RESEARCH PAPER

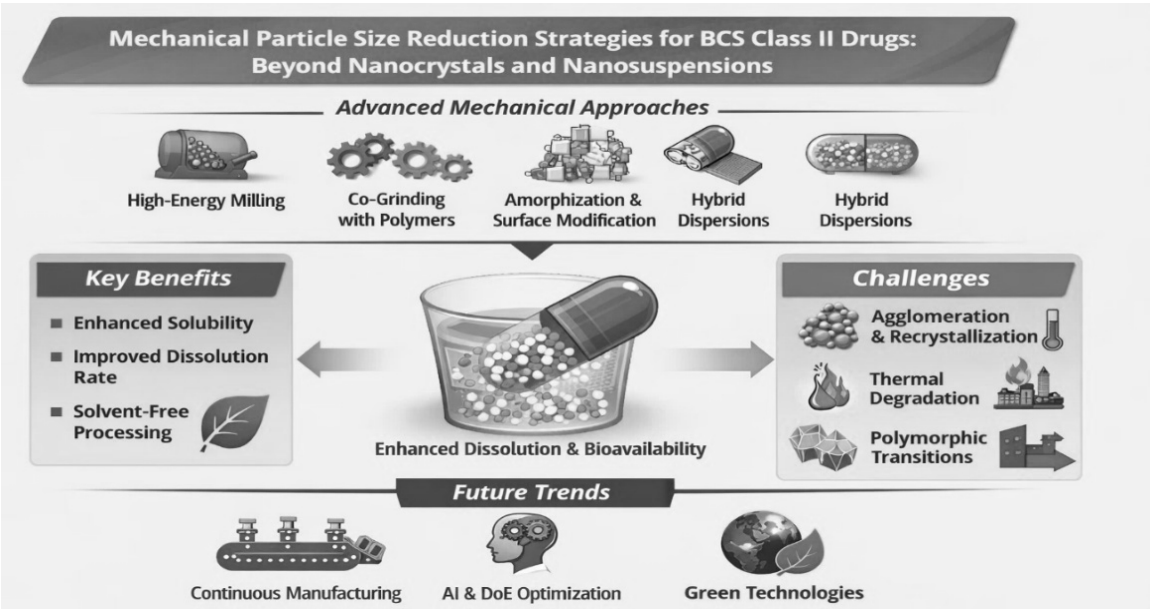
Mechanical Particle Size Reduction Strategies for BCS Class II Drugs: Beyond Nanocrystals and Nanosuspensions

Adil Patel[1]*, Chirag Parmar[2], Karishma Karia[1], Nirali Parmar[1], Zankhana Sheth[3]

[1]Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology (CHARUSAT), CHARUSAT Campus, Changa-388421, India
[2.]Shivam pharmaceutical studies and research centre, Valasan
[3.]Assistant Professor, Shivam Pharmaceutical Studies and Research Center,
Email: zankhnaz@gmail.com
Corresponding Author:
Dr. Adil Patel
Email: Adilpatel.ph@charusat.ac.in

ABSTRACT

Poor aqueous solubility of Biopharmaceutics Classification System (BCS) Class II drugs remains a major barrier to oral bioavailability and clinical performance. While nanocrystals and nanosuspensions have dominated recent formulation strategies, mechanical particle size reduction techniques offer a broader and more versatile toolkit for modifying solid-state properties beyond simple size minimization. This review critically examines advanced mechanical processing approaches—including high-energy milling, co-grinding, cryogenic milling, and mechanochemical treatments—as transformative strategies for enhancing dissolution, wettability, and interfacial behavior of poorly soluble drugs. Emphasis is placed on how mechanical forces can induce controlled amorphization, generate co-amorphous systems, promote drug–excipient interactions, and tailor surface energy without reliance on organic solvents. The role of polymers, surfactants, and processing aids in stabilizing milled systems and preventing recrystallization is discussed in depth, along with structure–property relationships governing performance. Emerging hybrid approaches that combine mechanical activation with solid-state engineering, such as co-crystals, eutectics, and composite particles, are highlighted as next-generation alternatives to conventional nanocrystals. Finally, the review addresses scalability, regulatory considerations, and industrial feasibility, positioning mechanical particle engineering as a sustainable and practical pathway for improving the biopharmaceutical performance of BCS Class II drugs..



Keywords: BCS Class II drugs, Mechanical milling, Amorphization, Co-grinding, Wettability enhancement, Solid-state engineering, Drug–excipient interactions, Bioavailability.

**Author for Correspondence: Saswati Sahoo*

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INTRODUCTION

In Biopharmaceutical Classification System the class II drugs are defined as having low solubility in aqueous media but high permeability across biological membranes. This means that while these drugs can be absorbed well once they are dissolved, their low solubility can limit their bioavailability when administered orally.

In pharmaceutical science, the slowest step determines the overall speed of the process. For Class II drugs, the rate-limiting step is Dissolution. Because these drugs dissolve slowly, they often pass through the "absorption window" in the small intestine before they have a chance to enter the solution. [1,2]

As a result, improving their solubility and dissolution rate is a major focus in formulation science. Various advanced delivery strategies, including particle size reduction and lipid-based systems, are employed to overcome these limitations and enhance therapeutic effectiveness.

Nanocrystals and nanosuspensions are widely used to improve the solubility and bioavailability of BCS Class II drugs by reducing particle size and enhancing dissolution. However, despite their advantages, these systems have several limitations i.e. Stability issues, Manufacturing and scalability challenges, Limited improvement in bioavailability, Safety and regulatory concerns and Dosage form limitations that affect their practical application. [3]

The rationale for exploring alternative mechanical particle size reduction strategies for BCS Class II drugs arises from the limitations and challenges associated with conventional approaches like nanocrystals and nanosuspensions. While these traditional methods effectively enhance dissolution and oral bioavailability by increasing surface area and saturation solubility, they are sometimes insufficient to fully overcome bioavailability barriers, especially when drug dissolution is not the sole limiting factor

Alternative mechanical approaches provide better control over particle size and also allow modification of important drug properties such as crystal shape, polymorphic form, and amorphous content, all of which strongly influence solubility and dissolution behavior. For instance, changes in crystal habit can affect surface characteristics and wettability, leading to improved dissolution and drug absorption . In addition, combining mechanical size reduction with advanced formulation strategies, such as polymeric nanomicelles or solid dispersions, offers a more comprehensive solution to solubility problems by improving formulation stability and enhancing overall bioavailability. [4,5]

Recent mechanical approaches offer advantages such as shorter processing times, lower energy requirements, and better control over particle size and surface properties, which support large-scale and industrial production These methods are particularly important for BCS Class II drugs, where drug absorption and solubility often show nonlinear and dose-dependent behavior, meaning that simple particle size reduction does not always result in proportional improvements in bioavailability

Therefore, the use of alternative mechanical strategies enables more precise control over drug physical properties, helps overcome the limitations of conventional size-reduction techniques, and supports the development of more effective and reliable oral formulations for poorly water-soluble drugs. [6,7]

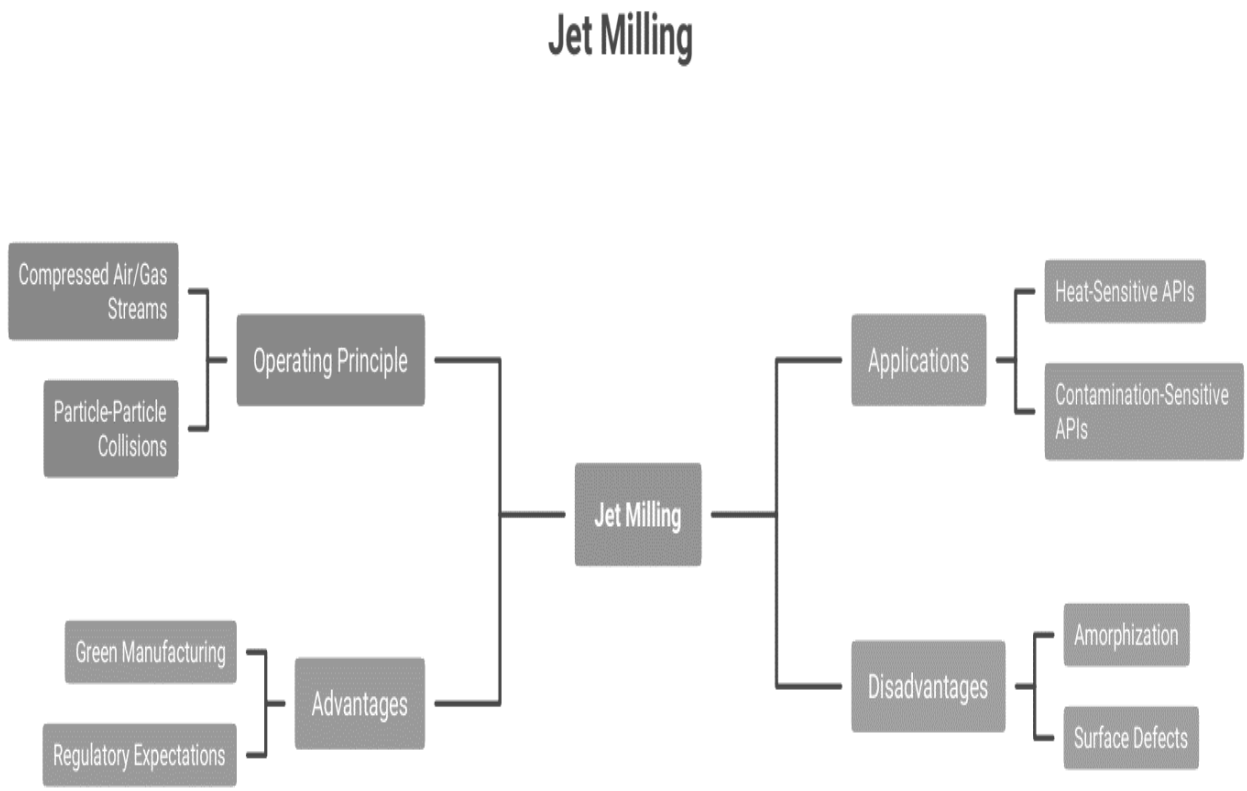
Advantages of mechanical methods over chemical modification approaches

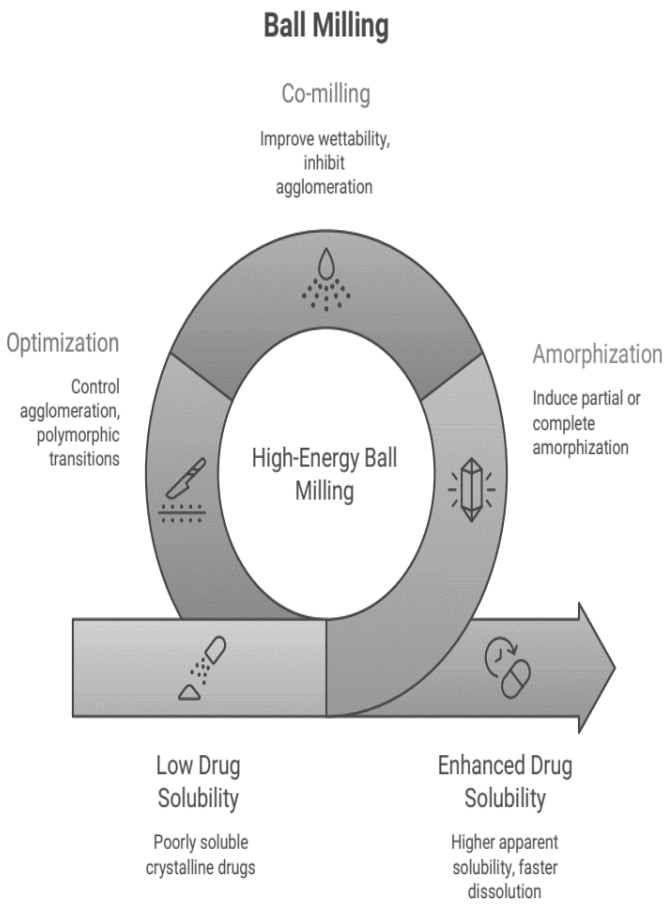
Preservation of Chemical Structure and Safety Profile
Simplicity and Direct Impact on Physical Properties
Flexibility and Applicability across Diverse Drugs
Avoidance of Chemical Stability Issues
Regulatory and Manufacturing Advantages
Environmentally Friendly and Cost-Effective
Residual Solvent Issues

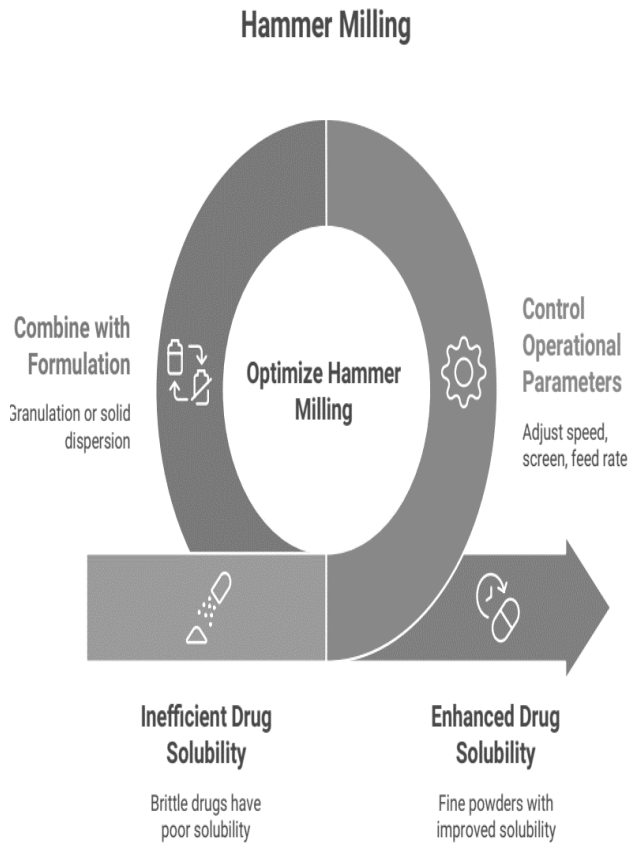
Some other problems that might occur includes rapid nucleation, uncontrolled crystal growth, Ostwald Ripening, difficulty in scaling up and reproducibility. [8,9]

Conventional Mechanical Size Reduction Techniques

Conventional mechanical size reduction techniques are widely used in pharmaceutical manufacturing to reduce particle size, improve flow, and enhance dissolution of poorly soluble drugs. These methods rely on the application of mechanical energy through impact, compression, shear, or attrition. Common techniques include hammer milling, ball milling, fluid energy (jet) milling, and attrition milling. Although these techniques are simple, scalable, and cost-effective, they may generate heat, induce amorphization, or cause aggregation, necessitating careful process control and use of stabilizers. [10,11,12]




Ball Milling
Co-milling
Improve wettability, inhibit agglomeration
Optimization
Control agglomeration, polymorphic transitions
High-Energy Ball Milling
Amorphization
Induce partial or complete amorphization
Low Drug Solubility
Poorly soluble crystalline drugs
Enhanced Drug Solubility
Higher apparent solubility, faster dissolution


Hammer Milling
Combine with Formulation
Granulation or solid dispersion
Optimize Hammer Milling
Control Operational Parameters
Adjust speed, screen, feed rate
Inefficient Drug Solubility
Brittle drugs have poor solubility
Enhanced Drug Solubility
Fine powders with improved solubility

Limitations of Conventional Micronization

Particle Aggregation

Uncontrolled Amorphization

Thermal Stress

Broad Particle Size Distribution

Limited Solubility Enhancement

Overall, these limitations have driven interest in advanced and hybrid particle engineering approaches beyond conventional micronization. [13,14]

High-Energy Milling Techniques in Pharmaceutical Nanotechnology

High-energy milling techniques have emerged as powerful top-down approaches for particle size reduction, amorphization, and nanostructuring of pharmaceutical materials. These methods are widely used to improve the solubility, dissolution rate, bioavailability, and stability of poorly water-soluble drugs. Unlike chemical synthesis routes, high-energy milling relies on mechanical energy to induce structural and morphological changes in materials without altering their chemical composition. Among the most prominent techniques are planetary ball milling, cryogenic milling, and bead milling innovations. [15,16,17]

Parameter	**Planetary Ball Milling**	**Cryogenic Milling**	**Bead Milling (Media Milling)**
Type of milling	Dry, high-energy milling	High-energy milling at very low temperature	Wet milling
Principle	Material is placed in rotating jars with grinding balls; jars rotate on their own axis and around a central axis	Material is milled under liquid nitrogen to make it brittle	Drug is dispersed in liquid with stabilizers and milled using tiny beads
Energy source	Centrifugal force causing collision, shear, and friction	Mechanical impact under cryogenic conditions	High shear and bead collision
Grinding media	Zirconia, stainless steel, or tungsten carbide balls	Not applicable (material becomes brittle due to cold)	Zirconia or ceramic beads (0.1–1.0 µm)

Temperature effect	Generates heat	Very low temperature prevents heat build-up	Controlled temperature systems minimize heat
Effect on drug	Can induce amorphization and reduce crystallinity	Preserves chemical stability of heat-sensitive drugs	Produces fine particles with good stability
Particle size achieved	Can reach nanometer range	Fine particle size without degradation	Nano-sized particles suitable for nanosuspensions
Main pharmaceutical use	BCS Class II & IV drugs, mechanochemistry, co-crystals	Polymers, waxes, resins, thermolabile drugs	Injectable, oral, and topical nanosuspensions
Advantages	Effective size reduction, induces amorphization	Prevents thermal degradation and agglomeration	Better control of particle size, scalable
Limitations	Heat generation, contamination risk, poor scalability	Expensive due to liquid nitrogen, specialized equipment	Requires stabilizers and additional processing steps
Industrial scalability	Limited	Limited	Highly scalable (continuous processing possible)

Table 1: comparison of different High-Energy Milling Techniques in Pharmaceutical Nanotechnology

Dry vs Wet Mechanical Processing in Pharmaceutical Milling

Mechanical processing is a widely used top-down approach for particle size reduction and modification of solid-state properties of pharmaceutical materials. [18,19,20]

Parameter	**Dry Mechanical Processing**	**Wet Mechanical Processing**
Definition	Milling carried out without any liquid medium	Milling carried out in a liquid medium with stabilizers/surfactants

Common Techniques	Planetary ball milling, jet milling, cryogenic milling	Bead milling, high-pressure homogenization
Use of solvent	No solvent required (solvent-free process)	Requires liquid medium (solvent or aqueous dispersion)
Drying step required	Not required	Required (filtration/evaporation/lyophilization)
Heat generation	High heat generation possible	Lower heat generation (better temperature control)
Control over particle size	Less control; broader size distribution	Better control; narrow size distribution
Risk of agglomeration	High risk due to static charges and surface energy	Low risk due to dispersing medium
Effect on drug structure	Can induce amorphization (improves solubility)	Generally maintains stability; less structural damage
Suitability of materials	Best for brittle, heat-stable materials	Suitable for thermolabile and sensitive drugs
Pharmaceutical application	Used for micronization of powders	Preferred for nanosuspensions and nanocrystals
Process complexity	Simple and faster	More complex with extra steps
Cost & scalability	Generally lower cost but limited control	Higher cost but better product quality

Table 2: Comparison of Dry vs Wet Mechanical Processing

Role of stabilizers and processing aids: In wet milling, stabilizers (e.g., PVA, PVP, Poloxamer 188, HPMC, and lecithin) play a crucial role in preventing particle aggregation by providing steric or electrostatic stabilization. Processing aids such as surfactants reduce interfacial tension, improve wettability, and enhance milling efficiency. In dry milling, small amounts of glidants (e.g., silica or

magnesium stearate) may be used to reduce friction and agglomeration. [20,21]

Co-grinding and Solid-State Mechanical Approaches in Pharmaceuticals

Co-grinding and solid-state mechanical processing have gained significant attention as green, solvent-minimized, and scalable strategies for modifying the physicochemical properties of pharmaceutical materials. These approaches rely on mechanical energy to induce structural, morphological, and intermolecular changes without the need for chemical synthesis or extensive solvent use. They are particularly valuable for enhancing solubility, dissolution rate, stability, and processability of poorly water-soluble drugs.

Co-grinding with polymers or surfactants

Co-grinding involves simultaneous milling of a drug with polymers, surfactants, or other excipients using high-energy techniques such as planetary ball milling, vibratory milling, or bead milling. The presence of polymers (e.g., PVP, HPMC, PEG, PVA, Soluplus®) or surfactants (e.g., Poloxamer 188, Tween 80, SLS, lecithin) facilitates intimate mixing at the molecular or nano-scale level. These excipients act as stabilizers, dispersants, and crystal growth inhibitors. During co-grinding, they adsorb onto the drug particle surface, preventing agglomeration and Ostwald ripening while improving wettability. This process often leads to the formation of solid dispersions, amorphous dispersions, or drug–polymer complexes that significantly enhance dissolution performance. [21,22]

Mechanochemical interactions

Mechanochemistry refers to chemical or physicochemical changes induced by mechanical energy. During co-grinding, high-impact collisions generate localized heat, pressure, and shear forces that can disrupt intermolecular bonds and promote new interactions such as hydrogen bonding, van der Waals forces, or ionic interactions between drug and excipient. These interactions can lead to the formation of co-amorphous systems, eutectic mixtures, or co-crystals. Mechanochemical activation can also facilitate solid-state reactions without solvents, making this approach environmentally sustainable and industrially attractive. [23,24]

Effect on crystallinity and wettability

One of the most critical effects of co-grinding is the reduction or complete loss of drug crystallinity. Many crystalline drugs transform into partially or fully amorphous forms during high-energy milling. Amorphous drugs possess higher free energy and molecular mobility, which translates into improved solubility and faster dissolution rates. Additionally, co-grinding with hydrophilic polymers or surfactants enhances surface wettability by lowering interfacial tension and increasing surface hydrophilicity. This dual effect—amorphization plus improved wettability—results in markedly better biopharmaceutical performance, particularly for BCS Class II and IV drugs. [25,26]

Mechanical Amorphization and Partial Disorder

Mechanical amorphization and partial disorder refer to the loss or disruption of long-range crystalline order in drug particles induced by high-energy particle size reduction techniques such as ball milling, jet milling, or co-grinding. During intense mechanical stress, lattice defects, dislocations, and amorphous regions are generated, leading to increased internal energy and surface disorder. This structural modification

enhances apparent solubility and dissolution rate of poorly water-soluble drugs by reducing lattice energy barriers. However, mechanically induced amorphous or partially disordered states may exhibit physical instability and risk of recrystallization, necessitating careful control and stabilization strategies during formulation development. [27,28]

Mechanical size reduction combined with solid dispersions involves co-processing the drug with hydrophilic polymers during milling. In this approach, mechanical energy not only reduces particle size but also facilitates molecular mixing of the drug with polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), or hydroxypropyl methylcellulose (HPMC). This leads to partial or complete amorphization and improved wettability. Solid dispersions produced by co-grinding exhibit faster dissolution due to reduced lattice energy, improved drug–polymer interactions, and inhibition of recrystallization during dissolution. [29,30,31]

Surface modification through mechanical processing is another effective strategy. During milling, surfactants or polymers adsorb onto the newly generated particle surfaces, altering surface energy and interfacial properties. This surface coating improves wettability, reduces agglomeration, and enhances dispersion of drug particles in aqueous media. Surface-modified particles demonstrate improved dissolution kinetics even when the bulk crystallinity remains largely unchanged. [32,33]

In situ amorphization refers to the generation of amorphous regions within drug particles during mechanical processing, either alone or in the presence of suitable excipients. High-energy milling induces lattice defects, dislocations, and disordered domains, increasing the thermodynamic activity of the drug. Unlike conventional amorphous solid dispersions prepared by solvent-based methods, mechanically induced *in situ* amorphization is a solvent-free and scalable approach. The presence of polymers during milling stabilizes the amorphous regions and delays recrystallization. [34,35]

Key Challenges and Limitations in Mechanical Particle Size Reduction Approaches

Despite the proven advantages of mechanical particle size reduction techniques for enhancing the dissolution and bioavailability of poorly water-soluble drugs, several critical challenges and limitations must be addressed to ensure successful pharmaceutical development and commercialization. [36,37,38]

Agglomeration and Re-crystallization

Scale-Up and Reproducibility

Thermal Degradation and Polymorphic Transitions

Regulatory and Quality Control Concerns

Regulatory agencies require thorough characterization of particle size, solid-state properties, polymorphic form, and stability throughout the product lifecycle. Any changes in crystallinity or polymorphic form require comprehensive documentation under quality-by-design (QbD) and ICH guidelines. In addition, ensuring consistent product performance over shelf life demands robust analytical tools such as X-ray diffraction, differential scanning calorimetry, and dissolution testing. [39,40]

Impact on Solid-State Properties (ICH Q6A Relevance)

ICH Q6A provides guidance on specifications for new drug substances and products, emphasizing the importance of controlling critical quality attributes such as particle size distribution, polymorphic form, crystallinity, and solid-state stability. Mechanical

processing can induce partial or complete amorphization, lattice defects, or polymorphic transitions, all of which may directly influence solubility, dissolution rate, stability, and bioavailability. Under ICH Q6A, any change in solid-state form is considered a critical material attribute and must be thoroughly justified, characterized, and controlled. Regulatory submissions must include appropriate analytical data (e.g., XRPD, DSC, FTIR) demonstrating consistency of the solid-state properties throughout development and shelf life. Failure to adequately control these attributes may raise concerns regarding product equivalence, stability, and clinical performance. [41,42,43]

Process Validation and Control

Regulatory authorities expect robust **process validation** for mechanical size reduction operations, particularly when high-energy milling is used. Process parameters such as milling time, energy input, temperature rise, feed rate, and equipment scale have a direct impact on particle size and solid-state outcomes. Inadequate control can result in batch-to-batch variability in amorphization level or polymorphic composition. According to ICH Q8 (Pharmaceutical Development) and ICH Q11 (Development and Manufacture of Drug Substances), manufacturers are encouraged to apply Quality by Design (QbD) principles to identify critical process parameters and establish a defined design space. Continuous monitoring and in-process controls are essential to ensure reproducibility and compliance during scale-up and commercial manufacturing. [44,45,46]

Acceptance of Mechanically Modified APIs

The regulatory acceptance of mechanically modified APIs depends on the ability of the manufacturer to demonstrate **safety, efficacy, and quality consistency**. Regulatory agencies generally accept mechanical modification as long as it does not introduce uncontrolled solid-state changes or compromise stability. However, APIs exhibiting significant amorphization or polymorphic conversion may require additional justification, including comparative dissolution studies, stability data, and, in some cases, bioequivalence or clinical bridging studies. Regulatory filings must clearly document the rationale for mechanical modification, its benefits, and the risk mitigation strategies employed. Any post-approval changes to milling conditions may be considered a variation or change requiring regulatory notification or approval. [47,48,49]

Future Perspectives and Emerging Trends

Mechanical particle size reduction continues to evolve as a critical enabling technology for improving the dissolution and bioavailability of poorly water-soluble drugs. Recent advances focus on improving process efficiency, reproducibility, sustainability, and regulatory compliance, while addressing the limitations of conventional batch-based approaches.

Continuous Manufacturing Approaches

The shift from batch processing to continuous manufacturing represents a major future direction in pharmaceutical particle engineering. Continuous milling systems allow for real-time control of particle size, reduced batch-to-batch variability, and improved process robustness. Integration of continuous milling with downstream processes such as blending, granulation, and tableting enables streamlined production and enhanced quality assurance. Regulatory agencies increasingly support continuous manufacturing due to its potential for improved product consistency and reduced risk of human error,

aligning well with Quality by Design (QbD) principles. [50,51,52]

AI and DoE-Driven Optimization of Milling Parameters

The application of **artificial intelligence (AI)** and **Design of Experiments (DoE)** is transforming the optimization of mechanical size reduction processes. DoE enables systematic evaluation of critical process parameters such as milling speed, time, temperature, and media size, reducing experimental effort while identifying optimal operating conditions. AI and machine learning algorithms further enhance this approach by analyzing large datasets, predicting process outcomes, and enabling adaptive process control. These tools support rapid scale-up, improved reproducibility, and data-driven decision-making in pharmaceutical development. [53,54]

Green and Solvent-Free Mechanical Technologies

Environmental sustainability is becoming a key consideration in pharmaceutical manufacturing. Mechanical size reduction techniques, particularly dry milling and co-grinding, are inherently **solvent-free** and therefore align with green chemistry principles. Emerging trends include low-energy milling, cryogenic milling, and hybrid mechanical processes that minimize energy consumption and thermal stress. The elimination of organic solvents reduces environmental impact, improves worker safety, and simplifies regulatory compliance related to residual solvents. [55,56]

Industrial Scalability and Commercialization Potential

Advancements in equipment design, process monitoring, and control strategies have significantly improved the industrial scalability of mechanical size reduction technologies. Modern milling systems offer enhanced temperature control, scalable energy input, and compatibility with continuous manufacturing lines. These improvements support broader commercial adoption for both drug substances and drug products. Additionally, the increasing regulatory acceptance of mechanically modified APIs, supported by advanced solid-state characterization and robust validation strategies, enhances their commercialization potential. As pharmaceutical pipelines continue to include a high proportion of poorly water-soluble molecules, mechanically assisted solubility enhancement strategies are expected to play a central role in future product development. [57,58]

Conclusion

Advanced mechanical particle engineering strategies have emerged as powerful and versatile tools for improving the dissolution behavior and bioavailability of poorly water-soluble drugs. Beyond simple particle size reduction, modern mechanical approaches integrate controlled amorphization, co-processing with polymers and surfactants, surface modification, and hybrid solid-state transformations to achieve meaningful performance enhancement. These strategies address one of the most persistent formulation challenges in contemporary drug development — the increasing prevalence of low-solubility, high-permeability molecules. Through careful control of milling energy, environment, and excipient selection, mechanical processing can tailor solid-state and surface properties to optimize dissolution kinetics while maintaining manufacturability.

Traditionally, nanocrystal technologies have dominated discussions around particle engineering for solubility enhancement. However, advanced mechanical strategies provide a broader and often

more practical alternative framework. Techniques such as co-grinding–based solid dispersions, mechanically induced partial amorphization, and surface-engineered micronized systems can deliver comparable dissolution benefits without always requiring nanoscale particle production or complex wet processing. These approaches are frequently solvent-free, scalable, and compatible with continuous manufacturing concepts. In many cases, they also reduce formulation complexity and cost compared with nanocrystal production and stabilization requirements. As a result, mechanical approaches should be positioned not merely as pre-processing tools, but as stand-alone enabling technologies within the solubility enhancement toolbox.

From an industrial perspective, the evolution of process analytical technologies, continuous milling platforms, and data-driven optimization methods such as Design of Experiments and artificial intelligence modeling is strengthening the reliability and reproducibility of mechanical processes. Regulatory frameworks grounded in Quality by Design principles increasingly support such approaches when supported by robust solid-state characterization and process validation. This alignment between technology capability and regulatory expectation enhances the commercial feasibility of mechanically engineered drug products.

Looking forward, formulation scientists are expected to adopt more integrated and mechanistically informed strategies when applying mechanical processing techniques. Future progress will likely depend on combining mechanical methods with polymer science, surface chemistry, and predictive modeling to achieve stable, high-performance drug systems. Emphasis on green, solvent-free, and energy-efficient processing will further increase the attractiveness of mechanical technologies. For industry, the opportunity lies in leveraging these advanced mechanical strategies to develop scalable, regulatory-compliant, and cost-effective formulations for challenging drug candidates

REFERENCE

1. Tarivitla LP, Reddy MS. An overview of the Biopharmaceutics Classification System (BCS). GSC Biol Pharm Sci. 2021;14(2):217–221.

2. Agrawal P, Kushwaha V, Siddiqui S, Singh SR, Rana GS. Biopharmaceutics Classification System (BCS) – an overview. Int J Pharm Sci Rev Res. 2025;85(4):98–104.

3. Laffleur F, Millotti G, Lagast J. Oral bioavailability enhancement through self-emulsifying drug delivery systems: an overview. Expert Opin Drug Deliv. 2025;22(5):659–671.

4. Tehler U, Fagerberg JH, Bergström CAS, Larhed M, Artursson P, Svensson R. Optimizing solubility and permeability of a BCS class 4 antibiotic using lipophilic fragments disturbing the crystal lattice. J Med Chem. 2013;56(6):2690–2694.

5. Hashmi AR, Sekar M, Zahra F, Molugulu N, Wong LS. Advanced drug delivery strategies to overcome solubility and permeability challenges. ACS Omega. 2025;10(36).

6. Jain S, Arora S, Reddy VA, Patel K. Surface-stabilized candesartan cilexetil nanocrystals for enhanced dissolution and oral bioavailability. Drug

Deliv Transl Res. 2016;6(5):498–510.

7. Kesisoglou F, Mitra A. Crystalline nanosuspensions for BCS II/IV compounds. AAPS J. 2012;14(4):677–687. Krishnaiah YSR. Technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioequiv Bioavail. 2010;2(2).

8. Patel VR, Agrawal YK. Nanosuspension: an approach to enhance solubility of drugs. J Adv Pharm Technol Res. 2011;2(2):81–87.

9. Gan Y, Xu Y, Zhang X, Hu H, Xiao W, Yu Z, et al. Revisiting supersaturation of a BCS IIB drug using multi-cup dissolution and molecular dynamics. Molecules. 2023;28(19):6962.

10. Rao YM, Apte S, Kumar MP. Nanosuspensions of albendazole for oral administration. Curr Nanosci. 2008;4(1):53–58.

11. Phan CU, Shen J, Tang G, Mao J, Yu K. Impact of crystal habit on dissolution and pharmacokinetics of sorafenib tosylate. Molecules. 2021;26(11):3469.

12. Jiang T, Han N, Zhao B, Xie Y, Wang S. Simvastatin nanocrystals prepared by sonoprecipitation. Drug Dev Ind Pharm. 2012;38(10):1230–1239.

13. Takano R, Shiraki K, Aso Y, Takata N, Furumoto K, Yamashita S, et al. Rate-limiting steps of oral absorption of poorly soluble drugs in dogs. Pharm Res. 2008;25(10):2334–2344.

14. Pignatello R, Zingale E, Carbone C, Bonaccorso A, Corsaro R, Musumeci T. Soluplus® nanomicelles for BCS class II drugs. Drug Deliv Transl Res. 2022;12(8):1991–2006.

15. Giri BR, Kwon J, Vo AQ, Bhagurkar AM, Bandari S, Kim DW. Hot-melt extruded amorphous solid dispersion of telmisartan. Pharmaceuticals. 2021;14(1):73.

16. Khan BA, Rashid F, Khan MK, Alqahtani SS, Sultan MH, Almoshari Y. Capsaicin-loaded nanocrystals: characterization and in vivo evaluation. Pharmaceutics. 2021;13(6):841.

17. Marano S, Barker SA, Raimi-Abraham BT, Missaghi S, Rajabi-Siahboomi A, Craig DQM. Micro-fibrous solid dispersions via centrifugal spinning. Eur J Pharm Biopharm. 2016;103:84–94.

18. Bikiaris DN. Solid dispersions: new manufacturing strategies. Expert Opin Drug Deliv. 2011;8(12):1663–1680.

19. Khames A. Liquisolid technique to improve risperidone bioavailability. Drug Deliv. 2017;24(1):328–338.

20. Modi SR, Sangamwar AT, Bansal AK, Pawar YB, Nandekar P, Perumalla SR, et al. Crystal habit and biopharmaceutical performance of celecoxib. Cryst Growth Des. 2013;13(7):2824–2832.

21. Sathisaran I, Dalvi S. Engineering cocrystals of poorly soluble drugs. Pharmaceutics.

2018;10(3):108.

22. Tsume Y, Garcia-Arieta A, Amidon GL, Langguth P. In silico prediction of dissolution and absorption of ibuprofen and ketoprofen. Biopharm Drug Dispos. 2012;33(7):366–377.

23. Rao MRP, Caldera F, Trotta F, Chaudhari J. Cyclodextrin-based nanosponges for rilpivirine delivery. AAPS PharmSciTech. 2018;19(5):2358–2369.

24. Jaftor OF, Lee S, Park J, Cabanetos C, Lungerich D. Navigating ball mill specifications for theory-to-practice reproducibility in mechanochemistry. Angew Chem Int Ed. 2024;63:e202409731.

25. Bochat A, Wesołowski L, Zastempowski M. A comparative study of new and traditional designs of a hammer mill. Trans ASABE. 2015;58:585–596.

26. K Fahim, Sarker MZ, Abu Bakar MR, Uddin MS, Awang M, Ferdosh S, Jalal K, Khan MS, Cchem MRSC. Particle formation and micronization using non-conventional techniques: a review. Chem Eng Process. 2014.

27. Chaudhari, S. P., et al. Pharmaceutical Nanotechnology: Fundamentals and Applications. Springer, 2019.

28. Giri, T. K., & Badwaik, H. (2016). "High-energy milling techniques in drug delivery." Journal of Pharmaceutical Sciences, 105(4), 1158–1172.

29. Müller, R. H., & Keck, C. M. (2004). "Nanosuspensions and nanocrystals: Applications in drug delivery." Advanced Drug Delivery Reviews, 56(9), 1257–1272.

30. Rabinow, B. E. (2004). "Nanosuspensions in drug delivery." Nature Reviews Drug Discovery, 3, 785–796.

31. Suryanarayana, C. (2001). "Mechanical alloying and milling." Progress in Materials Science, 46(1–2), 1–184.

32. Van Eerdenbrugh, B., et al. (2008). "Top-down production of drug nanocrystals by wet media milling." International Journal of Pharmaceutics, 364(1), 64–75.

33. Müller, R. H., & Keck, C. M. (2004). Nanosuspensions and nanocrystals for drug delivery. Advanced Drug Delivery Reviews, 56, 1257–1272.

34. Van Eerdenbrugh, B., et al. (2008). Top-down production of drug nanocrystals by wet media milling. International Journal of Pharmaceutics, 364, 64–75.

35. Suryanarayana, C. (2001). Mechanical alloying and milling. Progress in Materials Science, 46, 1–184.

36. Giri, T. K., & Badwaik, H. (2016). High-energy milling in pharmaceuticals. Journal of Pharmaceutical Sciences, 105, 1158–1172.

37. Boldyreva, E. (2013). Mechanochemistry of pharmaceutical solids. Chemical Society Reviews, 42,

7719–7738.

38. Chavan, R. B., et al. (2016). Co-grinding and solid dispersions for solubility enhancement. Journal of Drug Delivery Science and Technology, 32, 70–81.

39. Hancock, B. C., & Parks, M. (2000). What is the true solubility advantage for amorphous pharmaceuticals? Pharmaceutical Research, 17(4), 397–404.

40. Rasenack, N., & Müller, B. W. (2002). Micronization of drugs by jet milling. International Journal of Pharmaceutics, 254, 69–82.

41. Suryanarayana, C. (2001). Mechanical alloying and milling. Progress in Materials Science, 46, 1–184.

42. Van Eerdenbrugh, B., et al. (2008). Top-down production of drug nanocrystals by wet media milling. International Journal of Pharmaceutics, 364, 64–75.

43. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86(1):1–12.

44. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86(1):1–12.

45. Yu L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv Drug Deliv Rev. 2001;48(1):27–42.

46. Descamps M, Willart JF. Perspectives on the amorphization/milling relationship in pharmaceutical materials. Adv Drug Deliv Rev. 2016;100:51–66.

47. Van den Mooter G. The use of amorphous solid dispersions: a formulation strategy to overcome poor solubility and dissolution rate. Drug Discov Today Technol. 2012;9(2):e79–e85

48. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86(1):1–12.

49. Yu L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv Drug Deliv Rev. 2001;48(1):27–42.

50. Descamps M, Willart JF. Perspectives on the amorphization/milling relationship in pharmaceutical materials. Adv Drug Deliv Rev. 2016;100:51–66.

51. Van den Mooter G. The use of amorphous solid dispersions: a formulation strategy to overcome poor solubility and dissolution rate. Drug Discov Today Technol. 2012;9(2):e79–e85.

52. Aaltonen J, Rades T. Towards physico-relevant dissolution testing of amorphous pharmaceutical solids. Eur J Pharm Sci. 2009;36(1):1–11.

53. ICH Q6A. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. International Council for Harmonisation; 1999.

54. ICH Q8(R2). Pharmaceutical Development. International Council for Harmonisation; 2009.

55. ICH Q11. Development and Manufacture of Drug Substances. International Council for Harmonisation; 2012.

56. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86(1):1–12.

57. Descamps M, Willart JF. Perspectives on the amorphization/milling relationship in pharmaceutical materials. Adv Drug Deliv Rev. 2016;100:51–66.

58. Singh R, et al. Artificial intelligence and machine learning in pharmaceutical manufacturing and development. Int J Pharm. 2021;600:120508.