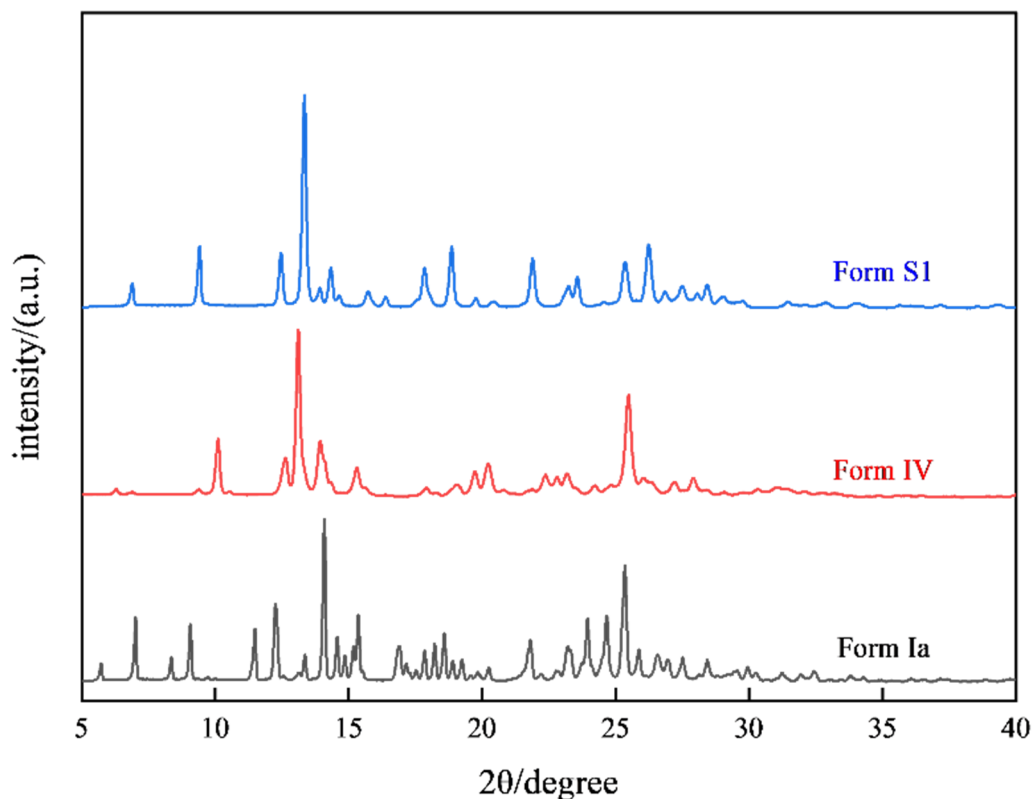


Figure 6. Experimental PXRD patterns of nicosulfuron products: Form S1 obtained via methanol washing, Form IV derived from drying Form S1, and Form Ia obtained via ethanol-mediated slurry. The patterns identify Form S1 after methanol washing, Form IV after drying of the methanol-derived solid, and anhydrous Form Ia after ethanol-mediated slurry treatment.

To elucidate the underlying phase transformation mechanisms and solvent retention behaviors, a comprehensive thermal analysis was conducted using the TGA-DSC profiles. As shown in Figure 7 (the combined thermal profiles of the methanol system), the methanol-mediated process exhibits an inescapable kinetic trap. Regardless of whether the crystallization is driven by intense kinetic forces (anti-solvent addition) or proceeds under mild thermodynamic equilibrium (slurry process), the system invariably crystallizes into the metastable Form S1. The 40 °C-dried samples shown in Figure 7a,b display a characteristic solvent-loss step and a desolvation-related endothermic event at approximately 130–140 °C. In contrast, this distinct desolvation event is absent from the fully desolvated 80 °C-dried samples shown in Figure 7c,d, consistent with prior solvent removal during drying. For the pure nicosulfuron methanol hemi-solvate (Form S1), the theoretical methanol content corresponds to a weight loss of approximately 3.76%. In comparison, the TGA profile of the methanol-slurry product (Figure 7a) shows a total weight loss of approximately 4.5%. The excess weight loss suggests the presence of additional physically retained solvent, which is consistent with the proposed mesoscopic trapping of residual mother liquor within the agglomerated solid. The subsequent structural rearrangement of Form S1 into Form IV during drying is supported by the PXRD results shown in Figure 8.

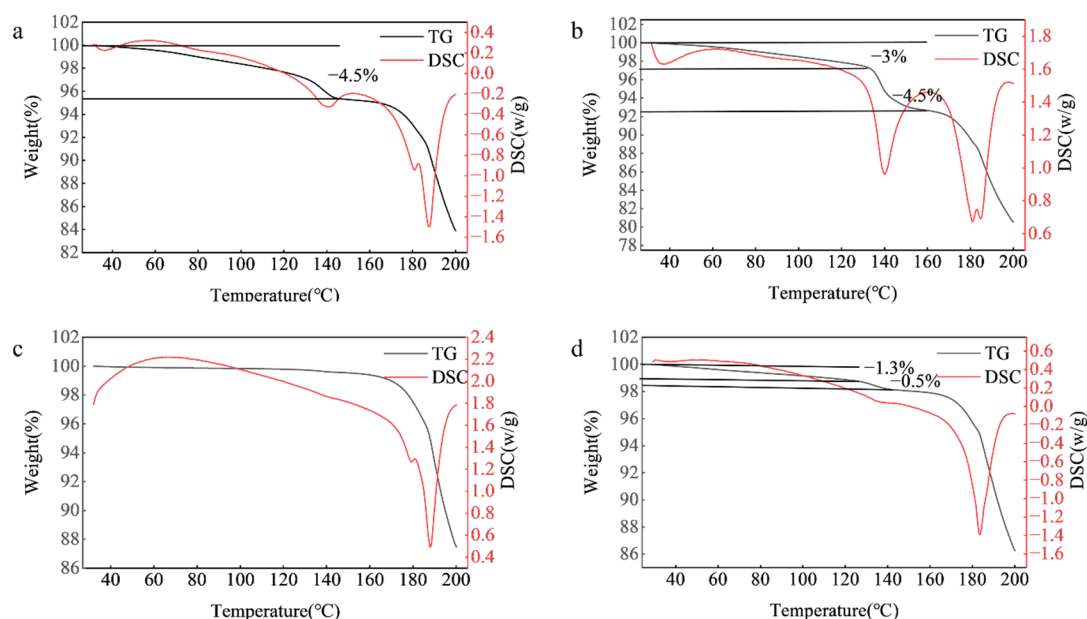


Figure 7. TGA-DSC curves of products obtained via different preparation routes and drying temperatures: (a) Methanol slurring, dried at 40 °C; (b) Anti-solvent crystallization with methanol, dried at 40 °C; (c) Methanol slurring, dried at 80 °C; (d) Anti-solvent crystallization with methanol, dried at 80 °C. The characteristic weight-loss step and desolvation-related endothermic event at approximately 130–140 °C (observed in a and b) are consistent with methanol incorporation into Form S1 across the tested preparation routes.

To investigate how residual solvent affects crystal structure, the wet filter cake from the methanol slurry was characterized by PXRD during a simulated drying process at 80 °C (Figure 8). Upon desolvation, the Form S1 lattice undergoes significant structural rearrangement, transforming entirely into the structurally defective Form IV. This solvent-mediated intermediate pathway inherently traps residual mother liquor and impurities within the collapsing mesoscopic grain boundaries, physically explaining the plateau in purification efficiency observed in the conventional methanol washing process.

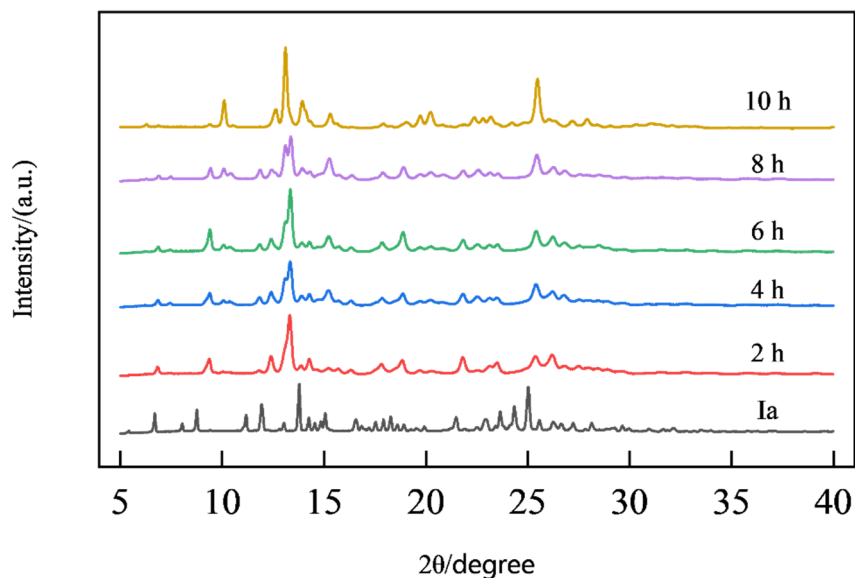


Figure 8. Changes in crystal form during drying at 80 °C of the wet filter cake obtained from methanol washing, with the reference pattern of anhydrous Form Ia included for comparison. The PXRD evolution shows the transformation of Form S1 into Form IV during drying, and comparison with the Form Ia confirms that Form IV remains structurally distinct from the stable anhydrous phase.

Conversely, the ethanol-mediated system demonstrates a fundamentally different phase-selection pathway, as revealed by the comparative thermal profiles in Figure 9. To explicitly differentiate kinetic solvate formation from true thermodynamic stability, extreme kinetic conditions were first evaluated. When ethanol was rapidly introduced as an anti-solvent, the intense

kinetic driving force forced the solute into a metastable ethanol solvate (Form S2), characterized by a distinct weight loss step and a sharp endothermic peak in the 80–100 °C range on the TGA-DSC curve.

In contrast, the ethanol-slurry product exhibits only a minor and broad weight loss of approximately 3.4% before drying (Figure 9a), without a distinct desolvation endotherm, suggesting the removal of residual solvent rather than the presence of a well-defined lattice solvate. After 12 h of drying at 80 °C, the TGA profile remains essentially unchanged before melting (Figure 9c), indicating that no significant additional solvent loss occurs at this stage. Meanwhile, the DSC thermogram exhibits a single sharp endothermic peak at approximately 185–190 °C, consistent with the melting of the anhydrous Form Ia identified by PXRD. Together, these thermal results support the absence of a distinct ethanol-solvate phase under the thermodynamically controlled slurry conditions.

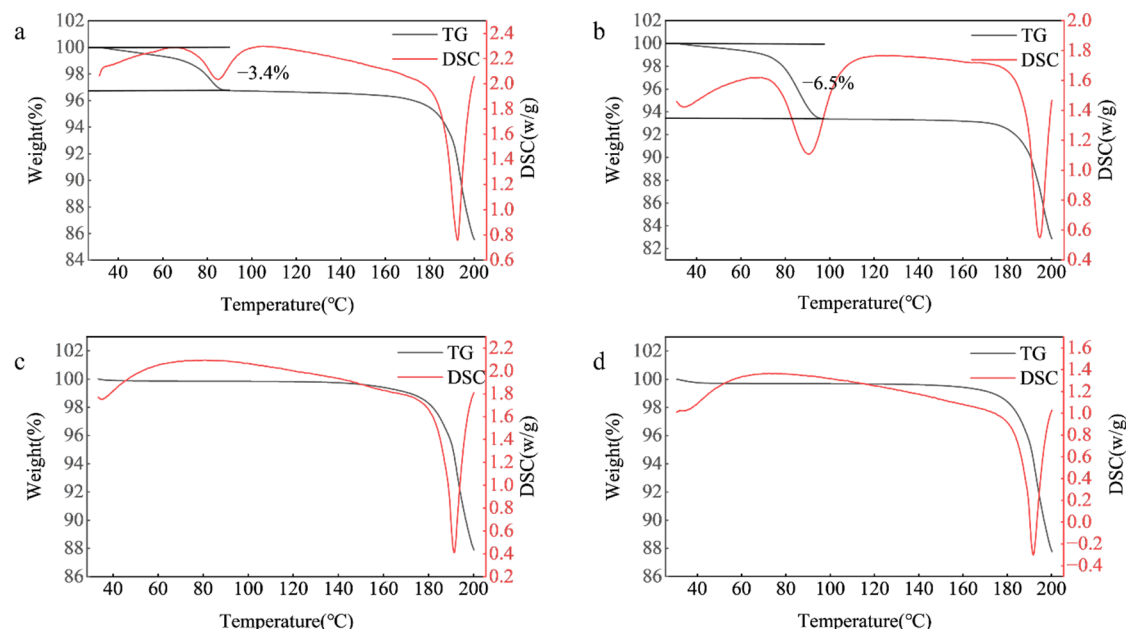


Figure 9. Comparison of TGA-DSC curves for products obtained via ethanol slurry and ethanol precipitation at different drying temperatures: (a) Ethanol slurry-dried at 40 °C; (b) Ethanol precipitation-dried at 40 °C; (c) Ethanol slurry-dried at 80 °C; (d) Ethanol precipitation-dried at 80 °C. Rapid ethanol precipitation produces a distinct solvate-related thermal event, whereas the ethanol-slurry products show no distinct desolvation event and exhibit thermal behavior consistent with anhydrous Form Ia.

The comparative thermal results strongly confirm that while an ethanol solvate can be kinetically trapped, strict thermodynamic control in the ethanol slurry system successfully shuts down the impurity-trapping solvate pathway. By avoiding this undesirable intermediate phase, the process directly produces highly pure and stable Form Ia.

4.3.3. Crystal Morphology Analysis

The effect of the purification strategy on crystal habits was further investigated using SEM (Figure 10). The observed morphological differences provide visual evidence consistent with the solvent-dependent phase selection mechanisms.

The crystals obtained from the conventional methanol washing initially exhibit an irregular, block-like habit corresponding to the solvate Form S1 (Figure 10(1a,1b)). Notably, the dried solids (Form IV) show rough surfaces and are characterized by visible fissures and defects (Figure 10(2a,2b)). These surface defects are induced by structural stress associated with the desolvation of the metastable Form S1 during the drying process, confirming that the solid underwent an undesirable phase transformation.

In contrast, the crystals produced via the ethanol-mediated slurry purification display a uniform, rod-like morphology (Figure 10(3a,3b)). These crystals are well-dispersed with smooth, distinct facets, indicating a growth process governed by the theoretical habit of the stable anhydrous Form Ia rather than impurity-driven inhibition. This morphological integrity further supports the proposed thermodynamic phase-selection mechanism. Bypassing metastable solvate formation favors the development of well-defined crystal surfaces and reduces the formation of visible structural defects. This behavior is consistent with the general principles of impurity rejection during crystal growth [24].

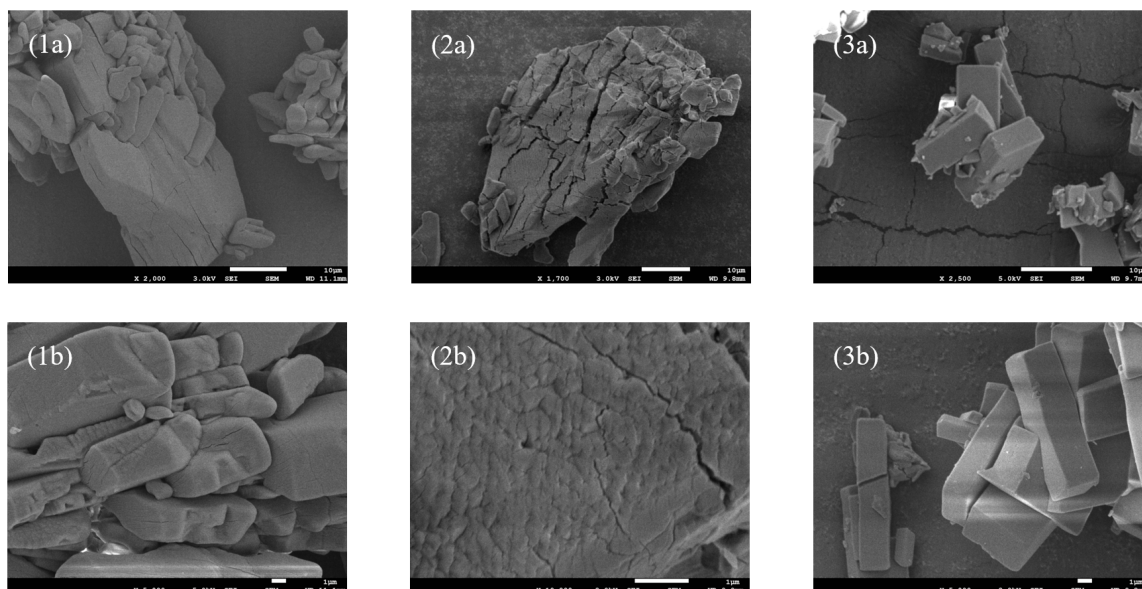


Figure 10. SEM images of crystal forms S1 (**1a,1b**), IV (**2a,2b**) and Ia (**3a,3b**). The methanol-derived forms exhibit irregular, agglomerated, and fissured morphologies, whereas the ethanol-derived Form Ia shows well-dispersed rod-like crystals with smoother and more distinct facets.

4.4. Industrial Implications and Limitations

From a process-engineering perspective, ethanol-mediated purification offers practical advantages for industrial scale-up. Operating at a low liquid-to-solid ratio (3:1 *w/w*) under ambient conditions circumvents the energy-intensive thermal cycles typical of conventional anti-solvent or cooling crystallization. Furthermore, replacing methanol with ethanol in the purification step improves the safety and regulatory profile of the process. Finally, the substantial boiling-point difference between ethanol (~78 °C) and the phenol impurity (~181 °C) facilitates straightforward solvent recovery via distillation. While a quantitative techno-economic evaluation—including energy balances and operating costs—is beyond the scope of this study, these qualitative features indicate strong potential for scalable, closed-loop operation.

While the ethanol-mediated phase selection strategy is highly effective for nicosulfuron, its direct generalization to other sulfonylurea herbicides requires cautious evaluation. Although the shared -SO₂-NH-CO-NH- bridge suggests that similar solute-impurity co-solvency and protic solvent displacement might occur in the liquid phase, final solid-state selection is heavily dictated by the specific conformational flexibility and steric hindrance of distinct substituent groups (e.g., pyrimidine or triazine rings). Therefore, the ability of an ethanol slurry to universally bypass solvate formation cannot be assumed. Future work must rely on case-by-case thermodynamic screening to map the structure-property relationships governing phase selection across the broader sulfonylurea family.

5. Conclusions

In this work, the profound co-solvency effect of phenol on nicosulfuron crystallization was fundamentally elucidated across macroscopic and molecular scales. To provide a robust basis for process design, the solid-liquid equilibrium data were mathematically correlated with exceptional accuracy using the modified Apelblat equation (maximum *RAD* = 0.34%). Concurrently, the ternary NRTL model captured strong non-ideal interactions in the DCM/phenol-containing liquid phase, consistent with the observed enhancement of nicosulfuron solubility and impurity retention. The molecular dynamics simulations further indicated preferential association of phenol with nicosulfuron through specific hydrogen-bonding interactions. To overcome this profound thermodynamic barrier, an ethanol-mediated slurry strategy was established. Unlike conventional methanol washing, which promotes the formation of a metastable solvate and subsequent defective desolvated crystals, the ethanol slurry process operates under strict thermodynamic control to exclusively drive structural reorganization toward the stable anhydrous Form Ia. In the studied nicosulfuron system, this mechanism-based approach achieved simultaneous polymorphic control and high chemical purity (>99%). Operation at ambient temperature and a low liquid-to-solid ratio, together with the potential for conventional solid-liquid separation and solvent recovery, supports its promise for industrial scale-up. More broadly, the integrated thermodynamic and molecular framework may be adapted to guide solvent selection, impurity rejection, and solid-form control in other highly non-ideal agrochemical systems.

However, its applicability to other sulfonylurea herbicides should be evaluated on a case-by-case basis because differences in molecular structure, solvation behavior, and solid-form landscapes may lead to different phase-selection outcomes.

Author Contributions

M.Z.: investigation, methodology, formal analysis, data curation, visualization, writing—original draft preparation; C.T.: resources; Y.Z.: conceptualization, supervision, methodology, project administration, writing—review and editing; G.Z.: methodology, supervision; S.Z.: resources, investigation; W.H.: resources, investigation, validation; J.C.: supervision, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

C.T. and S.Z. were employed by Hubei Xingfa Chemical Group Co., Ltd. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Use of AI and AI-Assisted Technologies

During the proofreading of this work, the authors used ChatGPT (OpenAI) for language editing. The authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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