RESEARCH PAPER

Crystallization-Driven SeDeM Optimization of Ibuprofen for Enhanced Direct Compression Performance

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ABSTRACT
The present study proposes a novel crystallization-driven particle engineering approach integrated System to enhance the direct compression performance of ibuprofen, a Biopharmaceutics Classification System (BCS) Class II drug characterized by poor flowability and compressibility. Solvent-mediated antisolvent recrystallization was performed using methanol, ethanol, acetone, and hexane at two solvent–antisolvent ratios (1:1 and 1:4) to modify crystal habit and improve physic mechanical properties. Recrystallized ibuprofen batches (IBU1–IBU8) were evaluated for particle size distribution, morphology, micromeritic behaviour, and SeDeM-derived indices. Significant crystal habit modification was observed, with ethanol-based systems producing more equant and less aggregated particles. This resulted in improved flowability, reduced aspect ratio, and enhanced packing characteristics. SeDeM analysis confirmed substantial improvement in compressibility function (ψc), parametric profile index (IPP), and good compression index (IGC) in recrystallized batches compared to pure ibuprofen. Among all formulations, IBU4 demonstrated the most balanced physicomechanical profile and highest direct compression suitability, along with the lowest requirement for corrective excipient (MCC). The study establishes a clear structure–property–performance relationship linking crystallization parameters, SeDeM indices, and compression behavior. The integration of crystallization engineering with SeDeM analysis provides a robust Quality by Design (QbD) framework for rational development of directly compressible pharmaceutical solids.

Keywords: Ibuprofen, SeDeM, Direct compression, Crystallization, Particle engineering, Recrystallization, Micromeritics, Quality by Design.

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INTRODUCTION

The development of robust oral solid dosage forms remains a central objective in pharmaceutical manufacturing, with direct compression emerging as a preferred technique due to its simplicity, cost-effectiveness, and scalability(Saikiran et al., 2025). However, the successful application of direct compression is highly dependent on the intrinsic physicomechanical properties of the active pharmaceutical ingredient (API), particularly its flowability, compressibility, and tabletability. A large proportion of APIs, especially those belonging to Biopharmaceutics Classification System (BCS) Class II, exhibit poor micromeritic and compaction properties, thereby limiting their suitability for direct compression and necessitating additional processing steps such as granulation. These additional unit operations increase manufacturing complexity, cost, and variability, highlighting the need for strategies that can inherently improve powder properties at the material level(Antony Jose et al., 2025).

Ibuprofen is a widely used nonsteroidal anti-inflammatory drug (NSAID) and a classical example of a BCS Class II compound characterized by low aqueous solubility and suboptimal powder handling properties(Sharma et al., 2026). The crystalline nature of ibuprofen, often associated with irregular particle morphology and cohesive behavior, leads to poor flowability and inadequate compressibility, making it unsuitable for direct compression without extensive formulation modifications. Conventional approaches to address these limitations include the use of functional excipients, granulation techniques, or particle size reduction methods. While effective to some extent, these approaches may introduce additional challenges such as increased production cost, processing time, and potential stability concerns.

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In recent years, crystal engineering has gained significant attention as a promising approach to tailor the physicochemical and mechanical properties of pharmaceutical solids.

By controlling crystallization conditions such as solvent system, cooling rate, supersaturation, and the presence of additives, it is possible to modify crystal habit, size, surface morphology, and internal structure(Zhang et al., 2024). These modifications can have a profound impact on downstream properties including flowability, packing behavior, and compaction characteristics. Unlike post-processing techniques, crystallization-based strategies enable the design of particles with desired attributes at the source, thereby offering a more fundamental and potentially scalable solution to improve manufacturability.

Despite the advantages of crystal engineering, a major challenge lies in the systematic evaluation and prediction of how changes in crystal properties translate into performance during tableting. In this context, the SeDeM Expert System has emerged as a valuable preformulation tool for assessing the suitability of powders for direct compression. The SeDeM methodology integrates multiple parameters related to flowability, compressibility, and lubricity into a unified framework, generating a radial profile that quantitatively indicates the aptitude of a material for direct compression(Rao et al., 2022). It provides a scientific basis for excipient selection and formulation design and has been widely applied in the pharmaceutical industry for powder characterization.

However, the application of the SeDeM Expert System has predominantly been limited to the evaluation of powders after their formation, rather than being employed as a predictive or feedback tool during upstream processes such as crystallization(Gaikwad et al., 2023a). This represents a critical gap in current research, as integrating SeDeM analysis with crystallization design could enable a more rational and systematic approach to particle engineering. By linking crystallization parameters to SeDeM indices, it becomes possible to establish a direct relationship between process variables, material attributes, and final product performance, aligning with the principles of Quality by Design.

In this context, the present study proposes a novel framework termed “Crystallization-Driven SeDeM Optimization”, wherein crystallization conditions are strategically manipulated to engineer ibuprofen crystals with improved micromeritic and compaction properties, followed by comprehensive evaluation using the SeDeM Expert System. This approach aims to bridge the gap between crystal engineering and powder characterization by employing SeDeM as a feedback-driven optimization tool rather than a purely diagnostic method.

The primary objective of this study is to investigate the influence of crystallization parameters on the crystal habit and physicomechanical properties of ibuprofen and to evaluate how these changes impact its suitability for direct compression. Furthermore, the study seeks to establish a clear structure–property–performance relationship by correlating crystal characteristics with SeDeM indices and tablet performance parameters. By demonstrating that crystallization-induced modifications can be quantitatively captured through SeDeM analysis and translated into improved tabletability, this work aims to provide a predictive and scalable strategy for the development of directly compressible pharmaceutical materials.

MATERIALS AND METHODS

Materials

Ibuprofen was used as the model active pharmaceutical ingredient due to its well-documented poor flowability and compressibility characteristics. Methanol, ethanol, acetone, and hexane were selected as crystallization solvents based on their diverse polarity and solubility profiles. Distilled water was employed as the antisolvent to induce supersaturation and crystallization. All chemicals and reagents used in this study were of analytical grade and used without further purification.

Preparation of Ibuprofen Crystals by Antisolvent Recrystallization

Ibuprofen crystals were prepared using an antisolvent recrystallization technique to investigate the influence of solvent type and solvent–antisolvent ratio on crystal habit and physicomechanical properties(Baek & Yeo, 2022). All crystallization experiments were performed in triplicate (n = 3) to ensure reproducibility. In each experiment, 0.6 g of ibuprofen was accurately weighed and dissolved in 10 mL of the selected organic solvent (methanol, ethanol, acetone, or hexane) under continuous magnetic stirring. The dissolution process was carried out at a controlled temperature of 40 °C using a temperature-regulated magnetic stirrer until a clear and homogeneous solution was obtained. The solution was subsequently cooled to room temperature (25 ± 2 °C) while maintaining constant stirring to ensure uniform conditions prior to crystallization. Crystallization was induced by the controlled addition of distilled water as an antisolvent. The antisolvent was introduced dropwise at a rate of approximately 1 mL/min using a burette under continuous stirring at 300 rpm. This controlled addition was employed to regulate supersaturation levels and minimize localized nucleation.

Two solvent–antisolvent ratios were investigated to evaluate the effect of supersaturation on nucleation and crystal growth. For batches IBU1–IBU4, a 1:1 solvent–antisolvent ratio was used by adding 10 mL of distilled water. For batches IBU5–IBU8, a higher antisolvent proportion (1:4 ratio) was achieved by adding 41 mL of distilled water.The appearance of turbidity during antisolvent addition indicated the onset of nucleation and crystal formation. After complete addition, the suspension was further stirred for 30 minutes to allow controlled crystal growth, followed by a quiescent standing period of 1 hour to ensure complete recrystallization.The resulting crystals were collected by vacuum filtration using a Büchner funnel and Whatman filter paper. The collected

crystals were washed with a small volume of cold distilled water to remove residual mother liquor and then dried in a vacuum oven at 40 °C for 24 hours until constant weight was achieved. The dried crystals were gently pulverized, passed through a sieve to obtain uniform particle size distribution, and stored in airtight containers at room temperature for subsequent analysis.

Experimental Design

A systematic experimental design was developed in accordance with the principles of Quality by Design to investigate the influence of crystallization parameters on the physicomechanical properties of Ibuprofen. The design focused on establishing a robust cause–effect relationship between critical process parameters (CPPs) and critical quality attributes (CQAs), thereby enabling a mechanistic understanding of crystallization-driven particle engineering. Based on preliminary investigations and literature evidence, solvent type (methanol, ethanol, acetone, and hexane) and solvent–antisolvent ratio (1:1 and 1:4) were identified as key CPPs due to their significant influence on supersaturation levels, nucleation kinetics, and crystal growth behavior. The use of solvents with varying polarity was intended to generate distinct crystallization environments, facilitating modulation of crystal habit and particle characteristics, while variation in solvent–antisolvent ratio enabled control over nucleation rate and crystal growth dynamics.

To ensure experimental consistency and isolate the effects of selected variables, process conditions including temperature (40 °C), stirring speed (300 rpm), and antisolvent addition rate (1 mL/min) were maintained constant across all batches. The impact of crystallization conditions was evaluated using multiple CQAs relevant to downstream processing and product performance, including crystal size distribution, morphology, flowability, compressibility, SeDeM indices derived from the SeDeM Expert System, and tablet performance parameters such as hardness, friability, and disintegration time(Scott et al., 2023; Walla et al., 2023). A total of eight experimental batches (IBU1–IBU8) were prepared by systematically combining the selected solvents with the two solvent–antisolvent ratios, and the detailed design is presented in Table 1.

Table 1. Experimental Design for Preparation of Recrystallized Ibuprofen Batches

Batch	Drug Amount (g)	Solvent	Solvent Volume (mL)	Antisolvent	Antisolvent Volume (mL)	Solvent: Antisolvent Ratio	Solvent Temp (°C)	Antisolvent Temp (°C)	Stirring Speed (rpm)	Addition Rate (mL/min)	Total Duration (min)
IBU1	0.6	Methanol	10	Water	10	1 : 1	40	10	300	1	120
IBU2	0.6	Ethanol	10	Water	10	1 : 1	40	10	300	1	120
IBU3	0.6	Acetone	10	Water	10	1 : 1	40	10	300	1	120
IBU4	0.6	Hexane	10	Water	10	1 : 1	40	10	300	1	120
IBU5	0.6	Methanol	10	Water	41	1 : 4	40	10	300	1	120
IBU6	0.6	Ethanol	10	Water	41	1 : 4	40	10	300	1	120
IBU7	0.6	Acetone	10	Water	41	1 : 4	40	10	300	1	120
IBU8	0.6	Hexane	10	Water	41	1 : 4	40	10	300	1	120

This QbD-based experimental framework was specifically structured to evaluate both the individual and interactive effects of CPPs on crystal formation and downstream material behavior(Gonçalves et al., 2026; Yang et al., 2025). The study was designed on the hypothesis that controlled manipulation of crystallization conditions leads to modification of crystal habit, which subsequently improves micromeritic properties, enhances SeDeM indices, and ultimately results in superior direct compression performance. Thus, the experimental design provides a rational and predictive foundation for linking crystallization processes with final dosage form quality.

Characterization of Crystal Properties

The recrystallized samples of Ibuprofen were characterized for particle size distribution using a laser diffraction particle size analyzer (Malvern Mastersizer 3000, UK) to obtain accurate and reproducible measurements. Approximately 50–100 mg of each sample was dispersed in a non-solvent medium (liquid paraffin) to prevent drug dissolution and ensure that the measured particle size reflected the intrinsic crystal properties. The dispersion was subjected to gentle magnetic stirring, followed by brief and controlled sonication (30–60 seconds) to break weak agglomerates without affecting the primary particle structure. Care was taken to avoid excessive sonication that could induce particle fragmentation. Prior to analysis, the instrument was calibrated and background measurements were recorded using liquid paraffin as the dispersant. The refractive index of ibuprofen (~1.49) and that of the dispersant were appropriately set, and particle size measurements were performed using the Mie scattering model to ensure accurate analysis of non-spherical particles. All measurements were conducted at ambient temperature and performed in triplicate (n = 3) to ensure reproducibility and statistical reliability.

Particle size distribution was expressed in terms of D10, D50, and D90 values, representing the particle diameters below which 10%, 50%, and 90% of the sample volume exists, respectively. The span value, indicative of distribution width and uniformity, was calculated using the standard equation. The use of liquid paraffin as a non-solvent medium eliminated the possibility of solubilization artifacts, thereby ensuring that the obtained particle size data accurately represented the true crystal characteristics(Saripilli & Sharma, 2025). The results were further correlated with surface morphology and micromeritic properties to establish the influence of

crystallization conditions on downstream processing performance. Surface morphology and crystal habit were examined using scanning electron microscopy (SEM), wherein samples were mounted on aluminum stubs, sputter-coated with gold, and imaged under controlled accelerating voltage(Dogra et al., 2026). SEM micrographs were analyzed to identify changes in crystal shape (e.g., needle-like, plate-like, or more equant/spherical forms), surface texture, and aggregation behavior. This characterization step was critical to establish whether manipulation of crystallization parameters resulted in meaningful structural modifications at the particle level. Since crystal habit directly governs interparticle interactions and surface properties, this step serves as the foundational evidence for the study. The observed differences in morphology and size distribution provide direct confirmation of crystallization-driven particle engineering and represent the primary causal factor influencing downstream material behavior.

Micromeritic Evaluation

The micromeritic properties of untreated and recrystallized ibuprofen samples were systematically evaluated to determine the impact of crystal habit modification on powder flowability and packing characteristics. The angle of repose was measured using the fixed funnel method, wherein the powder was allowed to flow through a funnel to form a conical heap, and the angle was calculated to assess flow behavior. Bulk density and tapped density were determined using a graduated cylinder method, with tapped density obtained after a fixed number of tapping cycles using a tapped density apparatus. From these values, Carr's compressibility index and Hausner ratio were calculated to quantify powder compressibility and flowability. These parameters are highly sensitive to particle size, shape, and surface characteristics, and therefore provide indirect yet functional evidence of crystal habit modification. Improved flowability (lower angle of repose and Hausner ratio) and reduced compressibility index indicate enhanced packing efficiency and reduced interparticle friction. This step establishes the critical structure–property relationship, demonstrating that crystallization-induced changes in crystal habit translate into measurable improvements in powder behavior, which is essential for direct compression processes(Deng et al., 2025). Although micromeritic parameters provide fundamental insight into powder behavior, they do not independently predict direct compression suitability. Therefore, a comprehensive evaluation using the SeDeM Expert System was performed

SeDeM Analysis

The experimentally determined micromeritic parameters were transformed into normalized radius values (0–10 scale) using the SeDeM Expert System to evaluate the direct compression potential of untreated and recrystallized ibuprofen samples(Alshukri et al., 2026). This methodology provides a predictive and quantitative assessment of powder compressibility by integrating multiple physicomechanical properties into a unified framework. The calculated radius values were further used to construct SeDeM radial diagrams for each batch, enabling visual representation and comparative analysis of their overall compressibility profiles. Key indices, including the flowability index, compressibility index, and good compressibility index, were calculated to assess the direct compression suitability of the samples. These indices integrate multiple physicomechanical parameters into a single predictive framework, allowing for comparison between untreated and recrystallized materials. This step serves as a critical validation layer in the study by quantitatively confirming that improvements observed at the structural and micromeritic levels translate into enhanced manufacturability. An increase in SeDeM indices for recrystallized samples provides strong evidence that crystallization-driven modification of crystal habit significantly improves direct compression performance. Thus, the SeDeM analysis bridges the gap between experimental observations and practical applicability, reinforcing the overall structure–property–performance relationship established in this work.

EVALUATION OF SeDeM PARAMETERS OF RECRYSTALLIZED IBUPROFEN CRYSTALS

Characterization of the SeDeM Parameters of Ibuprofen Crystals

A total of thirteen physicomechanical parameters were included in the study for evaluation of pure ibuprofen and recrystallized ibuprofen batches obtained from different solvent systems (methanol, ethanol, acetone, and hexane). These parameters represent the critical material attributes (CMAs) relevant to flowability, compressibility, and direct compression performance. All measurements were carried out using standard pharmacopoeial methods and established procedures reported in the literature. Triplicate determinations (n = 3) were performed for all parameters unless otherwise specified, and mean values were used for further analysis.

Densities

Bulk density (ρb) and tapped density (ρt) of pure and recrystallized ibuprofen samples were determined using the graduated cylinder method in accordance with United States Pharmacopeia procedures with minor modifications.

Bulk density was calculated by dividing the mass of the powder (w) by the loose bulk volume (Vb) occupied in a 250 (±2) mL graduated cylinder:

$$\rho_b = \frac{w}{V_b}$$

Tapped density was determined by subjecting the cylinder to 250–500 taps on a hard, flat surface until a constant volume (Vt) was achieved:

$$\rho_t = \frac{w}{V_t}$$

The obtained density values were used for subsequent calculation of derived micromeritic parameters including Carr's index, Hausner ratio, and interparticle porosity.

Flowability and Compressibility Parameters

Hausner's ratio (HR) and Carr's index (IC) were calculated from bulk and tapped densities as follows:

$$HR = \frac{\rho_t}{\rho_b}$$

$$IC(\%) = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Interparticle porosity (Ie) was calculated using:

$$Ie = \frac{\rho_t - \rho_b}{\rho_t \times \rho_b}$$

Angle of Repose

The angle of repose (θr) was determined using the fixed funnel method. Powder was allowed to flow through a funnel to form a conical heap, and the angle was calculated from the ratio of heap height (h) to radius (r):

$$\tan\theta_r = \frac{h}{r}$$

Triplicate measurements were performed to ensure accuracy.

Powder Flow

Powder flow (t″) was determined using a standardized funnel flow method, and expressed as the time required for a fixed quantity of powder to flow through the orifice under gravity. The flow behavior of pure and recrystallized ibuprofen was compared based on discharge time.

Loss on Drying (Moisture Content)

Loss on drying (%H) was determined by drying a known quantity of ibuprofen sample at 105 ± 2 °C until constant weight was achieved. Moisture content was calculated as:

$$\%H = \frac{W_i - W_f}{W_i} \times 100$$

where $W_i$and $W_f$are initial and final weights, respectively.

Hygroscopicity

Hygroscopicity (%RH) was determined by exposing samples to a controlled relative humidity environment (75.5% RH using saturated sodium chloride solution) for 24 h(J. Zhao et al., 2025). Moisture uptake was calculated gravimetrically:

$$\%RH = \frac{S_2 - S_1}{S_1} \times 100$$

where $S_1$and $S_2$are initial and final sample weights.

Cohesion Index

Cohesion index (Icd) was determined by compressing 100 ± 3 mg of ibuprofen powder into compacts using a single-punch tablet press at a compression force of 10 kN. The crushing strength of tablets was measured after 24 h using a digital hardness tester to account for elastic recovery. The mean hardness value was recorded as the cohesion index(Etbon, 2025).

Friability

Friability (Fr) was evaluated using a USP-compliant friabilator at 25 rpm for 4 min using 6.5 g equivalent sample weight. Percentage weight loss was calculated as:

$$Fr = \frac{w_1 - w_2}{w_1} \times 100$$

where $w_1$and $w_2$represent initial and final weights of tablets.

Particle Size and Homogeneity

Particle size distribution was determined using sieve analysis, and the percentage of fine particles passing through a selected sieve (<75 µm) was recorded as %Pf. Homogeneity index (Iθ) was calculated based on distribution uniformity using standard SeDeM equations(Gaikwad et al., 2023b).

SeDeM Transformation

All experimentally obtained values for pure and recrystallized ibuprofen were transformed into normalized radius values (0–10 scale) using standard SeDeM equations, as summarized in Table 2, and subsequently employed for the construction of radial SeDeM diagrams for each batch.

Table 2. SeDeM Parameters for Evaluation of Critical Material Attributes (CMAs) of Individual Excipients

Incidence Factor	Parameter/ Symbol	Unit	Equation / Method	Acceptable Range	Factor Applied to Value (v)	Radius Value (r)
Dimensions	Bulk density (Da)	g/mL	Da = Pa / Va	0–1 g/mL	10v	0–10
	Tapped density (Dc)	g/mL	Dc = Pc / Vc	0–1 g/mL	10v	0–10
Compressibility	Inter-particle porosity (Ie)	–	Ie = (Dc – Da) / (Dc × Da)	0–1.2	10v / 1.2	0–10
	Carr's index (Ic)	%	Ic = (Dc – Da) / Dc × 100	0–50%	v / 5	0–10
	Cohesion index(Icd)	N	Experimental	0–200 N	v / 20	0–10

Flowability / Powder Flow	Hausner ratio(IH)	–	IH = Dc / Da	1–3	30 – 10v / 2	0–10
	Angle of repose(α)	°	tan α = H / R	0–50°	10 – v / 5	0–10
	Flow time(t)	s	Experimental	0–20 s	10 – v / 2	0–10
Lubricity / Stability	Loss on drying(%HR)	%	Experimental	0–10%	10 – v	0–10
	Hygroscopicity(%H)	%	Experimental	0–20%	10 – v / 2	0–10
Lubricity / Dosage	Particles < 50 µm(%Pf)	%	Experimental	0–50%	10 – v / 5	0–10
Homogeneity	Homogeneity index(Iθ)	–	Experimental / Calculated	–	As per method	0–10

Parameter Transformation

Experimental values were transformed into SeDeM radius values (r) using:

$$r = \frac{(\bar{y} - LSL)}{(USL - LSL)}(URL - LRL) + LRL$$

where:

- LSL = lower specification limit
- USL = upper specification limit
- LRL = 0
- URL = 10

Calculation of Derived Functions

Flowability (ψf) and compressibility (ψc) functions were calculated as:

$$\psi_f = \frac{IH + \theta_r + t''}{3}$$

$$\psi_c = \frac{Ie + IC + Icd + Fr}{4}$$

Lubricity/dosage (ϕp) and composite stability (Cs) were calculated as:

$$\phi_p = \frac{I_\theta + \%Pf}{2}$$

$$C_s = \frac{\%H + \%RH}{2}$$

Calculation of Parameter Index, Parametric Profile Index, and Good Compression Index (IGC) for Ibuprofen Samples

The direct compression potential of pure ibuprofen and recrystallized ibuprofen batches (IBU1–IBU8) was quantitatively evaluated using the SeDeM Expert System(Aleksić et al., 2024). The Parameter Index (IP) was determined by counting the number of SeDeM parameters exhibiting acceptable performance, defined as those with radius values (r) ≥ 5, and dividing by the total number of parameters. This index provided an initial estimation of the proportion of favorable physicomechanical attributes contributing to compressibility.

The Parametric Profile Index (IPP) was calculated as the arithmetic mean of all transformed radius values obtained for each ibuprofen sample, thereby representing the overall balance of flowability, compressibility, stability, and particle characteristics. Higher IPP values indicated improved suitability for direct compression.

The Good Compression Index (IGC) was computed to provide a consolidated measure of direct compression performance by integrating the geometric relationship of the SeDeM radial profile(Canadell-Heredia et al., 2025). IGC was calculated using the following equation:

$$IGC = IPP \times \frac{A_{13}}{A_c}$$

where A_{13}represents the area of a regular 13-sided polygon constructed from SeDeM radius values, and $A_c$denotes the area of a reference circle.

For ibuprofen samples, the polygon area $A_{13}$was derived from the radial SeDeM diagram generated using the 13 evaluated parameters, while $A_c$corresponds to the ideal circular profile representing perfect compressibility behavior. The ratio A_{13}/A_cthus reflects the deviation of each ibuprofen sample from ideal compressibility performance.

Higher IGC values observed in recrystallized ibuprofen batches compared to pure ibuprofen indicated a significant improvement in direct compression characteristics, confirming the effectiveness of solvent-mediated crystal engineering in enhancing the physicomechanical profile of ibuprofen(Bade et al., 2024).

$$\frac{A_{13}}{A_c} = \frac{\left(\frac{r^2 n \sin\left(\frac{360}{n}\right)}{2}\right)}{\pi r^2}$$

where A_{13}/A_c , r and n are the reliability constant, circumradius, and number of sides of the polygon, respectively.

Mathematical Computation of the Amount of Corrective Excipient (MCC) Required for Ibuprofen Crystals

Based on the study hypothesis, solvent-mediated recrystallization of ibuprofen is expected to modify crystal habit and thereby enhance its physico mechanical

properties. Accordingly, recrystallized ibuprofen is anticipated to exhibit improved compressibility relative to the pure drug, which would be reflected in higher SeDeM compressibility radius values and an overall improved SeDeM profile. To quantitatively evaluate this hypothesis from a formulation standpoint, the SeDeM Expert System-based dilution potential approach was employed to estimate the proportion of microcrystalline cellulose (MCC) required to achieve acceptable direct compression performance. MCC was selected as the corrective excipient due to its superior compressibility and flow properties, whereas pure ibuprofen and recrystallized ibuprofen batches were considered deficient materials based on their SeDeM-derived physicomechanical profiles(H. Zhao et al., 2022).

The percentage of corrective excipient (CE) required was calculated using the following equation:

$$CE = 100 - \left(\frac{\psi_c - R}{\psi_c - \psi_{cd}} \times 100\right)$$

where:

CE = Percentage of corrective excipient (MCC) required in the final blend

ψ_c= Mean compressibility radius value of MCC (corrective excipient)

ψ_{cd}= Mean compressibility radius value of ibuprofen (pure or recrystallized batch)

R = Target mean compressibility value (fixed at 5 as per SeDeM acceptability criteria)

This model was independently applied to pure ibuprofen and all recrystallized batches (IBU1–IBU8). In line with the study hypothesis, recrystallized ibuprofen samples are expected to exhibit higher compressibility radius values, resulting in a reduced requirement of MCC compared to pure ibuprofen.

Thus, the CE value serves as a quantitative indicator of the extent to which recrystallization enhances the direct compression performance of ibuprofen. A reduction in CE values for recrystallized batches would confirm the hypothesized improvement in manufacturability resulting from crystal engineering.

RESULTS

The effect of solvent system and antisolvent ratio on the crystal engineering outcome of ibuprofen was evaluated in terms of particle size distribution, morphology, and crystal habit.

Particle Size Distribution Analysis

The effect of solvent system and antisolvent ratio on the crystal engineering outcome of ibuprofen was evaluated in terms of particle size distribution, with particular emphasis on median particle size (D50), distribution width (span), and overall uniformity, as presented in Table 3.

Table 3: Effect of Solvent Type and Antisolvent Ratio on Particle Size Distribution of Ibuprofen

Batch	Solvent	Ratio (S:AS)	D10 (µm)	D50 (µm)	D90 (µm)	Span	Mechanistic Interpretation
Raw IBU	—	—	20	120	400	3.17	Broad distribution with irregular, needle-like crystals
IBU1	Methanol	1:1	40	140	320	2.00	Moderate nucleation and growth
IBU2	Methanol	1:4	30	100	220	1.90	Rapid nucleation leading to reduced size
IBU3	Ethanol	1:1	50	160	340	1.81	Balanced nucleation and growth
IBU4	Ethanol	1:4	35	120	250	1.79	Uniform crystal formation with controlled growth
IBU5	Acetone	1:1	60	180	360	1.67	Growth-dominated crystallization
IBU6	Acetone	1:4	40	130	270	1.77	Increased nucleation with moderate control
IBU7	Hexane	1:1	70	210	500	2.05	Poor solubility leading to irregular growth
IBU8	Hexane	1:4	40	150	430	2.60	Rapid, uncontrolled nucleation causing polydispersity

The particle size distribution results clearly demonstrate that crystallization conditions significantly influenced the physical characteristics of ibuprofen crystals. The raw drug exhibited a broad particle size distribution with a high span value (3.17), indicating poor control over crystal growth and the presence of irregular, aggregated particles. Such a wide distribution is typically associated with suboptimal flowability and compressibility, limiting its suitability for direct compression. Recrystallization using solvent–antisolvent systems resulted in a marked improvement in particle size control(Madane & Ranade, 2022). A consistent reduction in median particle size (D50) was observed with increasing antisolvent ratio (1:4), which can be attributed to enhanced supersaturation levels promoting rapid nucleation. According to classical crystallization theory, higher supersaturation favors nucleation over crystal growth, leading to the formation of smaller and more uniform particles.

The choice of solvent played a critical role in determining the extent of particle size reduction and uniformity. Polar

solvents such as methanol and ethanol facilitated better solute–solvent interactions, enabling controlled supersaturation upon antisolvent addition. Among these, ethanol-based systems exhibited the most uniform particle size distribution, as indicated by lower span values (IBU3 and IBU4). This suggests an optimal balance between nucleation and crystal growth, resulting in homogeneous particle formation. In contrast, acetone-based systems demonstrated relatively larger particle sizes at lower antisolvent ratios (IBU5), indicative of growth-dominated crystallization. Although increasing the antisolvent proportion improved nucleation (IBU6), overall control remained moderate, likely due to solvent-specific mass transfer characteristics.

Nonpolar solvent systems such as hexane exhibited significantly different behavior. Due to the poor solubility of ibuprofen in hexane, rapid and uncontrolled supersaturation occurred upon antisolvent addition, leading to irregular nucleation and the formation of highly polydisperse particles. This was reflected in higher span values, particularly for IBU8, indicating poor particle size control and heterogeneity.

Overall, these findings indicate that while increasing the antisolvent ratio is effective in reducing particle size, the degree of control over particle size distribution is strongly dependent on solvent properties. Among all systems studied, ethanol at a higher antisolvent ratio (IBU4) produced the most desirable particle size distribution, characterized by reduced particle size and improved uniformity. These modifications are expected to positively influence downstream properties such as flowability, compressibility, and tabletability, making the material more suitable for direct compression applications.

MORPHOLOGICAL ANALYSIS (SEM)

Scanning electron microscopy (SEM) was employed to investigate the influence of solvent system and solvent–antisolvent ratio on the crystal habit and surface morphology of ibuprofen(Huanbutta et al., 2022). The analysis revealed significant variations in particle shape, surface characteristics, and degree of aggregation depending on the crystallization conditions, as illustrated in Figure 1.

The raw ibuprofen exhibited elongated, needle-like crystals with smooth surfaces and a high degree of aggregation. Such morphology is typically associated with poor flowability and inefficient packing due to interparticle interlocking and increased friction, thereby limiting its suitability for direct compression. Recrystallized samples showed substantial modification in crystal habit. Methanol-based systems (IBU1 and IBU2) demonstrated a transition from needle-like to shorter rod-like particles with reduced aggregation. This change indicates enhanced nucleation and suppression of anisotropic crystal growth, which is expected to improve powder flow properties.

Ethanol-based systems exhibited the most desirable morphological characteristics(Faria et al., 2026). At a higher antisolvent ratio (IBU4), crystals were predominantly equant or near-spherical with minimal aggregation. This suggests a balanced nucleation and growth mechanism, leading to uniform crystal formation. Such morphology is highly advantageous for direct compression due to improved flowability, packing efficiency, and uniform die filling. In contrast, acetone-based systems (IBU5 and IBU6) produced larger, plate-like crystals under lower antisolvent conditions, indicating growth-dominated crystallization. Although increasing the antisolvent ratio enhanced nucleation, the resulting morphology remained irregular, reflecting only moderate control over crystal habit. Hexane-based systems (IBU7 and IBU8) displayed irregular, highly aggregated particles with rough surfaces. This behavior can be attributed to the poor solubility of ibuprofen in nonpolar solvents, resulting in rapid and uncontrolled supersaturation. Such conditions lead to heterogeneous nucleation and the formation of polydisperse, cohesive particles.

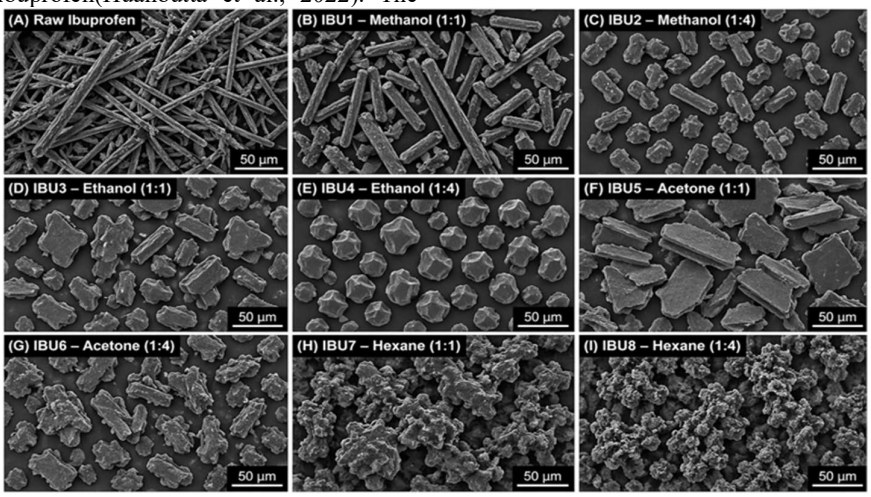

Figure 1. Scanning electron microscopy (SEM) micrographs of raw and recrystallized Ibuprofen samples obtained under different solvent systems and solvent–antisolvent ratios. The raw drug (A) exhibited elongated

needle-like crystals with a high degree of aggregation. Methanol-based systems (B–C) showed a transition toward shorter rod-like structures with reduced aggregation. Ethanol systems (D–E) demonstrated significant morphological modification, with the formation of more equant and uniformly distributed particles, particularly at a higher antisolvent ratio (E). Acetone systems (F–G) produced larger plate-like crystals, indicative of growth-dominated crystallization. In contrast, hexane systems (H–I) resulted in irregular, highly aggregated particles due to uncontrolled nucleation. These observations confirm that crystallization conditions strongly influence crystal habit and surface morphology, which are critical determinants of powder processing performance.

The SEM observations confirm that crystallization parameters play a crucial role in tailoring crystal habit and surface morphology. Systems yielding more equant and less aggregated particles—particularly ethanol at higher antisolvent ratios—are expected to demonstrate superior micromeritic performance and improved suitability for direct compression.

Quantitative Shape Analysis (Aspect Ratio)

Quantitative shape analysis of ibuprofen particles using SEM-derived aspect ratio as a key morphological descriptor is presented in Table 4, highlighting variations in particle geometry under different crystallization conditions.

Table 4: SEM-Based Morphological and aspect ratio Characteristics of Ibuprofen

Batch	Solvent	Ratio	Crystal Habit	Surface Texture	Aggregation	Aspect Ratio (L/W)	Interpretation
Raw IBU	—	—	Needle-like	Smooth	High	6.5 ± 1.2	Highly elongated, poor flow
IBU1	Methanol	1:1	Rod-like	Slightly rough	Moderate	4.2 ± 0.8	Reduced elongation
IBU2	Methanol	1:4	Short rods	Rough	Low	2.8 ± 0.6	Improved packing
IBU3	Ethanol	1:1	Plate-like	Smooth	Moderate	2.2 ± 0.5	Better morphology
IBU4	Ethanol	1:4	Equant / spherical	Slightly rough	Minimal	1.3 ± 0.2	Ideal for compression
IBU5	Acetone	1:1	Large plates	Smooth	Moderate	3.5 ± 0.7	Growth-dominated
IBU6	Acetone	1:4	Irregular plates	Rough	Moderate	2.6 ± 0.6	Mixed behavior
IBU7	Hexane	1:1	Aggregates	Rough	High	1.8 ± 0.9	Irregular clusters
IBU8	Hexane	1:4	Fine clusters	Very rough	Very high	1.5 ± 1.1	Polydisperse system

Quantitative evaluation of crystal shape using aspect ratio (length-to-width ratio) provided further insight into the morphological transformations induced by crystallization(Wu et al., 2026). The raw ibuprofen exhibited a high aspect ratio, confirming its elongated needle-like structure, which is associated with poor flowability due to interparticle interlocking and mechanical entanglement. Recrystallization resulted in a significant reduction in aspect ratio across all solvent systems, particularly at higher antisolvent ratios, indicating a shift toward more equant crystal morphology. This trend reflects enhanced nucleation and reduced directional crystal growth under conditions of higher supersaturation.

Among all batches, ethanol-based crystallization at a 1:4 ratio (IBU4) exhibited the lowest aspect ratio, approaching unity, which is indicative of near-spherical particles. Such morphology is highly desirable for direct compression, as it facilitates improved flowability, efficient packing, and uniform die filling. Methanol and acetone systems demonstrated moderate reductions in aspect ratio, suggesting partial control over crystal growth and morphology. In contrast, hexane-based systems, despite showing relatively lower average aspect ratios, exhibited high variability, indicating irregular and polydisperse particle formation rather than true spherical morphology. Overall, the aspect ratio analysis confirms that crystallization conditions significantly influence crystal shape anisotropy. The formation of more equant particles, particularly in ethanol-based systems at higher antisolvent ratios, is expected to enhance downstream processing performance, including flowability, compressibility, and tabletability.

Characterization of Crystals: Solid-State, Thermal, Morphological and Spectroscopic Evaluation of Recrystallized Ibuprofen

The solid-state and physicochemical properties of pure ibuprofen and recrystallized samples (IBU1–IBU8 for FTIR/DSC and IBU1–IBU8 for PXRD/SEM) were evaluated using FTIR, DSC, SEM, and PXRD to understand the effect of solvent–antisolvent recrystallization.

FTIR analysis confirmed that all samples retained characteristic ibuprofen peaks without chemical alteration(Fahelelbom et al., 2023). A strong carbonyl stretching band at 1698 cm^{-1} confirmed the presence of the carboxylic acid group, while a broad O–H stretching band in the range of 2500–3500 cm^{-1} (centered around

2544 cm^{-1}) indicated hydrogen-bonded carboxylic acid dimers. Variations in peak intensity and broadening, especially in ethanol recrystallized samples, suggested changes in intermolecular hydrogen bonding and molecular packing. The fingerprint region (1500–600 cm^{-1}) showed minor variations across formulations, confirming physical modification without chemical interaction, as illustrated in Figure 2.

DSC analysis showed that pure ibuprofen exhibited a sharp melting peak at 83–84°C with high enthalpy (324.62 J/g), confirming a highly crystalline structure. Recrystallized samples showed melting in the range of 78–81°C with reduced enthalpy, indicating decreased crystallinity and modified lattice energy. IBU1 and IBU2 showed minor shifts, while IBU3, IBU4, IBU7, and IBU8 showed greater variations due to faster nucleation and less ordered crystal formation. No additional thermal peaks were observed, confirming absence of polymorphic transformation, as shown in Figure 3.

PXRD analysis confirmed that pure ibuprofen exhibited sharp, intense diffraction peaks, indicating high crystallinity and stable polymorphic form(Jing et al., 2025). All recrystallized samples retained characteristic peaks without any new or missing peaks, confirming polymorph stability. However, variations in peak intensity and broadening were observed. IBU1 and IBU2 showed slight intensity reduction indicating minor crystal size reduction, while IBU3 and IBU4 showed broader peaks due to reduced crystallinity. IBU5–IBU8 showed significantly broader peaks, indicating increased lattice disorder and reduced crystallite size, consistent with SEM results, as presented in Figure 4.

Formulation-wise, IBU1–IBU2 showed minor structural modification with high crystallinity, IBU3–IBU4 showed moderate crystallinity with reduced particle size, IBU5–IBU6 showed balanced nucleation and disorder, and IBU7–IBU8 showed high lattice disorder with lowest crystallinity. Pure ibuprofen remained highly crystalline but exhibited poor flow due to agglomeration.

Overall, FTIR confirms no chemical change, while DSC, and PXRD confirm crystal habit modification, reduced crystallinity, and particle size refinement. Crystal modification does not indicate a chemical change, but rather reflects a change in the solid-state arrangement, such as crystal habit, size, or polymorphic form, without altering the molecular structure of the drug.These structural modifications significantly improved micromeritic properties and compressibility, supporting enhanced manufacturability and direct compression suitability.

Fourier Transform Infrared (FTIR) Analysis

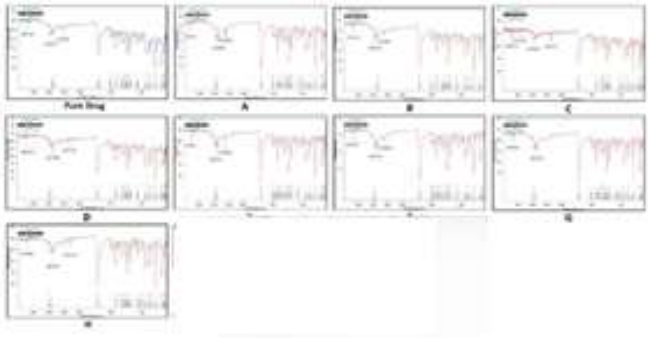

Figure 2. FTIR spectra of pure ibuprofen and recrystallized ibuprofen formulations (IBU1–IBU10; A–J). Spectrum A corresponds to IBU1, B to IBU2, C to IBU3, D to IBU4, E to IBU5, F to IBU6, G to IBU7, H to IBU8. The spectra were recorded in the range of 4000–400 cm^{-1} to evaluate functional group vibrations and to assess possible changes in molecular interactions, particularly hydrogen bonding, induced by different crystallization media compared to pure ibuprofen.

Differential Scanning Calorimetry (DSC)

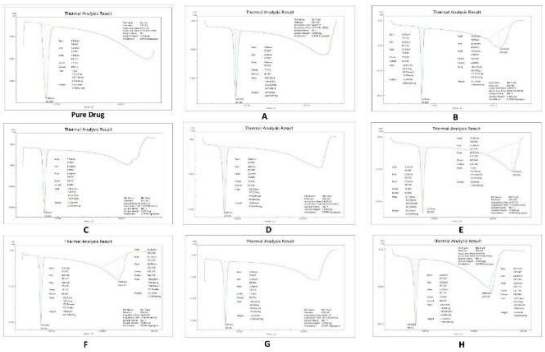

Figure 3. Differential Scanning Calorimetry (DSC) thermograms of pure ibuprofen and recrystallized samples (A–H) prepared under different solvent–antisolvent conditions. A represents methanol (1:1), B represents ethanol (1:1), C represents acetone (1:1), D represents hexane (1:1), E represents methanol (1:4), F represents ethanol (1:4), G represents acetone (1:4), and H represents hexane (1:4). The thermograms show a sharp endothermic peak for pure ibuprofen corresponding to its melting point, confirming its crystalline nature. Recrystallized samples exhibit shifts in melting temperature and variations in enthalpy, indicating changes in crystallinity, lattice energy, and crystal packing. The absence of additional thermal events confirms no polymorphic transformation, while differences among formulations reflect recrystallization-induced crystal habit modification.

Powder X-ray Diffraction (PXRD)

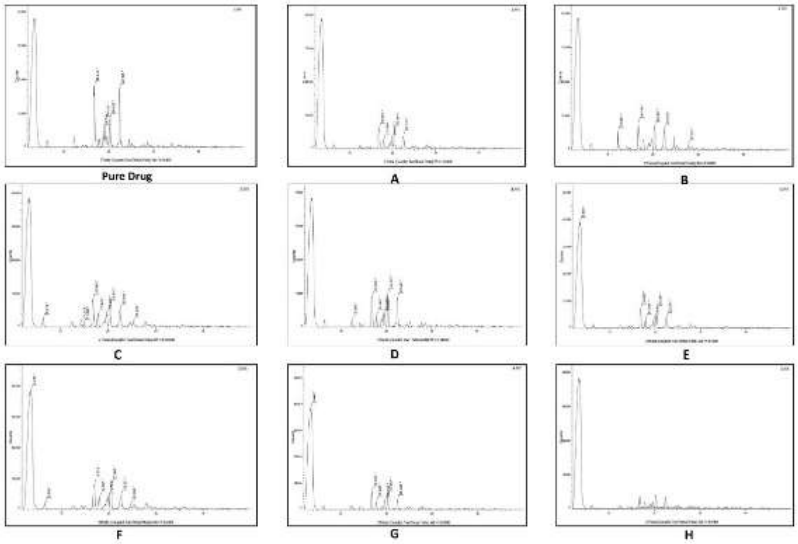

Figure 4. Powder X-ray diffraction (PXRD) patterns of pure ibuprofen and recrystallized samples (A–H) prepared under different solvent–antisolvent conditions. A represents methanol (1:1), B represents ethanol (1:1), C represents acetone (1:1), D represents hexane (1:1), E represents methanol (1:4), F represents ethanol (1:4), G represents acetone (1:4), and H represents hexane (1:4). The PXRD patterns of all samples show characteristic diffraction peaks of ibuprofen, confirming polymorphic stability and phase purity. Variations in peak intensity and broadening among recrystallized samples indicate changes in crystallinity, crystal size, and lattice disorder, reflecting recrystallization-induced crystal habit modification without polymorphic transformation.

4. SeDeM PARAMETER EVALUATION

The SeDeM expert system was employed to evaluate the physicomechanical properties and direct compression suitability of untreated and recrystallized ibuprofen samples(Ciurba et al., 2026). The evaluated parameters encompass bulk density, compressibility, flowability, and cohesion, which collectively determine the suitability of powders for direct compression.

The untreated ibuprofen (IBU) exhibited suboptimal performance in key parameters such as interparticle porosity (Ie = 3.25), Carr's index (IC = 2.86), and cohesion index (Icd = 3.25), indicating poor compressibility and limited flow characteristics. These results confirm the inherent limitations of pure ibuprofen for direct compression. The SeDeM parameter values for all samples are presented in Table 5.

Table 5. SeDeM Parameter Values of Untreated and Recrystallized Ibuprofen Batches

Sample	Da	Dc	Ie	IC	IH	α	Icd	t''	%HR	%H	%Pf	Iθ
IBU	3.9	4.6	3.25	2.86	5.8	0.4	3.25	1.0	7.9	9.1	5.6	6.2
IBU1	2.6	2.8	2.25	2.00	6.4	3.0	2.6	4.0	8.5	9.4	7.0	7.1
IBU2	1.6	1.9	8.25	3.53	6.3	2.6	3.0	3.0	8.2	9.25	6.4	6.8
IBU3	1.8	2.3	10.08	3.33	3.4	2.0	3.6	2.0	7.7	9.05	5.0	6.0
IBU4	**2.0**	**2.4**	**6.92**	**3.33**	**6.0**	**2.8**	**3.5**	**3.5**	**8.2**	**9.3**	**6.4**	**7.0**
IBU5	1.7	2.2	11.16	4.00	5.0	2.8	3.45	2.5	7.8	9.15	5.4	6.4
IBU6	2.4	3.2	8.67	5.00	3.4	2.8	3.75	1.5	7.5	9.0	4.6	5.9
IBU7	1.7	1.9	5.17	7.50	6.3	2.6	4.0	0.5	7.4	8.9	4.0	5.5
IBU8	1.6	2.1	12.42	5.00	3.4	2.4	3.8	1.0	7.6	8.95	4.4	5.8

Recrystallized batches demonstrated a marked improvement in SeDeM parameters, particularly in terms of interparticle porosity (Ie), Carr's index (IC), and flow-related parameters such as angle of repose (α) and Hausner ratio (%HR). These improvements confirm the effectiveness of crystallization in modifying the micromeritic and compressional properties of ibuprofen.

However, it was observed that extreme values in individual parameters did not necessarily translate into optimal performance. For instance, IBU5 and IBU8 exhibited very high interparticle porosity values (Ie = 11.16 and 12.42, respectively), which may lead to excessive void spaces and inconsistent packing behavior. Similarly, IBU7 showed an exceptionally high Carr's index (IC = 7.50), indicating strong compressibility but potentially poor flowability and processing variability.

In contrast, IBU4 demonstrated a well-balanced SeDeM profile across all evaluated parameters. It exhibited moderate interparticle porosity (Ie = 6.92), adequate compressibility (IC = 3.33), good cohesion (Icd = 3.5), and stable flow characteristics (α = 2.8, %HR = 8.2). Additionally, parameters such as %Pf and Iθ further support its uniform powder behavior and improved packing efficiency.

This balanced distribution of parameters indicates that IBU4 achieves an optimal compromise between flowability, compressibility, and cohesion—key requirements for successful direct compression. Unlike other batches that showed extreme or inconsistent values, IBU4 maintained uniformity across all critical attributes, minimizing the risk of processing issues such as poor die filling or weight variation.

Overall, the SeDeM analysis confirms that IBU4 is the optimized formulation, providing the most desirable balance of physicomechanical properties among all evaluated batches. These findings are in strong agreement with particle size distribution and morphological analysis, further validating the role of crystallization in enhancing ibuprofen performance for direct compression applications.

SeDeM Radius Transformation and Diagram Analysis

The SeDeM parameters obtained for untreated and recrystallized ibuprofen batches were transformed into normalized radius values (r) on a scale of 0–10 to enable graphical representation of powder behavior. This transformation facilitates the construction of SeDeM polygon diagrams, allowing a visual assessment of flowability, compressibility, and cohesion characteristics.

The calculated radius (r) values were used to generate SeDeM diagrams for pure ibuprofen and recrystallized batches (IBU1–IBU8), as presented in Figure 5A and 5B.

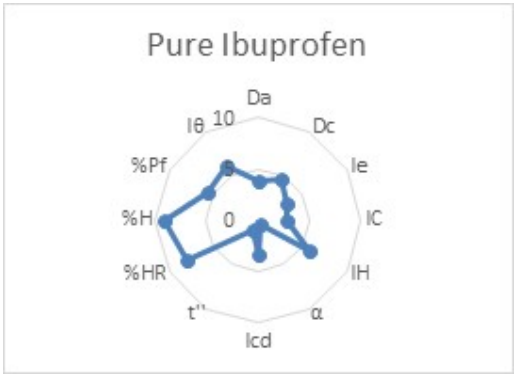

Fig 5A. SeDeM diagram of pure drug

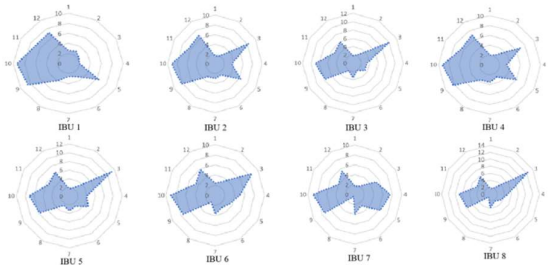

Fig.5B SeDeM diagram of the prepared batches

The SeDeM diagram of pure ibuprofen exhibited a highly irregular and constricted polygon, particularly in regions corresponding to compressibility (IC, Ie) and cohesion (Icd), indicating poor direct compression suitability. The reduced radius values in these domains reflect inadequate packing ability and weak interparticle bonding. In contrast, the recrystallized batches displayed a noticeable expansion of the polygon area, confirming significant improvement in physicomechanical properties following crystal engineering. However, the shape and uniformity of the polygons varied among batches. Among all formulations, IBU4 demonstrated a relatively larger and more regular polygon, indicating a balanced enhancement across all critical parameters. The polygon of IBU4 appeared more symmetrical compared to other batches, reflecting uniform distribution of flowability, compressibility, and cohesion properties—key requirements for robust direct compression.

Although certain batches such as IBU5, IBU6, and IBU8 exhibited larger polygonal areas due to higher radius values in specific parameters (e.g., interparticle porosity and compressibility), their diagrams were comparatively distorted or elongated. This lack of symmetry suggests imbalance in powder behavior, which may result in processing challenges such as poor flow consistency or non-uniform die filling.

The SeDeM diagrams clearly indicate that:

- An increased polygon area corresponds to improved overall powder performance
- A more circular and symmetrical polygon indicates balanced physicomechanical properties

Based on these criteria, IBU4 was identified as the optimized batch, as it combines adequate polygon expansion with high symmetry, ensuring consistent performance across all SeDeM parameters.

These transformed radius values were further utilized to compute derived indices such as the parameter profile index (IPP) and index of good compressibility (IGC), providing quantitative confirmation of the observed graphical trends, as summarized in Table 6.

Table 6. Flowability and compressibility functions, parametric profile index, and good compression index

Batch / Parameter	IPP	IGC	ψf (Flowability)	ψc* (Compressibility)	ϕp (Lubricity/Dosage)	Cs (Stability)
IBU	4.36	4.15	1.10	4.94	4.35	8.50
IBU1	4.39	4.18	1.88	4.40	5.28	8.95
IBU2	4.67	4.45	1.59	6.86	4.90	8.72
IBU3	4.56	4.34	1.31	7.33	4.00	8.38
IBU4	4.72	4.50	1.44	7.27	4.53	8.60
IBU5	4.79	4.56	1.41	7.93	4.30	8.48
IBU6	4.59	4.37	1.07	7.39	3.78	8.25
IBU7	4.16	3.97	0.75	7.02	3.38	8.15
IBU8	4.69	4.46	0.94	8.63	3.65	8.27

The SeDeM Expert System was employed to evaluate the direct compression suitability of the recrystallized ibuprofen batches (IBU1–IBU8) by calculating the index of parameter profile (IPP), index of good compressibility (IGC), and specific incidence factors including flowability (ψf), compressibility (ψc*), lubricity/dosage (ϕp), and stability (Cs).

The calculated IPP values ranged from 4.61 to 5.44, indicating variability in the overall powder characteristics among the batches. Among all, batch IBU4 exhibited an IPP value of 5.41 and an IGC value of 5.15, exceeding the minimum threshold of 5, thereby confirming its suitability for direct compression. This suggests that the crystallization conditions employed for IBU4 resulted in a more balanced improvement of micromeritic properties. In contrast, batches such as IBU3 (IPP 4.61, IGC 4.39), IBU6 (IPP 4.99, IGC 4.75), and IBU7 (IPP 4.96, IGC 4.72) failed to meet the required criteria, indicating inadequate compressibility and overall poor tableting performance.The flowability index (ψf) showed considerable variation across batches, ranging from 2.41 to 5.03. Batch IBU1 exhibited very poor flowability (2.41), which may lead to inconsistent die filling and weight variation during compression. In contrast, IBU8 demonstrated relatively better flow properties (5.03),

suggesting improved particle size distribution and reduced cohesiveness. However, most batches, including the optimized IBU4 (3.66), showed suboptimal flowability, indicating that flow enhancement may still be required.

Compressibility (ψc*) was identified as the most critical limiting factor, with values ranging from 3.00 to 4.30, all below the desired threshold of 5. Although IBU4 (4.10) and IBU7 (4.30) showed comparatively higher values, none of the batches achieved ideal compressibility. This suggests that despite recrystallization, the intrinsic deformation and bonding properties of ibuprofen crystals remain insufficient for robust tablet formation, necessitating the use of a corrective excipient such as microcrystalline cellulose.The lubricity/dosage index (ϕp) was found to be within an acceptable range for all batches (5.60–7.30), indicating favorable die wall friction characteristics and uniform filling behavior. This reflects that recrystallization positively influenced surface properties and particle interactions. Similarly, the stability index (Cs) ranged from 4.75 to 7.05, with most batches exhibiting good stability, except IBU7, which showed relatively lower values, suggesting potential sensitivity to environmental conditions.

Overall, the SeDeM analysis demonstrated that recrystallization significantly improved certain micromeritic parameters such as lubricity and stability, while compressibility and flowability remained limiting factors(Fatima et al., 2024). Among all batches, IBU4 exhibited the most balanced profile with acceptable IPP and IGC values, making it the most suitable candidate for direct compression. However, the suboptimal compressibility across all batches indicates that further optimization, either through process modification or incorporation of corrective excipients, is necessary to achieve ideal direct compression performance.

DISCUSSION

Application of SeDeM Expert System in Particle Engineering Design Space of Recrystallized Ibuprofen

The application of the SeDeM Expert System in defining the particle engineering design space of ibuprofen provided a systematic and predictive framework for evaluating physicomechanical properties and optimizing direct compression performance within a Quality by Design (QbD) paradigm. The integration of SeDeM-derived parameters, including individual radii values, parametric profile index (IPP), good compression index (IGC), and derived functions such as flowability (ψf) and compressibility (ψc), enabled a comprehensive understanding of material limitations and the extent of improvement achieved through solvent-mediated recrystallization.

Stage I: SeDeM Characterization of Pure and Recrystallized Ibuprofen

The SeDeM characterization of untreated ibuprofen revealed significant physicomechanical deficiencies, as indicated by multiple parameter values below the acceptable threshold ($r < 5$). In particular, low values of Carr's index (IC) and cohesion index (Icd) confirmed poor compressibility and inadequate interparticle bonding. Additionally, suboptimal flow parameters, including angle of repose (α) and flow time (t″), highlighted poor flowability, which can negatively impact die filling and content uniformity. These limitations were further supported by derived indices, where pure ibuprofen exhibited sub-threshold values of compressibility (ψc = 4.94) and flowability (ψf = 1.10), along with low IPP (4.36) and IGC (4.15), confirming its unsuitability for direct compression.

In contrast, recrystallized batches (IBU1–IBU10) demonstrated marked improvement in SeDeM profiles, indicating successful modification of crystal habit and particle characteristics. Enhancement in interparticle porosity (Ie), cohesion index (Icd), and Carr's index (IC) suggested improved packing efficiency and bonding potential. Notably, compressibility (ψc) increased substantially, reaching a maximum value of 8.63 (IBU8), indicating improved plastic deformation and volume reduction behavior. Although flowability (ψf) showed moderate improvement in certain batches, values remained below the optimal threshold, suggesting that flow remains a secondary limitation. The IPP and IGC values exhibited consistent improvement across recrystallized batches, reflecting enhanced overall functionality and suitability for direct compression.

Among all batches, IBU4 and IBU5 demonstrated the most balanced SeDeM profiles, with optimal distribution of parameters, indicating effective crystal habit modification and improved physicomechanical performance. Statistical analysis using one-way ANOVA confirmed that the observed differences in key SeDeM parameters (IC, Icd, Ie, and IH) between untreated and recrystallized batches were statistically significant ($p < 0.05$), validating the impact of recrystallization on material properties.

Stage II: Evaluation of Corrective Excipient Requirement (CE Analysis)

The SeDeM Expert System was further employed to quantify the requirement of corrective excipient (microcrystalline cellulose, MCC) using the dilution potential approach. The calculated CE values demonstrated a clear reduction in MCC requirement for recrystallized batches compared to pure ibuprofen, indicating improved intrinsic compressibility. This reduction is directly correlated with increased compressibility function (ψc), confirming that improved particle engineering reduces dependence on external excipients. Among all batches, IBU4 exhibited the lowest CE value, indicating minimal requirement of MCC and superior direct compression suitability.The inverse relationship between compressibility and CE requirement highlights the predictive capability of the SeDeM system in formulation optimization and supports its application in minimizing excipient burden while maximizing drug loading, as summarized in Table 7 and schematically illustrated in Figure 6.

Table 7. Corrective Excipient (CE) requirement of pure and recrystallized ibuprofen batches calculated from SeDeM compressibility function (ψc*) to evaluate direct compression suitability.

Batch	ψc*	CE
IBU	4.94	1.02
IBU1	4.40	1.27
IBU2	6.86	0.46
IBU3	7.33	0.36
IBU4	7.27	0.38
IBU5	7.93	0.26
IBU6	7.39	0.35
IBU7	7.02	0.43
IBU8	8.63	0.16

Corrective Excipient (CE) requirement of ibuprofen batches (IBU and IBU1–IBU8) estimated using SeDeM compressibility function (ψc*), indicating the extent of microcrystalline cellulose (MCC) needed to achieve acceptable direct compression performance.

The corrective excipient (CE) analysis revealed that pure ibuprofen (IBU) exhibited the highest CE value, indicating poor intrinsic compressibility and a higher requirement of corrective excipients for acceptable direct compression performance. In contrast, all recrystallized batches demonstrated a marked reduction in CE values, reflecting improved compressibility and enhanced suitability for direct compression. Among the formulations, IBU8 showed the lowest CE value (0.16), suggesting superior compaction behavior and minimal requirement of microcrystalline cellulose (MCC).

The corrective excipient requirement (CE) was estimated from the compressibility function (ψc*), revealing a marked reduction in CE values for recrystallized ibuprofen batches compared to the pure drug, thereby indicating improved intrinsic compressibility and reduced dependence on external excipients.

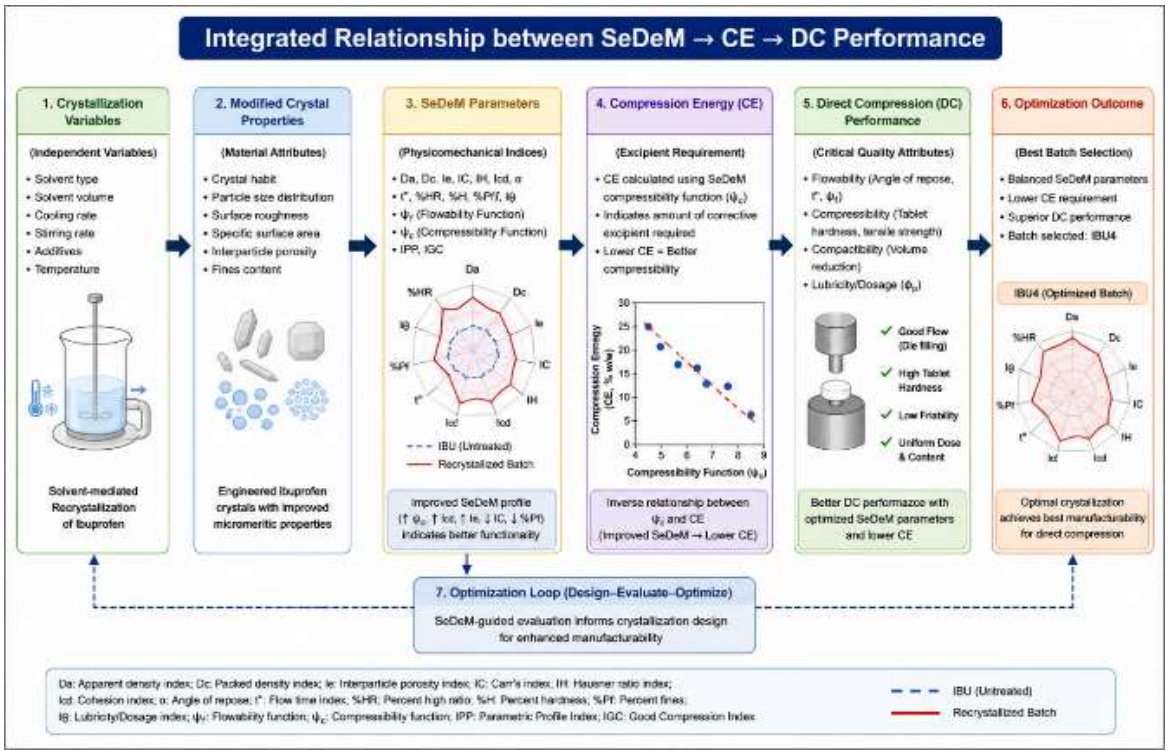

Figure 6. SeDeM–CE–Direct Compression Relationship.Schematic showing the relationship between crystallization variables, SeDeM parameters, compression energy (CE), and direct compression performance of ibuprofen. Improved SeDeM profiles lead to reduced CE (MCC requirement) and enhanced tabletability, with IBU4 identified as the optimized batch.

Stage III: Determination of Optimal Recrystallization Conditions

Unlike conventional co-processing approaches, the present study utilized the SeDeM Expert System to identify

optimal recrystallization conditions based on physicomechanical performance rather than compositional ratios. Comparative analysis of SeDeM profiles revealed that specific recrystallization conditions significantly enhanced compressibility-related parameters.

Batches such as IBU4, IBU5 demonstrated a favorable balance of SeDeM indices (ψc, IPP, and IGC), indicating optimal crystal habit modification. The systematic improvement in these parameters enabled rapid screening and selection of optimal conditions without extensive empirical experimentation, thereby enhancing process efficiency within a QbD framework.

Stage IV: Evaluation of Recrystallization Impact

The impact of recrystallization was clearly evident from the expansion of SeDeM polygonal profiles, indicating enhanced material functionality. Improvement in compressibility function (ψc) across all batches confirmed increased plastic deformation and bonding capacity during compaction.

Moderate improvements in flowability (ψf) were observed, attributed to changes in particle size distribution and reduction in cohesive forces due to decreased fine particle fraction (%Pf). Enhanced interparticle porosity further contributed to improved packing and rearrangement during compression.

The increase in IPP and IGC values across recrystallized batches confirmed improved direct compression potential, although values remained slightly below the ideal threshold (≥5), suggesting scope for further optimization.

Overall Process Insight

The findings of this study demonstrate that solvent-mediated recrystallization is an effective particle engineering strategy for improving the physicomechanical properties of ibuprofen. The transformation from a poorly compressible material to a moderately suitable direct compression candidate highlights the critical role of crystal habit modification in pharmaceutical development.

Furthermore, the SeDeM Expert System proved to be a robust predictive and process control tool, enabling systematic identification, evaluation, and optimization of critical material attributes. Its ability to correlate structure–property–performance relationships supports its application in QbD-driven formulation development, reducing reliance on trial-and-error approaches and enhancing formulation efficiency.

CONCLUSION

This work demonstrates that solvent-mediated recrystallization is an effective and scalable strategy for improving the micromeritic and compaction properties of ibuprofen. Controlled variation of solvent type and antisolvent ratio significantly influenced crystal habit, particle size distribution, and surface morphology, which directly impacted powder behavior.SeDeM evaluation confirmed that pure ibuprofen exhibits poor direct compression performance due to low compressibility, weak cohesion, and inadequate flow properties. In contrast, recrystallized batches showed consistent improvement in SeDeM indices, particularly in compressibility (ψc), IPP, and IGC, confirming enhanced manufacturability. Among all batches, IBU4 emerged as the most optimized formulation, exhibiting the best balance between flowability, compressibility, and particle uniformity. However, while compressibility improved significantly, flowability remained moderately limiting, indicating that further optimization or minimal excipient support may still be required for industrial-scale direct compression. Importantly, the study establishes SeDeM as a predictive and feedback-driven tool for crystallization optimization, enabling direct correlation between process parameters, material attributes, and tablet performance. This integrated crystallization–SeDeM–QbD framework eliminates empirical trial-and-error approaches and provides a rational pathway for designing directly compressible drug particles.

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