RESEARCH PAPER

BEYOND SOLVENTS: SOLID-STATE ENGINEERING STRATEGIES FOR SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS

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ABSTRACT

Background:

Poor aqueous solubility of active pharmaceutical ingredients remains a major challenge in pharmaceutical development, as it can lead to slow dissolution, inadequate drug absorption, variable bioavailability, and reduced therapeutic performance. Conventional solubility enhancement techniques, including micronization, solvent-based solid dispersion, and the use of solubilizing agents, may involve limitations related to solvent consumption, processing complexity, physical instability, and environmental sustainability. Mechanochemistry has emerged as a promising solid-state engineering approach that uses mechanical energy to modify the physicochemical properties of drug substances, often with reduced or no solvent use.

Objective:

This review aims to explore mechanochemical approaches for enhancing the solubility and dissolution performance of poorly water-soluble drugs. It emphasizes the fundamental mechanisms, major processing technologies, formulation strategies, and recent developments that support the application of mechanochemistry in pharmaceutical formulation development.

Methods:

The review examines mechanochemical techniques, including mortar–pestle grinding, ball milling, liquid-assisted grinding, mechanochemical cocrystallization, co-amorphization, and polymer-assisted solid-state processing. It discusses the influence of drug properties, polymeric carriers, coformers, drug-to-carrier ratios, and processing parameters on formulation performance. Analytical and characterization techniques, including Fourier-transform infrared spectroscopy, powder X-ray diffraction, differential scanning calorimetry, and microscopic methods, are considered alongside solubility measurements, dissolution testing, and physical stability assessment.

Results:

Mechanochemical processing offers considerable potential for improving the apparent solubility and dissolution rate of poorly water-soluble drugs through particle-size reduction, crystal lattice disruption, defect formation, amorphization, and modification of drug–excipient interactions. The effectiveness of these approaches depends on formulation composition, processing conditions, and the physical properties of the resulting solid. The review also highlights challenges associated with recrystallization, moisture sensitivity, process reproducibility, and the translation of laboratory-scale methods to industrial manufacturing. Emerging applications of process analytical technology, predictive modelling, and continuous processing provide opportunities to improve process control and scalability.

Conclusion:

Mechanochemistry represents a versatile and potentially sustainable strategy for improving the pharmaceutical performance of poorly water-soluble drugs. Its advantages include the potential to reduce solvent consumption, minimize waste, and enable targeted solid-state modifications. However, successful implementation requires systematic formulation optimization, comprehensive characterization, long-term stability evaluation, and reliable scale-up strategies. Further research into standardized protocols, quality control, and industrial processing is essential to establish mechanochemistry as a reproducible and practical platform for pharmaceutical development.

Keywords: Mechanochemistry, solubility enhancement, poorly water-soluble drugs, solid-state engineering; ball milling, cocrystallization, amorphous solid dispersions, dissolution, sustainable pharmaceutical processing.

How to cite this article: Anjani Kumar Dwivedi, Ritesh Kumar Tiwari. BEYOND SOLVENTS: SOLID-STATE ENGINEERING STRATEGIES FOR SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS. Int J Drug Deliv Technol. 2026;16(88s):751-777. DOI: 10.25258/ijddt.16.88s.78.

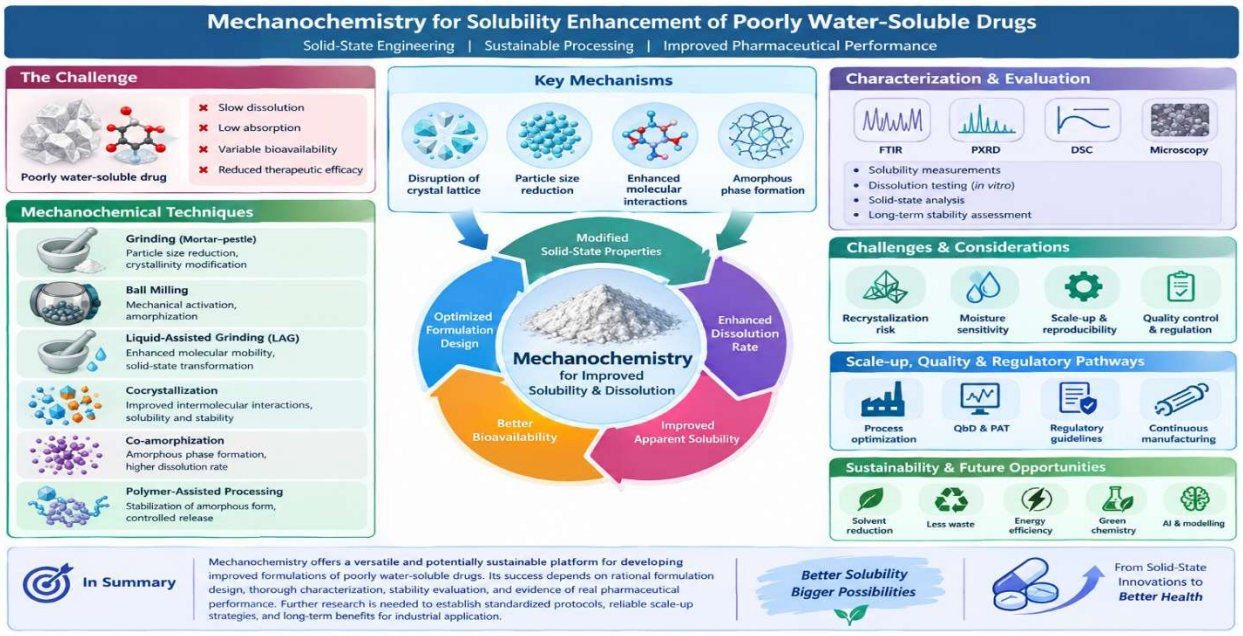


Figure 1: Graphical abstract

1. INTRODUCTION

1.1. PHARMACEUTICAL SIGNIFICANCE OF POOR AQUEOUS SOLUBILITY

The development of effective oral pharmaceutical formulations is frequently challenged by the poor aqueous solubility of active pharmaceutical ingredients. A drug must generally dissolve in gastrointestinal fluids before it can be absorbed, although the extent of absorption also depends on permeability, gastrointestinal physiology, metabolism, and other biopharmaceutical factors. Insufficient aqueous solubility can therefore contribute to slow dissolution, variable drug exposure, and reduced oral bioavailability, particularly when dissolution is the rate-limiting step in absorption. Improving the solubility and dissolution performance of such compounds remains an important objective in pharmaceutical formulation research. Established strategies include particle-size reduction, salt formation, complexation, cocrystallization, lipid-based formulations, and solid dispersions. However, their effectiveness depends on the physicochemical properties of the drug, the formulation composition, and the intended route of administration. Consequently, selecting an appropriate enhancement strategy requires a systematic understanding of drug solubility, solid-state properties, and formulation behaviour rather than relying on a single universal technique [1,2].

1.2. LIMITATIONS OF CONVENTIONAL SOLUBILITY-ENHANCEMENT APPROACHES

Conventional formulation technologies have substantially expanded the possibilities for improving the pharmaceutical performance of poorly water-soluble drugs, but their implementation can present technical and manufacturing challenges. Solvent-based preparation of solid dispersions, for example, may involve organic-solvent handling, solvent recovery, drying operations, and control of residual solvent levels. In addition, some conventional approaches improve dissolution primarily through particle-size reduction, whereas others alter crystallinity or generate amorphous material; these mechanisms do not necessarily produce equivalent changes in equilibrium solubility. Milling can reduce particle dimensions and increase specific surface area, while sufficiently energetic processing may also introduce structural disorder or induce amorphization. The extent of improvement depends on the material, processing conditions, and resulting solid state. Moreover, amorphous pharmaceutical systems can undergo recrystallization during storage or dissolution, potentially diminishing their performance. These considerations support evaluating solubility-enhancement technologies using multiple endpoints, including equilibrium solubility, dissolution rate, solid-state stability, and manufacturing feasibility [3,4].

1.3. RATIONALE FOR SOLVENT-FREE SOLID-STATE ENGINEERING

Solvent-free solid-state engineering offers an alternative approach in which mechanical energy, thermal processing, or combinations of these operations are used to modify the structure and performance of pharmaceutical materials without requiring a conventional solvent-based preparation step. Mechanochemical techniques, including neat

grinding and ball milling, can promote particle-size reduction, crystal defects, structural disorder, and, under suitable conditions, amorphization or the formation of new crystalline phases. Melt-based technologies, particularly hot-melt extrusion, facilitate drug–excipient mixing through the combined effects of heat and mechanical shear, enabling the production of solid dispersions without a solvent-evaporation stage. Nevertheless, the suitability of these approaches depends on factors such as thermal stability, polymer compatibility, processing temperature, energy input, and the physical stability of the final product. Solvent-free processing should not automatically be considered superior in every situation; its pharmaceutical and environmental advantages must be established through appropriate experimental and process-level comparisons [5,6].

1.4. SCOPE, OBJECTIVES, AND NOVELTY OF THE REVIEW

Although pharmaceutical literature contains reviews of milling, amorphous solid dispersions, hot-melt extrusion, and mechanochemical cocrystallization, these technologies operate through different mechanisms and present distinct formulation and manufacturing considerations. A comprehensive assessment should therefore compare them using consistent criteria rather than ranking their effectiveness solely by reported increases in solubility. Mechanochemical cocrystallization, for example, can generate alternative crystalline forms through solid-state reactions, whereas mechanical activation and melt processing may produce different degrees of disorder or molecular dispersion. This review consequently aims to examine the major solvent-free technologies used for improving the pharmaceutical performance of poorly water-soluble drugs, their underlying mechanisms, the selection of drugs and excipients, and the analytical approaches used to characterize the resulting materials. Further attention will be given to dissolution performance, physical stability, scale-up, energy requirements, sustainability, quality control, and regulatory considerations. The objective is to develop a critical comparative framework that supports rational technology selection and identifies research priorities for future pharmaceutical development [7,8].

2. FUNDAMENTALS OF POOR DRUG SOLUBILITY AND SOLID-STATE ENGINEERING

2.1. CLASSIFICATION OF POORLY WATER-SOLUBLE DRUGS

A fundamental understanding of drug solubility is essential for selecting appropriate solid-state engineering strategies. The Biopharmaceutics Classification System (BCS) categorizes orally administered drug substances according to their aqueous solubility and intestinal permeability, providing a framework for anticipating absorption-related challenges. Class II drugs exhibit low solubility and high permeability, whereas Class IV drugs exhibit both low solubility and low permeability. Improving dissolution may therefore be particularly beneficial for Class II compounds when dissolution limits absorption, while Class IV compounds can require additional strategies addressing permeability and other absorption barriers. Importantly, poor water solubility alone does not establish the BCS class of a compound; solubility must be assessed against the relevant dose and specified experimental conditions. Classification also does not independently predict the performance of every formulation, because excipients, gastrointestinal conditions, and drug release characteristics can influence in vivo behaviour. Accordingly, BCS classification provides an initial framework for formulation selection rather than a substitute for experimental evaluation [9,10].

2.2. THERMODYNAMIC AND KINETIC ASPECTS OF SOLUBILITY

Drug solubility is governed by the balance between the energetic requirements of transferring molecules from the solid state into solution and their interactions with the surrounding solvent. Equilibrium solubility represents the concentration attained under defined conditions when the relevant phases reach equilibrium, whereas kinetic measurements describe concentration changes over a specified period. These distinctions become particularly important when comparing crystalline drugs with amorphous materials. Amorphous solids generally possess higher free energy than their corresponding stable crystalline forms and can consequently produce elevated concentrations during dissolution. However, this advantage may be temporary because supersaturated solutions can undergo liquid–liquid phase separation, nucleation, or precipitation. The measured concentration may also include drug-rich colloidal species, depending on the analytical method and sample preparation. Therefore, the concentration detected during dissolution should not automatically be interpreted as the equilibrium molecular solubility. A scientifically meaningful assessment requires clearly defined conditions, suitable separation methods, and differentiation between thermodynamic solubility and transient supersaturation [11,12].

2.3. INFLUENCE OF CRYSTAL STRUCTURE AND SOLID-STATE PROPERTIES

The solid-state structure of a pharmaceutical compound plays a major role in determining its dissolution behaviour and apparent solubility. Crystalline materials possess ordered molecular arrangements stabilized by intermolecular interactions, and the energy required to disrupt these

arrangements contributes to the resistance encountered during dissolution. Polymorphism, in which a compound exists in more than one crystalline form, can lead to differences in thermodynamic stability, melting behaviour, dissolution rate, and solubility. Metastable polymorphs may dissolve more rapidly or exhibit greater apparent solubility than a more stable form, although their advantages can diminish if they transform during storage or contact with a dissolution medium. Solid-state engineering therefore aims not merely to reduce particle size but also, where appropriate, to modify crystal packing, generate defects, or produce alternative solid forms. Reliable identification of these changes is essential before attributing observed improvements to a particular structural mechanism [13,14].

2.4. RELATIONSHIP BETWEEN SOLUBILITY, DISSOLUTION, AND BIOPHARMACEUTICAL PERFORMANCE

Solubility and dissolution are closely related but distinct properties, and their effects on drug absorption must be interpreted together. Solubility determines the concentration that can be achieved under specified equilibrium conditions, whereas dissolution describes the rate at which a solid drug enters the surrounding medium. For poorly soluble drugs, faster dissolution can increase the amount available for absorption during gastrointestinal transit, particularly when permeability is sufficiently high. Nevertheless, an increase in dissolution rate does not necessarily produce a proportional increase in systemic exposure because precipitation, intestinal permeability, metabolism, and physiological variability may limit the final outcome. Recent biopharmaceutical approaches have therefore emphasized linking dissolution measurements with dose, solubility, and absorption-relevant parameters rather than relying exclusively on a single dissolution time point. For solid-state formulations, these considerations are especially important when the formulation generates supersaturation, because the duration of elevated drug concentration can influence its opportunity for absorption [15,16].

2.5. SOLID-STATE ENGINEERING AS A FORMULATION-SELECTION FRAMEWORK

Solid-state engineering involves deliberately modifying the physical form, molecular arrangement, or microstructure of a drug to improve one or more pharmaceutical performance attributes. Depending on the material and process, these modifications may include particle-size reduction, crystal-defect generation, polymorphic transformation, cocrystal formation, or conversion from a crystalline to an amorphous state. The choice of approach must account for the balance between achievable performance and the stability of the resulting material. Amorphous systems may generate higher transient drug concentrations but can be susceptible to recrystallization, while alternative crystalline forms may offer improved dissolution without eliminating the underlying limitations of crystal stability. Formulation development should consequently consider both the initial enhancement and its persistence during storage and dissolution. This framework also supports the comparison of solvent-free methods, because mechanical and thermal processes can produce different solid states even when they are applied to the same drug. The subsequent sections examine these technologies and the evidence required to evaluate their effectiveness [17].

3. MECHANISTIC BASIS OF SOLUBILITY AND DISSOLUTION ENHANCEMENT

3.1. CRYSTAL LATTICE DISRUPTION AND AMORPHIZATION

The enhancement of drug solubility through solid-state engineering depends partly on changes in the molecular organization and energetic state of the active pharmaceutical ingredient. Crystalline drugs possess an ordered molecular arrangement that must be disrupted before individual molecules can enter solution. Mechanical processing, including grinding and milling, can introduce lattice defects, reduce crystallite dimensions, increase structural disorder, and, under suitable conditions, convert crystalline material into an amorphous phase. Because amorphous materials generally possess higher free energy than their corresponding stable crystalline forms, they may exhibit greater apparent solubility and generate supersaturated solutions during dissolution. However, the extent of enhancement depends on the degree of amorphization, drug–excipient compatibility, and processing conditions. Partial amorphization should not be assumed to produce the same effect as complete amorphization, and the resulting material may recrystallize during storage or dissolution. Therefore, establishing the relationship between structural disorder and pharmaceutical performance requires direct solid-state characterization alongside quantitative dissolution and solubility measurements [18,19].

3.2. PARTICLE-SIZE REDUCTION, SURFACE AREA, AND WETTABILITY

Particle-size reduction is another important mechanism through which mechanical processing can improve drug dissolution. For a given mass of material, reducing particle dimensions generally increases the total surface area available for contact with the dissolution medium. Under suitable conditions, this can increase the dissolution rate by improving the area across which mass transfer occurs. Nevertheless, particle-size reduction does not necessarily cause a comparable increase in equilibrium

solubility, and its effect can be influenced by particle aggregation, surface energy, crystallinity, and the wetting characteristics of the drug. Hydrophobic particles may resist penetration by aqueous media even when their dimensions are reduced, limiting the practical benefit of micronization or milling. Incorporating hydrophilic carriers or suitable surfactants can improve wetting and dispersion, although excipient selection must also account for compatibility and stability. Consequently, particle size, surface properties, crystallinity, and wettability should be assessed as related but distinct formulation attributes when explaining improvements in dissolution performance [20,21].

3.3. DRUG–POLYMER INTERACTIONS AND MOLECULAR DISPERSION

Drug–polymer interactions can influence both the formation of solid dispersions and their behaviour after exposure to aqueous media. Depending on the chemical structures involved, hydrogen bonding, ionic interactions, dipole-related interactions, and other intermolecular forces may affect drug miscibility, molecular mobility, and resistance to crystallization. A suitable polymer can help maintain the drug in a disordered state during storage while also influencing the release of drug molecules during dissolution. However, stronger drug–polymer interactions do not invariably produce faster dissolution, because the same interactions that stabilize the solid formulation may also retard drug release or alter the formation of drug-rich colloidal phases. The performance of an amorphous solid dispersion therefore reflects a balance between solid-state stability, polymer hydration, drug release, and supersaturation maintenance. Rational formulation design should evaluate these competing effects rather than selecting a carrier solely on the basis of hydrogen-bonding potential or the disappearance of crystalline peaks in diffraction patterns [22,23].

3.4. SUPERSATURATION, NUCLEATION, AND PRECIPITATION INHIBITION

Supersaturation is an important mechanism through which amorphous formulations can temporarily achieve drug concentrations above the equilibrium solubility of the stable crystalline form. During dissolution, the elevated free energy of an amorphous drug may promote rapid release and generate a transient concentration increase, often described using the spring-and-parachute concept. The initial increase in concentration represents the spring effect, whereas the maintenance of supersaturation through inhibition of nucleation, crystal growth, or precipitation represents the parachute effect. These processes are influenced by polymer properties, drug loading, solution composition, pH, and the formation of drug-rich colloidal phases. Importantly, total measured drug concentration may differ from the freely dissolved molecular concentration, and this distinction can affect interpretation of the formulation's potential for absorption. Consequently, a formulation that produces a high initial concentration may not necessarily provide sustained supersaturation or improved bioavailability unless precipitation behaviour and the duration of elevated concentration are also investigated [24,25].

3.5. MECHANOCHEMICAL TRANSFORMATION AND FORMATION OF ALTERNATIVE SOLID FORMS

Mechanochemical processing can enhance pharmaceutical performance through mechanisms extending beyond particle-size reduction and amorphization. Repeated mechanical impacts and shear can promote intimate contact between components, disrupt existing crystal arrangements, and facilitate solid-state reactions between a drug and a suitable coformer. Under appropriate conditions, these processes can produce pharmaceutical cocrystals, polymorphic transformations, or other multicomponent solid forms with physicochemical properties that differ from those of the starting materials. The resulting change in dissolution behaviour depends on the structure and stability of the new phase, the properties of the coformer, and the conditions under which the material is tested. Formation of a new crystalline phase does not automatically guarantee increased solubility, because the new phase may have its own thermodynamic stability and dissolution characteristics. Mechanochemical formulation development should therefore combine careful control of processing parameters with phase identification, quantitative solubility assessment, and dissolution testing to establish the actual mechanism responsible for any observed improvement [26,27].

4. SOLVENT-FREE SOLID-STATE PROCESSING TECHNOLOGIES

Solvent-free solid-state processing encompasses several pharmaceutical manufacturing approaches in which mechanical energy, thermal energy, or pressure is used to modify material structure, promote mixing, or produce dosage-form intermediates without relying on conventional solvent-based preparation. These technologies differ considerably in their operating principles, achievable solid states, thermal exposure, scalability, and suitability for particular drug molecules. Mechanochemical milling can promote particle-size reduction, structural disorder, and solid-state reactions, whereas melt-based processes can facilitate drug–polymer mixing and the formation of solid dispersions. Dry granulation and compaction primarily improve powder handling and dosage-form manufacturability, although their effects on

dissolution depend on formulation and processing conditions. Consequently, these methods should not all be assumed to increase equilibrium solubility through the same mechanism. Their relative suitability must be established by examining material properties, process parameters, resulting solid-state characteristics, and measured pharmaceutical performance [28,29].

Table 1. Major solvent-free technologies, operating principles, advantages and limitations

S. No.	Technology	Operating principle	Advantages	Limitations
1	Mortar–pestle grinding	Manual application of compressive and shear forces	Simple, inexpensive and suitable for preliminary formulation screening	Low throughput and limited control over energy input and reproducibility
2	Ball milling	Repeated impact, friction and shear between milling media and material	Effective mechanical activation, particle-size reduction and potential amorphization	Heat generation, possible contamination from milling media and scale-up challenges
3	Neat grinding	Mechanical processing without added liquid	Minimal solvent use and simple processing	May produce nonuniform mixing or incomplete solid-state transformation
4	Liquid-assisted grinding (LAG)	A small quantity of liquid facilitates molecular mobility during grinding	Can accelerate cocrystal formation and influence phase selectivity	Requires optimization of liquid identity and quantity; not entirely solvent-free
5	Twin-screw extrusion	Conveying, compression and shear between rotating screws	Continuous processing potential and suitability for industrial throughput	High equipment cost, temperature sensitivity and complex process optimization
6	Mechanochemical cocrystallization	Mechanical activation promotes interactions between a drug and a coformer	Can modify crystal packing and improve dissolution for suitable drug–coformer combinations	Compound-specific performance; phase purity and stability require confirmation
7	Mechanochemical co-amorphization	Mechanical energy disrupts crystalline order in drug–coformer mixtures	May increase apparent solubility and dissolution rate	Risk of recrystallization and moisture-induced instability

8	Polymer-assisted co-grinding	Drug and polymer are mechanically processed together	Can improve drug dispersion, wetting and drug–polymer interactions	Carrier selection, composition and processing conditions require optimization

4.1. MECHANOCHEMICAL AND DRY MILLING APPROACHES

4.1.1. NEAT GRINDING, BALL MILLING, AND HIGH-ENERGY MILLING

Mechanochemical processing uses mechanical forces generated by grinding, milling, impact, or shear to induce changes in pharmaceutical materials. Neat grinding is performed without intentionally adding a liquid, while ball milling enables repeated collisions between the milling media, drug particles, and other formulation components. Depending on the material and operating conditions, these processes can reduce particle size, disrupt crystal packing, introduce defects, or facilitate amorphization and the formation of alternative solid phases. The resulting pharmaceutical performance depends on factors such as milling duration, rotational speed, ball-to-powder ratio, vessel material, and temperature generated during processing. Excessive milling can also cause aggregation, contamination from equipment, or unwanted phase transformations. Therefore, a successful milling process should be optimized rather than judged solely by the extent of particle-size reduction. Powder X-ray diffraction, thermal analysis, particle-size measurements, and dissolution testing can help determine whether the observed improvement results from changes in surface area, solid-state structure, or both [30,31].

4.1.2. CRYOMILLING AND TEMPERATURE-CONTROLLED MILLING

Cryomilling is a specialized milling approach in which cooling is used to limit the temperature rise associated with mechanical processing. It can be useful when conventional milling produces excessive heat, promotes material softening, or increases the risk of thermally induced degradation. Lower processing temperatures may help preserve the chemical integrity of temperature-sensitive compounds while enabling mechanical activation and particle-size reduction. However, cryogenic processing does not guarantee amorphization or improved solubility, because the response depends on the crystal structure, mechanical properties, and milling behaviour of the particular drug. Comparative research on dry-milled poorly soluble compounds has demonstrated that different active ingredients can respond differently to similar milling approaches: changes in crystallinity and dissolution may occur for one compound while another exhibits little improvement. This finding emphasizes the importance of drug-specific process development. Cryomilling should therefore be assessed through comparative solid-state and dissolution studies rather than assumed to be superior to conventional milling in every formulation [32,33].

4.1.3. CO-AMORPHOUS SYSTEMS AND MECHANOCHEMICAL COCRYSTALLIZATION

Ball milling can also be used to prepare co-amorphous systems, in which a drug is combined with a suitable low-molecular-weight coformer to form a disordered solid phase. Such systems may improve apparent solubility by reducing the energetic contribution of a crystalline lattice, while intermolecular interactions between the components can help inhibit molecular mobility and recrystallization. Mechanochemical cocrystallization follows a different pathway: mechanical energy promotes the formation of a new crystalline phase through interactions between the active ingredient and a suitable coformer. The resulting cocrystal may exhibit altered dissolution, solubility, or other physicochemical properties, depending on its structure and stability. These approaches should be distinguished because a co-amorphous material lacks long-range crystalline order, whereas a cocrystal has a defined crystalline structure. Neither approach guarantees a solubility improvement in every case, and the effects must be confirmed using phase characterization, solubility testing, and dissolution experiments [34,35].

4.2. MELT-BASED PROCESSING TECHNOLOGIES

4.2.1. HOT-MELT EXTRUSION

Hot-melt extrusion is a continuous processing technology in which drug substances, polymers, and other excipients are conveyed through a heated barrel and mixed by rotating screws before being forced through a die. The combined influence of temperature, shear, and mixing can promote drug–polymer interactions and produce amorphous solid dispersions or other solid formulations. Its major pharmaceutical advantages include the possibility of continuous operation, reduced reliance on organic solvents, and integration with downstream manufacturing processes. However, processing conditions must be carefully selected to achieve adequate mixing without causing thermal degradation or undesirable phase transformations. Drug loading, polymer viscosity, screw configuration, residence time, and temperature distribution all influence the properties of the

extrudate. Accordingly, successful formulation development requires a balance between processability, solid-state stability, dissolution performance, and manufacturing throughput. Hot-melt extrusion is especially attractive when the drug and carrier can tolerate the required thermal and mechanical conditions [36,37].

4.2.2. KINETISOL AND OTHER HIGH-ENERGY FUSION-BASED TECHNOLOGIES

KinetiSol processing uses intense mechanical energy to generate heat rapidly within a formulation, allowing suitable drug–polymer mixtures to be processed without relying on a conventional external heating profile. This technology can be useful for materials that are difficult to process using conventional hot-melt extrusion because of their thermal sensitivity or processing requirements. Its performance depends on the formulation composition, energy input, processing duration, and resulting material structure. Studies comparing KinetiSol-produced dispersions with spray-dried formulations have demonstrated that manufacturing routes can produce different particle characteristics and dissolution behaviours, even when the same drug and polymer are used. Such differences reinforce the importance of considering process history alongside formulation composition. Nevertheless, high-energy processing may still cause local heating, degradation, or other material changes, and the energy requirement must be evaluated rather than presumed to be lower than that of competing methods. The technology is best assessed through formulation-specific characterization and comparative performance testing [38,39].

4.2.3. MELT GRANULATION AND TWIN-SCREW MELT GRANULATION

Melt granulation is a solvent-free agglomeration technique in which a meltable binder softens or melts during processing and binds powder particles together. Unlike hot-melt extrusion designed to generate a molecularly dispersed drug–polymer system, melt granulation may primarily improve granule formation, flow, compressibility, or controlled drug release. Its effect on solubility and dissolution depends on the properties and concentration of the binder, the distribution of the drug within the granules, and the resulting microstructure. Twin-screw melt granulation offers the additional advantage of continuous mixing and processing, allowing formulation and process variables to be adjusted systematically. Research using poorly soluble drugs has investigated the effects of meltable lipid binders and surface adsorbents on dissolution and physical stability, demonstrating the importance of formulation composition and process conditions. However, excessive binder content or formation of a hydrophobic surface layer may retard drug release. Therefore, melt granulation should be regarded as a potentially useful solvent-free formulation method whose dissolution benefits must be established experimentally [40,41].

4.3. DRY-STATE FORMULATION AND HYBRID PROCESSING

4.3.1. DRY GRANULATION, ROLLER COMPACTION, AND DIRECT COMPRESSION

Dry granulation produces granules through mechanical compaction of powders without the addition of a liquid granulation medium. Common approaches include slugging and roller compaction, in which powders are compressed into larger masses or ribbons and subsequently milled into granules. These operations are particularly useful for moisture-sensitive materials and can simplify manufacturing by avoiding liquid binders and subsequent drying. However, dry granulation is primarily intended to improve powder flow, content uniformity, and manufacturability; it should not automatically be classified as a direct solubility-enhancement technique. Compaction can alter porosity, particle bonding, and disintegration behaviour, potentially accelerating or slowing dissolution depending on the formulation. Recent research has emphasized the importance of evaluating granule dissolution during formulation development, particularly when the active ingredient already exhibits poor dissolution characteristics. Direct compression similarly avoids wet granulation but does not itself guarantee improved drug solubility [42,43].

4.3.2. SOLVENT-FREE MELT GRANULATION FOR MODIFIED DRUG RELEASE

Solvent-free melt granulation can also be used to design formulations in which drug release is controlled by the properties of a meltable binder. During processing, the binder forms bridges between particles and may create a matrix that influences water penetration and drug diffusion. Depending on the formulation, this approach can provide extended release, taste masking, or improved processability without the need for conventional liquid binders. These benefits are distinct from increasing equilibrium solubility, and the desired release profile may sometimes involve deliberately slowing dissolution rather than accelerating it. Consequently, studies involving melt-granulated formulations should be interpreted according to their intended therapeutic objective and compared using appropriate performance measures. Relevant variables include binder identity, binder concentration, impeller speed, granulation duration, particle-size distribution, and tablet structure. This distinction is important for the present review because not all solvent-free processing techniques are designed to increase solubility, even though they may contribute to the development of more effective pharmaceutical dosage forms [44,45].

4.3.3. PHARMACEUTICAL THREE-DIMENSIONAL PRINTING AND FUSION-BASED FABRICATION

Pharmaceutical three-dimensional printing provides a flexible platform for manufacturing dosage forms with tailored geometries, drug loading, and release characteristics. Fused deposition modelling uses a heated nozzle to deposit a softened drug–polymer filament layer by layer, while other printing technologies rely on different mechanisms of material deposition and solidification. When the feed material is designed appropriately, printing can facilitate the manufacture of amorphous solid dispersions or formulations in which processing induces partial or substantial amorphization. Nevertheless, the thermal history, polymer properties, drug distribution, and physical stability of the printed product must be evaluated carefully. Comparative studies of fused deposition modelling and powder-based printing have shown that manufacturing methods can influence solid-state properties, mechanical characteristics, and dosage-form uniformity. Pharmaceutical printing should therefore be considered a specialized manufacturing approach that may incorporate solvent-free processing, rather than assuming that all printing methods are solvent-free or automatically enhance drug solubility [46,47].

4.4. MECHANOCHEMICAL CRYSTALLIZATION AND ALTERNATIVE SOLID FORMS

4.4.1. SOLVENT-FREE COCRYSTALLIZATION AND POLYMORPHIC TRANSFORMATION

Mechanochemical cocrystallization uses mechanical energy to facilitate the formation of crystalline multicomponent materials from an active pharmaceutical ingredient and an appropriate coformer. The process can provide a practical alternative to solution-based crystallization, particularly when suitable components can react or reorganize in the solid state. The properties of the resulting cocrystal depend on the molecular interactions between its components, the crystal packing arrangement, and the stability of the newly formed phase. Mechanochemical processing may also induce polymorphic transformations, producing alternative crystalline forms of the same compound. These transformations can influence dissolution and solubility, although the direction and magnitude of the change are material-specific. Process selection should account for reaction efficiency, product purity, milling conditions, and the feasibility of scaling up the process. In particular, the presence of a small quantity of liquid during liquid-assisted grinding should be explicitly reported, because such processing is solvent-minimized rather than strictly solvent-free [48,49].

4.4.2. HYBRID SOLID-STATE PROCESSING AND TECHNOLOGY SELECTION

Hybrid solid-state processing combines complementary operations to obtain material properties that may be difficult to achieve through a single manufacturing step. For example, mechanochemical activation may be followed by thermal processing, or a prepared solid dispersion may undergo dry granulation and compaction to produce a final dosage form. Such combinations can help balance molecular dispersion, powder flow, mechanical integrity, and dissolution performance. However, every additional processing stage can alter the material's physical state and must be evaluated for its effects on stability and product quality. A suitable technology-selection framework should therefore consider drug thermal sensitivity, required mechanical energy, polymer compatibility, desired solid form, scale-up requirements, and the intended dissolution profile. Environmental claims should likewise be based on process-specific measurements, including solvent use, energy consumption, material losses, and equipment requirements. Ultimately, solvent-free solid-state engineering is most effective when the process is selected to match the drug's physicochemical limitations and the formulation's intended performance [50,52].

5. FORMULATION DESIGN: DRUGS, CARRIERS AND PROCESSING PARAMETERS

5.1. SELECTION OF THE DRUG AND ASSESSMENT OF ITS PHYSICOCHEMICAL PROPERTIES

The design of an effective solid-state formulation begins with a comprehensive assessment of the physicochemical properties of the active pharmaceutical ingredient (API). Important parameters include aqueous solubility, crystal-lattice stability, melting behaviour, thermal sensitivity, molecular structure, particle-size distribution, and the tendency to undergo amorphization or recrystallization. These characteristics help determine whether the drug is more likely to benefit from mechanical activation, particle-size reduction, co-amorphous formulation, or dispersion within a suitable carrier. Drug–polymer miscibility is particularly important when developing amorphous solid dispersions because phase separation and crystallization can compromise both dissolution performance and storage stability. Computational prediction, thermal analysis, and experimental compatibility studies can provide complementary information during early formulation screening. Therefore, drug selection and preformulation assessment should guide the choice of processing

technology and carrier rather than relying on poor aqueous solubility as the sole criterion for formulation development [53, 54].

5.2. SELECTION OF SUITABLE CARRIERS AND FUNCTIONAL EXCIPIENTS

Carrier selection is a major determinant of solid-state formulation performance because excipients influence drug dispersion, wettability, molecular mobility, crystallization, and dissolution behaviour. Commonly investigated polymers include polyvinylpyrrolidone, copovidone, polyethylene glycol, hydroxypropyl cellulose, hypromellose, and hypromellose acetate succinate. Their suitability depends on molecular weight, glass-transition temperature, hygroscopicity, thermal properties, and compatibility with the drug. Hydrophilic carriers can improve wetting and facilitate drug release, whereas appropriate drug–polymer interactions may reduce molecular mobility and inhibit recrystallization. However, the properties of these polymers differ substantially, and no single carrier is optimal for all APIs. Carrier screening should therefore assess the polymer's ability to support the desired solid-state transformation, maintain physical stability, and provide reproducible dissolution performance. The selected excipient must also be compatible with the intended manufacturing method and acceptable for the proposed route of administration [53, 55].

Drug–polymer interactions should be evaluated in both the solid state and the dissolution medium because the mechanisms governing storage stability may differ from those controlling drug release. Hydrogen bonding, electrostatic interactions, and other intermolecular forces can influence drug–polymer miscibility and the physical stability of an amorphous formulation. Solid-state nuclear magnetic resonance can provide molecular-level information about interactions that are difficult to establish using a single conventional characterization technique. Nevertheless, strong interactions alone do not guarantee rapid dissolution or sustained supersaturation. Polymer hydration, medium pH, ionic strength, and the concentrations of dissolved drug and polymer can also influence precipitation and drug release. Consequently, carrier selection should consider both the ability to stabilize the formulation during storage and its behaviour under relevant dissolution conditions [55, 60].

Table 2. Drug–carrier combinations, processing conditions and reported solubility improvement

S. No.	Drug	Carrier/coformer	Processing method and conditions	Reported improvement	Key observation
1	Ibuprofen	Polygonatum sibiricum polysaccharide	Ball milling; drug-to-carrier ratio 1:10; 300 rpm for 4 h	8.22-fold increase in solubility	Carrier-assisted processing improved solubility compared with untreated drug
2	Ibuprofen	Hydroxypropyl methyl cellulose (HPMC)	Co-milling; 18 Hz for 15 min	Approximately 4–5-fold increase in kinetic solubility	Enhancement depended on polymer selection and composition
3	Ibuprofen	Soluplus	Co-milling; 18 Hz for 15 min	Approximately 10–20-fold increase in kinetic solubility	Greater enhancement was reported than with HPMC in the same study
4	Metronidazole	Propyl gallate	Mechanochemical cocrystallization; 1:1 cocrystal composition	Approximately 1.54–2.37-fold increase in solubility	Cocrystal formation modified physicochemical and biopharmaceutical

					properties
5	Brexpiprazole	Succinic acid or catechol	Ball milling; milling conditions optimized	Approximately 2.5-fold enhancement reported	Cocrystal formation influenced solubility and dissolution performance
6	Puerarin	2-Hydroxypropyl-β-cyclodextrin	Ball milling; equimolar ratio; 250 rpm for 90 min	25.33-fold increase in solubility	Inclusion-complex formation also improved drug release and reported bioavailability
7	Indomethacin	Lactose	High-speed vibrating ball milling; 1:1 weight ratio	2.76-fold increase in apparent solubility	Reduced crystallinity and particle size were associated with improved performance

5.3. OPTIMIZATION OF DRUG-TO-CARRIER RATIO AND FORMULATION COMPOSITION

The drug-to-carrier ratio should be optimized experimentally because increasing the polymer concentration does not necessarily produce a proportional improvement in drug solubility or dissolution. An insufficient amount of carrier may provide inadequate stabilization of the amorphous drug, whereas excessive carrier content can reduce drug loading and increase the mass of the final dosage form. The optimal ratio depends on the drug's physicochemical properties, the carrier's functional characteristics, and the selected manufacturing process. Formulation screening should therefore investigate different drug-to-carrier ratios under controlled processing conditions. Relevant responses include apparent solubility, dissolution efficiency, residual crystallinity, drug content, and physical stability. Drug–polymer miscibility is also important because an apparently favourable initial dissolution response may not translate into a stable formulation if phase separation or recrystallization occurs during storage [54, 56].

For formulations containing two or more carriers, the composition should be optimized by considering the individual and combined effects of the excipients. One carrier may improve wettability and powder dispersion, whereas another may provide stronger interactions with the drug or inhibit recrystallization. These functions may complement one another, but they can also produce competing effects on drug release and physical stability. Factorial experimental designs can help identify the influence of individual formulation variables and their interactions, while response-surface approaches can support the optimization of multiple responses. For mechanochemical formulations, the proportions of the drug and carriers should be investigated alongside processing conditions because composition can affect powder behaviour and the outcome of mechanical treatment. The predicted optimum should subsequently be confirmed through independent preparations and suitable solid-state and dissolution testing [56, 57].

5.4. OPTIMIZATION OF PROCESSING PARAMETERS

Processing parameters determine the mechanical and thermal history experienced by the drug and excipients. In dry milling and mechanochemical co-grinding, important variables include milling time, grinding speed, equipment geometry, grinding-media characteristics, and temperature generated during processing. Inadequate mechanical input may leave the drug substantially crystalline, whereas excessive processing can promote agglomeration, unwanted structural transformations, or degradation. The effects of these variables also depend on the formulation composition and the properties of the individual components. Consequently, milling conditions should be optimized together with the drug-to-carrier ratio rather than investigated in isolation. The resulting formulation should be evaluated for particle-size

distribution, crystallinity, dissolution performance, and stability to establish whether the selected conditions have produced a meaningful and reproducible improvement [56, 58].

For thermally driven processing, formulation development should consider processing temperature, residence time, feed rate, and the thermal properties of the drug–carrier mixture. These variables influence polymer softening, drug dispersion, and the risk of thermal degradation. A formulation that initially exhibits an amorphous structure may still be unsuitable if recrystallization occurs during storage or if dissolution performance deteriorates. Manufacturing strategy must therefore be evaluated together with drug–polymer compatibility and physical stability. Insoluble polymers may also be useful in selected solid dispersions, particularly when their properties support drug dispersion or controlled release; however, their inclusion does not automatically improve dissolution in every system. The suitability of the carrier and process should be established experimentally, taking account of the intended drug-release profile and dosage-form requirements [58, 59].

5.5. DESIGN OF EXPERIMENTS AND SELECTION OF THE OPTIMIZED FORMULATION

Design of experiments (DoE) provides a structured approach for investigating how formulation composition and processing parameters influence critical quality attributes. Unlike one-factor-at-a-time experimentation, factorial designs can evaluate multiple variables simultaneously and identify interactions that may affect the response. Potential factors include drug-to-carrier ratio, concentration of individual excipients, milling time, and processing speed, whereas responses may include solubility, percentage drug released, dissolution efficiency, particle size, crystallinity, and physical stability. Statistical modelling can help estimate the effects of these variables and identify promising experimental conditions. However, the design should be appropriate to the number of factors, the expected response behaviour, and the practical experimental range. Any predicted optimum must be confirmed experimentally because a statistically favourable response does not, by itself, establish that the formulation is physically stable, manufacturable, or suitable for pharmaceutical development [54, 57].

The final formulation should be selected using a multi-attribute assessment rather than a single response such as maximum apparent solubility. A formulation that produces a high initial drug concentration may still be unsuitable if precipitation occurs rapidly, drug loading is inadequate, or the product exhibits poor physical stability. A comprehensive evaluation should consider solubility and dissolution enhancement alongside drug content, carrier compatibility, processability, and storage performance. Where appropriate, the optimized formulation should be compared with the untreated drug and a physical mixture prepared using the same excipients. These comparisons help distinguish improvements attributable to the processing method from those caused by the carrier alone. The formulation should then undergo appropriate stability and performance testing before further development. This integrated strategy supports more rational selection of solid-state formulations and reduces the risk of advancing candidates based only on short-term dissolution results [59, 60].

6. SOLID-STATE CHARACTERIZATION AND ANALYTICAL EVALUATION

6.1. IMPORTANCE OF COMPREHENSIVE SOLID-STATE CHARACTERIZATION

Solid-state characterization is essential for establishing whether a formulation process has produced the intended physical transformation and whether the resulting material is suitable for further pharmaceutical development. In poorly water-soluble drug formulations, an increase in apparent solubility does not independently confirm amorphization, molecular dispersion, or the formation of a new crystalline phase. The observed improvement may instead arise from particle-size reduction, enhanced wettability, or changes in drug–excipient interactions. Therefore, analytical evaluation should combine complementary techniques that examine crystallinity, thermal behaviour, molecular interactions, morphology, and dissolution performance. The choice of methods should reflect the formulation composition, drug loading, manufacturing process, and expected solid-state characteristics. A combination of established analytical techniques and advanced methods can provide a more reliable interpretation than any single measurement and help establish links between material properties, formulation stability, and pharmaceutical performance [61].

Table 3. Mechanisms of enhancement and supporting characterization techniques

S. No.	Mechanism	Expected Physicochemical Change	Characterization Technique	Purpose
1	Particle-size reduction	Increased specific surface area	Scanning electron microscopy (SEM),	Evaluates particle morphology and size

			particle-size analysis	distribution.
2	Crystal lattice disruption	Reduced long-range crystalline order	Powder X-ray diffraction (PXRD)	Detects changes in crystallinity and crystalline phases.
3	Amorphous-phase formation	Loss of long-range molecular order	PXRD, differential scanning calorimetry (DSC)	Evaluates amorphous character and thermal transitions.
4	Drug–carrier interactions	Changes in intermolecular interactions	Fourier-transform infrared spectroscopy (FTIR), solid-state nuclear magnetic resonance (ssNMR)	Investigates molecular interactions and chemical environments.
5	Cocrystal formation	Formation of a new crystalline phase	PXRD, FTIR, DSC and single-crystal X-ray diffraction, where feasible	Confirms phase formation and supports structural characterization.
6	Improved wetting	Increased contact between drug particles and the dissolution	Contact-angle measurement, wetting studies and	Evaluates surface wettability and its contribution to
		on medium	dissolution testing	dissolution.
7	Drug–polymer miscibility	More uniform drug distribution within the carrier	DSC, microscopy and solid-state spectroscopy	Assesses phase separation and drug–polymer compatibility.
8	Recrystallization during storage	Development or growth of crystalline drug domains	PXRD, DSC and microscopy	Monitors physical stability and detects recrystallization during storage.
9	Thermal transitions	Changes in glass-transition or melting behaviour	DSC, modulated DSC and thermogravimetric analysis (TGA), where relevant	Evaluates thermal behaviour and potential instability.
10	Improved dissolution performance	Faster or greater drug release into the dissolution medium	In vitro dissolution testing and validated analytical assay	Quantifies drug-release behaviour and dissolution performance.

6.2. POWDER X-RAY DIFFRACTION ANALYSIS

Powder X-ray diffraction (PXRD) is widely used to evaluate the crystalline or amorphous character of pharmaceutical materials. Crystalline substances generally produce characteristic diffraction peaks associated with their ordered lattice structures, whereas amorphous materials typically exhibit broad diffuse scattering. In solid dispersions and co-ground formulations, the reduction or disappearance of

characteristic drug peaks may indicate decreased crystallinity; however, it does not automatically establish complete amorphization. Low drug loading, overlapping peaks from excipients, particle orientation, and instrumental detection limits can affect interpretation. Quantitative analysis may require validated calibration procedures and suitable reference mixtures. PXRD is particularly informative when interpreted alongside thermal analysis and spectroscopic measurements, allowing the investigator to distinguish genuine changes in solid-state order from limitations in detection sensitivity. This combined assessment is important when evaluating whether mechanical processing has altered the crystalline structure of a poorly water-soluble drug [62].

6.3. DIFFERENTIAL SCANNING CALORIMETRY AND THERMAL ANALYSIS

Differential scanning calorimetry (DSC) is used to investigate thermal transitions, including melting, crystallization, and glass-transition behaviour, in pharmaceutical solid dispersions. A reduction or disappearance of the drug's melting endotherm may be consistent with reduced crystallinity or drug incorporation into a carrier matrix. However, the interpretation depends on drug concentration, thermal history, the sensitivity of the instrument, and possible overlap between the thermal events of the drug and excipients. A missing melting peak alone cannot prove that a drug is completely amorphous because the drug may be present below the detection limit or dissolve into the polymer during heating. Modulated DSC can provide additional information by separating reversing and non-reversing thermal events. Thermal results should therefore be interpreted together with PXRD and other suitable methods to establish the physical state of the formulation more confidently [63].

6.4. FOURIER-TRANSFORM INFRARED AND RAMAN SPECTROSCOPY

Fourier-transform infrared (FTIR) spectroscopy is frequently used to investigate functional groups and potential interactions between drugs and excipients. Changes in peak position, intensity, width, or shape may indicate differences in the molecular environment, including possible hydrogen bonding or other intermolecular interactions. Raman spectroscopy provides complementary vibrational information and can be particularly useful when infrared bands overlap or when minimal sample preparation is desirable. Nevertheless, spectral shifts alone do not establish a specific chemical interaction, and the disappearance of a characteristic drug band may result from dilution, signal overlap, or changes in the physical state. Spectral interpretation should therefore consider the spectra of the individual components, physical mixtures, and processed formulations. When combined with thermal analysis and diffraction data, vibrational spectroscopy helps determine whether observed formulation changes are consistent with altered drug–excipient interactions or changes in solid-state organization [64].

6.5. SCANNING ELECTRON MICROSCOPY AND MORPHOLOGICAL EVALUATION

Scanning electron microscopy (SEM) is used to examine particle morphology, surface characteristics, agglomeration, and changes in the appearance of pharmaceutical materials after processing. Comparison of untreated drug, individual excipients, physical mixtures, and co-ground formulations can reveal differences in particle shape, surface roughness, and aggregation patterns. Such observations may help explain changes in powder handling, wetting, and dissolution, particularly when mechanical treatment produces smaller or more irregular particles. However, SEM images cannot independently establish molecular-level dispersion or confirm amorphization because materials with different crystalline states can exhibit similar external morphologies. Sample preparation, coating procedures, and imaging conditions may also influence the observed appearance. Morphological analysis should therefore be treated as complementary evidence and interpreted alongside PXRD, DSC, particle-size measurements, and dissolution testing when evaluating the consequences of solid-state processing [65].

6.6. ATOMIC FORCE MICROSCOPY AND NANOSCALE CHARACTERIZATION

Atomic force microscopy (AFM) provides information about surface topography and nanoscale material properties that may not be resolved adequately by conventional electron microscopy. In amorphous solid dispersions, AFM can help investigate surface heterogeneity, phase-separated domains, local mechanical properties, and changes occurring during storage or dissolution. These measurements are relevant because a formulation may appear homogeneous at the micrometre scale while containing distinct domains at smaller length scales. AFM-based approaches can also contribute to understanding the distribution of drug-rich and polymer-rich regions and how surface properties evolve when the material contacts a dissolution medium. However, interpretation requires appropriate sample preparation, measurement conditions, and complementary analytical evidence. AFM should therefore be used to address specific questions about nanoscale structure rather than as a replacement for bulk techniques such as PXRD and DSC [66].

6.7. ADVANCED THERMAL AND MOLECULAR-LEVEL ANALYTICAL TECHNIQUES

Advanced characterization methods can provide information about structural heterogeneity and local thermal behaviour that conventional bulk measurements may overlook. Nano-thermal analysis combines localized thermal measurements with nanoscale surface characterization, allowing the investigation of transition temperatures and differences between material domains. Solid-state nuclear magnetic resonance (SSNMR) can provide complementary information about molecular environments, mobility, and crystalline or amorphous components. These techniques can be valuable when DSC or PXRD results are inconclusive, particularly in multicomponent formulations or systems containing low levels of residual crystallinity. Nevertheless, advanced methods may require specialized instrumentation, more extensive data analysis, and carefully designed experiments. Their application should therefore be guided by the limitations of routine methods and the specific questions raised during formulation development. Combining bulk and localized measurements can improve understanding of material structure and support more informed evaluation of formulation performance and stability [67].

6.8. INTEGRATED ANALYTICAL EVALUATION AND QUALITY OF EVIDENCE

No single characterization technique can establish all the structural and functional properties required to evaluate a complex solid-state formulation. PXRD assesses long-range crystalline order, DSC investigates thermal transitions, vibrational spectroscopy examines molecular environments, and microscopy reveals morphology or spatial heterogeneity. In combination, these methods provide a stronger basis for interpreting the effects of mechanochemical processing, carrier incorporation, and alternative solid-state formulations. Analytical results should be compared with suitable controls, including the untreated drug, individual excipients, and physical mixtures, wherever appropriate. Method sensitivity, sample representativeness, repeatability, and the possibility of overlapping signals should also be considered when drawing conclusions. Ultimately, characterization findings should be linked to dissolution and stability results rather than interpreted as isolated endpoints. This integrated strategy helps establish whether a formulation has achieved the intended transformation and whether the observed physicochemical changes are relevant to its pharmaceutical performance [68].

7. COMPARATIVE EVALUATION OF SOLUBILITY, DISSOLUTION AND BIOPHARMACEUTICAL PERFORMANCE

7.1. EQUILIBRIUM AND APPARENT SOLUBILITY ASSESSMENT

Comparative solubility assessment is essential for determining whether a solvent-free formulation improves the amount of drug that can be maintained in solution under defined experimental conditions. Equilibrium solubility generally refers to the concentration established in the presence of the thermodynamically stable solid form, whereas apparent or kinetic solubility may reflect transiently elevated concentrations generated by amorphous materials, supersaturation, colloidal species, or drug-rich phases. These measurements should not be treated as interchangeable. Results depend on the medium composition, pH, temperature, equilibration period, solid form, separation method, and analytical procedure. For amorphous formulations, measurements taken at a single time point may miss rapid dissolution followed by precipitation. Therefore, comparative studies should define the solubility term used, describe the experimental protocol, and, where possible, measure concentration as a function of time [69, 70].

Experimental limitations become particularly important when comparing formulations prepared using different technologies. Incomplete separation of suspended particles, adsorption of drug onto filters, changes in the solid form during testing, and differences in analytical sensitivity can all influence the measured concentration. Furthermore, the solubility of an amorphous drug can decrease during the experiment if crystallization occurs before sampling. A meaningful comparison therefore requires appropriate controls, replicate measurements, a validated analytical method, and characterization of residual solids when solid-state transformation is suspected. The magnitude of improvement should be calculated against a clearly identified reference, such as the untreated crystalline drug tested in the same medium. Reporting absolute concentration alongside fold improvement is preferable because fold changes alone can exaggerate the apparent significance of results when the baseline solubility is extremely low [70, 71].

7.2. DISSOLUTION TESTING AND COMPARATIVE RELEASE PROFILES

Dissolution testing provides information about the rate and extent of drug release from a formulation and is therefore complementary to equilibrium solubility assessment. A formulation may exhibit improved apparent solubility but still release the drug slowly because of poor wetting, aggregation, matrix erosion, or limited transport through the carrier. Conversely, a rapidly dissolving formulation may generate a temporary supersaturated concentration that subsequently decreases because of precipitation. Comparative release profiles should therefore report percentage drug released at defined time points, the

dissolution medium and volume, temperature, agitation conditions, sampling procedure, and analytical method. Intrinsic dissolution testing, where appropriate, can help investigate the dissolution behaviour of a material independently of certain dosage-form effects. For solid-state formulations, both discriminating quality-control methods and biorelevant development methods may be needed because they address different questions [70, 72].

Dissolution methods must be selected according to the purpose of the experiment rather than assuming that one method is suitable for all formulation comparisons. Sink conditions are useful for assessing release under conditions where the medium can accommodate the dissolved dose, whereas non-sink methods can reveal supersaturation, precipitation, and differences between crystalline and amorphous materials. For amorphous solid dispersions, a conventional sink dissolution test may not adequately capture the formulation's ability to maintain elevated concentrations in solution. On the other hand, non-sink methods can be sensitive to medium volume, pH, hydrodynamics, sampling time, and the presence of nucleation-promoting particles. Accordingly, formulation screening, mechanistic investigation, and routine product quality control may require different dissolution approaches. Results should be interpreted within the context of the selected method, with particular attention to reproducibility and the ability to distinguish meaningful differences between formulations [70, 71].

7.3. SUPERSATURATION, PRECIPITATION KINETICS AND BIOPHARMACEUTICAL PERFORMANCE

Amorphous and other high-energy solid-state formulations can generate concentrations above the equilibrium solubility of the stable crystalline drug. This phenomenon, known as supersaturation, can increase the concentration gradient available for drug transport across biological membranes. However, the benefit depends not only on the maximum concentration achieved but also on how long the elevated concentration is maintained before nucleation and crystal growth reduce the dissolved fraction. Precipitation inhibitors and suitable carriers may prolong supersaturation, although their effectiveness varies with drug properties, polymer concentration, and gastrointestinal conditions. Experimental approaches that monitor concentration over time, including solvent-shift, pH-shift, and nanoseeded desupersaturation tests, can provide useful information about precipitation risk. Such measurements help distinguish formulations that produce a brief concentration spike from those that maintain potentially useful drug concentrations for longer periods [71, 73].

In vitro dissolution performance does not necessarily translate directly into improved oral bioavailability. Drug absorption depends on the concentration of absorbable drug at the intestinal membrane, permeability, gastrointestinal transit, precipitation, and the dynamic movement of drug between gastrointestinal compartments. Some polymers may increase apparent solubility while simultaneously affecting the free-drug fraction or membrane transport, so total measured concentration may not be a reliable proxy for permeable drug. Biorelevant media, sequential gastric-to-intestinal pH conditions, and dissolution–permeation models can help evaluate these effects. More complex gastrointestinal simulation systems may provide additional mechanistic information, but their predictive value depends on method validation and the biological processes represented. Consequently, in vitro–in vivo relationships should be established using appropriate pharmacokinetic evidence rather than inferred from solubility enhancement or a single dissolution endpoint alone [69, 74].

7.4. COMPARATIVE ASSESSMENT OF REPRESENTATIVE FORMULATIONS

Comparative assessment should distinguish improvements in solubility, dissolution rate, and systemic exposure because these outcomes describe different aspects of pharmaceutical performance. Mechanochemically processed crystalline systems may benefit from particle-size reduction, improved wetting, or changes in crystal form, whereas co-amorphous formulations and amorphous solid dispersions may generate supersaturation through their higher-energy solid state. Cocrystals can modify dissolution behaviour through changes in lattice properties and solid-state interactions. However, the magnitude of improvement depends on the drug, coformer or carrier, composition, processing conditions, and experimental medium. A numerical increase reported for one compound should not be assumed to apply to another compound or technology. Comparative tables should report the original and optimized values, the test conditions, the reference formulation, and whether the reported outcome concerns equilibrium solubility, apparent solubility, dissolution, or pharmacokinetics [75, 76].

A useful comparative framework should also evaluate the practical advantages and limitations of each solvent-free technology. Dry milling and mechanochemical co-grinding can reduce solvent requirements and are suitable for screening solid-state transformations, but they may face challenges related to scale-dependent energy transfer, agglomeration, contamination from equipment, and reproducibility. Hot-melt extrusion offers continuous processing and can produce relatively homogeneous drug–polymer

systems, but it requires suitable thermal stability and rheological behaviour. Dry granulation and roller compaction can improve manufacturability without a liquid binder, although densification may affect disintegration and dissolution. Fusion-based printing can combine formulation and dosage-form fabrication, but thermal exposure and equipment constraints need to be considered. Therefore, technology selection should balance the magnitude of performance improvement with processability, stability, material compatibility, and the intended commercial dosage form [77, 78].

8. PHYSICAL STABILITY AND LONG-TERM PERFORMANCE

8.1. RECRYSTALLIZATION, PHASE SEPARATION AND MOLECULAR MOBILITY

Physical stability is a major challenge for amorphous pharmaceutical formulations because the amorphous state generally possesses higher free energy than the corresponding stable crystalline form. During storage, molecular mobility may permit nucleation, crystal growth, phase separation, or other structural changes that reduce the original solubility and dissolution advantage. These processes are influenced by drug–polymer miscibility, intermolecular interactions, residual crystallinity, and the molecular mobility of the formulation. Even a small amount of residual crystalline material can act as a nucleation site under favourable conditions. Consequently, the initial absence of prominent diffraction peaks does not guarantee long-term stability. Stability evaluation should investigate whether the formulation maintains its solid-state characteristics and performance during storage, using complementary analytical methods and dissolution testing rather than relying exclusively on its initial characterization [79, 80].

8.2. INFLUENCE OF TEMPERATURE, HUMIDITY AND PACKAGING

Temperature and relative humidity can substantially influence the physical stability of amorphous formulations. Increasing temperature may enhance molecular mobility, while absorbed moisture can plasticize certain polymers and reduce their effective glass-transition temperature. These effects may increase the probability of phase separation or recrystallization, although the response depends on the particular drug–carrier system. Packaging therefore forms an important part of stability strategy: moisture-barrier materials, appropriate container closure systems, and desiccants where justified can reduce exposure to destabilizing environmental conditions. The influence of storage conditions should be evaluated experimentally rather than assumed from the properties of the individual ingredients. Studies of spray-dried naproxen–polyvinylpyrrolidone dispersions, for example, have specifically investigated the relationship between storage humidity and formulation stability. Such evidence illustrates why environmental control and packaging selection must be considered during formulation development [81, 82].

8.3. POLYMER SELECTION AND MAINTENANCE OF DISSOLUTION PERFORMANCE

Polymer selection influences physical stability through its effects on drug–polymer miscibility, molecular mobility, nucleation, and crystal growth. A carrier with suitable interactions and sufficient capacity to accommodate the drug may help maintain an amorphous structure, while an unsuitable combination may undergo phase separation even when the initial formulation appears homogeneous. Glass-transition behaviour is also relevant because the molecular mobility of a formulation depends not only on the glass-transition temperature of the pure polymer but also on composition, moisture content, and the properties of the drug–polymer mixture. Stability studies should therefore monitor both structural changes and functional performance. A formulation may retain an apparently amorphous character yet show changes in dissolution due to surface transformations, aggregation, or changes in drug–excipient distribution. Periodic assessment of crystallinity, thermal properties, drug content, and dissolution helps establish whether the formulation maintains its intended performance [83, 84].

9. SCALE-UP, SUSTAINABILITY, QUALITY CONTROL AND REGULATORY CONSIDERATIONS

9.1. LABORATORY-TO-INDUSTRIAL SCALE-UP AND REPRODUCIBILITY

Translating a solvent-free formulation from laboratory preparation to industrial manufacture requires evidence that the process remains reproducible when equipment geometry, throughput, material handling, and energy transfer change. Laboratory mortar–pestle grinding and small-scale milling are useful for initial screening, but their operating conditions do not necessarily translate directly to larger equipment. In mechanochemical processing, the distribution of mechanical energy, powder loading, residence time, temperature rise, and equipment wear may influence the final solid-state characteristics. Continuous processing approaches, including twin-screw extrusion, offer opportunities to control material flow and integrate processing stages, but they require appropriate process development and validation. Scale-up should therefore establish relationships between operating parameters and critical quality attributes, supported by representative batches, material balances, and suitable analytical testing. Reproducibility should be demonstrated across

batches rather than inferred from a single successful preparation [85, 86].

9.2. QUALITY BY DESIGN, CRITICAL QUALITY ATTRIBUTES AND PROCESS ANALYTICAL TECHNOLOGY

Quality by Design provides a systematic framework for identifying how material properties and process parameters influence final product quality. The approach begins with defining the intended product profile, followed by identifying critical quality attributes, assessing risks, and establishing a control strategy. For solvent-free formulations, potentially important attributes include drug content, solid-state form, residual crystallinity, particle-size distribution, dissolution performance, and physical stability. Critical process parameters may include milling time, processing temperature, screw speed, feed rate, or compaction force, depending on the technology. Process Analytical Technology (PAT) can support this framework through measurements that monitor material or product properties during manufacture. Spectroscopic tools, including near-infrared and Raman spectroscopy, may be useful for monitoring selected attributes when suitable calibration, validation, and data interpretation procedures are established [87, 88].

The value of PAT depends on whether the measured signals reliably represent the quality attributes of interest. A sensor may detect changes in a material spectrum, for example, without uniquely identifying the cause of those changes. Calibration models must therefore be developed using representative samples and validated across the intended operating range. Process monitoring should also distinguish normal variability from deviations that could affect the final product. When integrated with appropriate statistical process control and a defined response strategy, PAT can help identify deviations earlier than end-product testing alone. However, PAT does not eliminate the need for validated analytical methods, equipment qualification, or appropriate release testing. For solvent-free processing, the strongest approach combines process understanding, risk-based monitoring, and finished-product testing to establish a defensible control strategy [89, 90].

9.3. SUSTAINABILITY, ENERGY CONSUMPTION AND GREEN CHEMISTRY METRICS

Solvent-free processing can reduce or eliminate the need for organic solvents in the manufacturing step under consideration, potentially lowering solvent procurement, recovery, handling, and waste-treatment requirements. Nevertheless, the absence of solvent does not automatically establish that a process is environmentally superior. Grinding, extrusion, and other mechanically intensive operations consume energy, and their environmental impact depends on equipment efficiency, production scale, throughput, yield, cleaning requirements, and the source of electricity. Sustainability assessments should therefore compare complete and functionally equivalent processes rather than considering solvent use in isolation. Useful indicators include process mass intensity, E-factor, energy consumption, waste generation, and life-cycle environmental impacts. A process that eliminates solvent but requires excessive energy or produces substantial material loss may not deliver the expected overall benefit. Transparent reporting of system boundaries and assumptions is essential for meaningful comparison between solvent-free and conventional approaches [91, 92].

Table 4. Comparative performance, stability, scale-up readiness and sustainability

S. No.	Technology	Solubility and Dissolution Potential	Physical Stability Considerations	Scale-Up Readiness	Sustainability Considerations
1	Mortar–pestle grinding	Variable enhancement; suitable for preliminary formulation screening	Depends on formulation composition and extent of solid-state transformation	Low for commercial-scale production	Requires little or no solvent but has limited throughput.
2	Ball milling	Can substantially improve solubility and dissolution, depending on the drug and	Amorphous products may recrystallize, and crystalline phases may change	Moderate; industrial milling equipment is available	Often solvent-free, but energy consumption and milling-media wear must be

		formulation			considered.
3	Liquid-assisted grinding (LAG)	Can facilitate cocrystal formation and solid-state transformations	Depends on the resulting phase and potential effects of residual liquid	Moderate; liquid dosing and process control require optimization	Uses limited liquid compared with many solution-based methods but is not entirely solvent-free.
4	Mechanochemical cocrystallization	May improve solubility and dissolution for suitable drug–coformer combinations	Depends on crystal form, moisture exposure and phase stability	Moderate; composition and phase purity must be controlled	Can reduce solvent consumption and solvent-recovery requirements.
5	Mechanochemical co-amorphization	May increase apparent solubility and dissolution rate	Susceptible to recrystallization and moisture-induced instability	Moderate; requires formulation-specific stability evaluation	Offers potential solvent savings, although stability-related waste must also be considered.
6	Polymer-assisted co-grinding	Can improve drug wetting, dispersion and dissolution	Depends on drug–polymer miscibility and moisture sensitivity	Moderate; depends on process consistency and production throughput	May reduce solvent use, but polymer consumption and energy demand remain relevant.
7	Twin-screw extrusion	Can produce uniform solid dispersions and improve dissolution performance	Depends on polymer selection, processing temperature and drug loading	High potential for continuous, large-scale production	May reduce solvent use, although heating energy and equipment requirements must be assessed.

9.4. EQUIPMENT LIMITATIONS, PROCESS ECONOMICS AND REGULATORY TRANSLATION

The industrial feasibility of solvent-free technologies depends on equipment availability, material compatibility, maintenance requirements, contamination control, and the cost of achieving consistent product quality. High-energy milling may introduce wear-related contamination or generate heat that affects sensitive materials, whereas extrusion requires suitable thermal and rheological properties and can be constrained by torque, throughput, and residence-time distribution. Dry granulation can avoid liquid processing but may alter granule density, compactability, disintegration, and dissolution. These limitations should be evaluated alongside equipment

investment, energy use, cleaning, product yield, and process robustness. Regulatory translation also requires documented process understanding, appropriate validation, and evidence that the manufactured product consistently meets its specifications. Solvent-free processing should consequently be regarded as a manufacturing strategy that requires product-specific qualification, not as an automatic substitute for conventional processes in every pharmaceutical application [93, 94].

10. CRITICAL PERSPECTIVES, RESEARCH GAPS AND FUTURE DIRECTIONS

10.1. COMPARATIVE STRENGTHS AND LIMITATIONS OF SOLVENT-FREE TECHNOLOGIES

Solvent-free technologies offer several potential advantages, including reduced solvent handling, fewer solvent-removal steps, and opportunities for mechanochemical transformation or continuous manufacturing. However, the technologies differ substantially in their operating principles and material requirements. Dry milling is particularly useful for particle-size reduction and mechanically induced changes in solid-state structure, while melt-based processes can generate drug–polymer dispersions when suitable thermal conditions are available. Dry granulation supports the manufacture of solid dosage forms without a liquid binder, but its effect on compaction and release must be evaluated. Fusion-based printing can integrate formulation and dosage-form fabrication but is constrained by feedstock requirements, thermal exposure, and equipment-specific parameters. Consequently, no single solvent-free technology can be considered universally superior. Selection should be based on drug properties, the intended formulation mechanism, manufacturing requirements, and the quality attributes that must be maintained throughout the product lifecycle [95, 96].

10.2. STANDARDIZATION OF SOLUBILITY MEASUREMENTS AND REPORTING

A major research gap is the lack of consistent reporting across studies that evaluate solubility enhancement using different solid-state technologies. Investigations may differ in medium composition, pH, temperature, drug loading, equilibration time, sample separation, analytical method, and the definition of solubility itself. These differences can make it difficult to compare reported fold improvements directly. Apparent solubility, equilibrium solubility, kinetic solubility, and supersaturation should be distinguished explicitly, with concentration–time profiles reported when transient behaviour is important. Studies should also identify the reference formulation and provide absolute values alongside fold changes. In addition, reporting the physical state of the residual solid and describing replicate variability can improve interpretation of the results. Adoption of more harmonized experimental protocols would support more reliable cross-study comparisons, strengthen evidence synthesis, and help identify which solvent-free approaches produce reproducible improvements rather than method-dependent differences [97].

10.3. PREDICTIVE MODELLING, MOLECULAR SIMULATION AND ARTIFICIAL INTELLIGENCE

Predictive modelling may reduce reliance on trial-and-error formulation development by estimating drug–carrier compatibility, molecular interactions, phase behaviour, and the likelihood of maintaining an amorphous state. Molecular simulation can provide information about drug–excipient interactions and molecular mobility, while machine-learning methods can identify relationships between material descriptors, process parameters, and observed formulation outcomes. These approaches could be particularly useful when screening multiple carriers or optimizing several processing variables simultaneously. However, their reliability depends on the quality, diversity, and consistency of the training data. Models developed using one drug class, carrier family, or manufacturing process may not generalize to different systems without additional validation. Future studies should combine computational predictions with well-designed experiments, clearly documented datasets, and independent validation. Predictive models should be assessed not only for statistical accuracy but also for their practical value in selecting stable formulations and identifying operating conditions that are compatible with pharmaceutical manufacturing [98, 99].

10.4. CONTINUOUS MANUFACTURING, HYBRID PROCESSING AND FUTURE RESEARCH PRIORITIES

Future development of solvent-free pharmaceutical processing will likely involve improved integration of mechanochemical operations, continuous manufacturing, process monitoring, and data-driven control. Continuous systems may improve throughput and reduce batch-to-batch variability when material feeding, residence time, energy input, and product quality can be controlled adequately. Hybrid approaches may also combine mechanical activation with extrusion, dry granulation, or subsequent compaction to achieve specific solid-state and dosage-form properties. However, the benefits of integration must be demonstrated through process performance, product quality, and sustainability assessments. Important research priorities include defining robust scale-up principles, improving the comparability of solubility and dissolution measurements, developing reliable long-term stability predictions, and validating real-time analytical methods. Ultimately, successful

translation will depend on evidence that solvent-free formulations consistently maintain their intended performance during manufacture, storage, and use, while offering a demonstrable practical or environmental advantage over suitable alternatives [100].

Table 5. Research gaps and future opportunities in pharmaceutical mechanochemistry

S. No.	Research gap	Current challenge	Future research opportunity	Expected benefit
1	Limited process standardization	Milling speed, duration, energy input and equipment geometry vary between studies	Develop standardized protocols and report critical process parameters	Better reproducibility and comparability
2	Incomplete mechanistic understanding	Relationships between mechanical energy, molecular interactions and phase transformations remain formulation-dependent	Combine in situ measurements with complementary solid-state characterization	Improved understanding of transformation pathways
3	Physical instability	Amorphous systems may recrystallize during storage or moisture exposure	Investigate stabilizing carriers, moisture barriers and optimized compositions	Improved shelf life
4	Limited predictive formulation design	Carrier selection and processing conditions often rely on empirical screening	Integrate molecular modelling, machine learning and experimental design	Faster formulation development and reduced trial-and-error work
5	Scale-up challenges	Energy distribution and residence time may change with equipment and batch size	Compare laboratory, pilot and industrial processing using defined scale-up criteria	More reliable technology transfer
6	Insufficient process monitoring	Critical transformations may not be detected during processing	Develop process analytical technology using suitable in-line monitoring methods	Better process control and product consistency
7	Inconsistent performance testing	Solubility and dissolution results differ across media and test methods	Establish comparable test conditions and report methods transparently	More meaningful comparison between formulations
8	Limited long-term	Short studies	Conduct appropriat	Stronger

	stability evidence	may not identify delayed recrystallization or phase separation	ely designed long-term and accelerated stability studies	evidence for product quality
9	Incomplete sustainability assessment	Solvent reduction alone does not establish overall environmental benefit	Evaluate energy, material use, waste and life-cycle impacts	More defensible sustainability claims
10	Regulatory and quality-control uncertainties	Critical quality attributes and controls may differ across formulations	Apply quality-by-design, risk assessment and suitable analytical controls	Better manufacturing consistency and regulatory readiness
11	Limited continuous-processing evidence	Few formulations have comprehensive data linking continuous processing to long-term product quality	Evaluate continuous mechanochemical platforms and process monitoring	Greater industrial scalability
12	Inadequate links to biopharmaceutical outcomes	Increased apparent solubility may not translate directly into improved absorption	Combine dissolution, supersaturation, permeability and relevant biopharmaceutical studies	Better prediction of clinical relevance

11. CONCLUSION

Mechanochemical approaches have emerged as promising and sustainable strategies for enhancing the solubility and dissolution rate of poorly water-soluble drugs by modifying their solid-state properties. Techniques such as grinding, ball milling, liquid-assisted grinding, cocrystallization, and co-amorphization can reduce crystallinity, promote amorphous formation, and improve drug–carrier interactions, thereby enhancing dissolution performance. Compared with conventional solvent-intensive techniques, solvent-free mechanochemical processing offers potential advantages, including reduced solvent consumption, lower waste generation, and simplified manufacturing.

However, the effectiveness of these approaches depends on several factors, including drug properties, carrier selection, drug-to-carrier ratio, processing conditions, and the physical stability of the resulting formulation. Increased apparent solubility alone does not guarantee improved bioavailability; therefore, comprehensive evaluation through solubility and dissolution studies, solid-state characterization, and long-term stability testing remains essential.

Future research should focus on developing standardized processing protocols, improving scale-up and reproducibility, and integrating process analytical technologies and predictive modelling into formulation development. Quantitative sustainability assessments and appropriate quality-control strategies are also necessary to establish the industrial feasibility of these methods. Overall, mechanochemistry represents a valuable platform for solid-state engineering and pharmaceutical formulation development, with considerable potential to produce efficient, stable, and environmentally responsible formulations of poorly water-soluble drugs. Its successful application will depend on rigorous scientific evaluation, reliable manufacturing processes, and evidence that laboratory-scale improvements translate into meaningful pharmaceutical performance.

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