Macedonian Pharmaceutical Bulletin, 72 (Suppl 1) 13 - 14 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.005
Short communication

Mechanochemistry: A powerful engine for pharmaceutical innovation, sustainability, and solid-state design

Mario Jug*

University of Zagreb Faculty of Pharmacy and Biochemistry, A. Kovačića 1, 10 000, Zagreb

Introduction

Mechanochemistry encompasses reactions that predominantly occur in the solid state and are driven by mechanical energy input, providing a rapid, versatile, and inherently "green" route to tailor pharmaceutical solids. It enables the discovery of novel and alternative solid forms of active pharmaceutical ingredients (APIs), such as polymorphs, salts, cocrystals, solvates/hydrates, as well as amorphous phases, polymer dispersions, and cyclodextrin inclusion complexes, typically with reduced solvent consumption and favorable biopharmaceutical profiles. Mechanochemical activation is usually performed by neat grinding (NG) or liquid-assisted grinding (LAG) in high-energy mills, thereby minimizing residual solvent risks and environmental burden (Tan et al., 2016).

Mechanistic principles and process variables

In vibrational or planetary ball mills, energy transfer occurs via impact and shear of balls acting as milling media, first inducing comminution and then lattice defects that promote molecular activation and solid-state transformations. Interactions between reactants proceed through transient gaseous, liquid (eutectic/moisture mediated), or amorphous solid microenvironments. Although the exact pathways are system dependent, amorphous intermediates are frequently implicated. Key process parameters include milling frequency, milling time, and temperature control, including cryogenic conditions (Tan et al., 2016). Furthermore, the material type, size, and number of the milling balls, as well as their ratio to reactants, should be considered.

Polymorph screening and supramolecular products by grinding

Mechanochemistry has become a key technology for accelerating polymorph discovery and for engineering supramolecular assemblies that enhance solubility and dissolution. Praziquantel (PZQ) illustrates this potential (D'Abbrunzo et al., 2024): beyond the anhydrous Form A, mechanochemical protocols afforded an amorphous form, four novel polymorphs (B, C, D, F), one hemihydrate, two new solvates, multiple cocrystals, polymer, silica, or surfactant dispersions, and cyclodextrin complexes, each demonstrating improved biopharmaceutical properties relative to Form A. Form B can be obtained by milling commercial PZQ at ~20 Hz for ~4 h and is physically stable, with approximately two-fold higher solubility; Form C requires higher energy input and offers even greater solubility at the expense of physical stability, while D and F arise from extended milling or LAG (e.g., THF). Supramolecular products are equally accessible: LAG with organic acids yields cocrystals (e.g.,

*mario.jug@pharma.unizg.hr

PZQ–malic acid), and NG with hydroxypropyl-β-cyclodextrin (HPβCD) forms amorphous inclusion complexes, both markedly increasing apparent solubility and accelerating *in vitro* dissolution of the drug (Cugovčan et al., 2017).

Mechanochemical synthesis of bioactive molecules

Mechanochemistry enables rapid, solvent-free synthesis of new chemical entities with therapeutic potential. Efficient solid-state synthesis provides heterocyclic APIs such as hydantoins with antimicrobial or anticonvulsant activity; benzimidazoles, including fenbendazole; pyrimidine derivatives, like pyrimethamine via Minisci alkylation; and azomethines with antioxidant and antibacterial profiles (Bento et al., 2022). The structural diversity of the molecules synthesized so far is significant, and its application continues to expand. This suggests that mechanochemistry might have a key role in discovering new bioactive compounds and pharmaceuticals.

Quality and safety considerations

Mechanochemical processing may trigger unintended solid-state reactions; for instance, PZQ undergoes significant degradation when milled with povidone or crospovidone, an incompatibility absent in plain physical blends, underscoring the need for reaction-aware excipient selection and process design (Šagud et al., 2018). Another critical concern is elemental contamination from wear of jars and balls (e.g., Fe/Cr from stainless steel, Si from agate). Although measured patient exposures (e.g., to Cr) from PZQ-based mechanochemical products remained far below ICH Q3D(R1) limits, routine elemental impurity testing and inert contact materials are needed to ensure product safety and stability (Jablan et al., 2024).

Industrial translation

Laboratory vibrational mills are typically limited to ≤125 mL (≈ up to 10 g product), and scale-up is constrained by heat management and material compatibility of contact surfaces. Continuous twin screw extrusion is emerging as a promising platform for scalable mechanochemical synthesis: energy is imparted predominantly by shear during conveying/mixing, temperature can be precisely regulated, and transfer protocols from ball milling to extrusion are increasingly available, enabling efficient production while maintaining product quality (Bento et al., 2022).

Conclusion

Mechanochemistry offers a multifunctional, solvent-minimizing approach for rationally engineering pharmaceutical solids, from polymorphs to supramolecular complexes, with enhanced biopharmaceutical properties, and for the solid-state synthesis of new APIs. To fully assess its translational value, future work should prioritize mechanistic *in situ* analytics, excipient-aware risk assessment of degradation pathways, robust elemental impurity controls, and process scale-up via continuous platforms such as extrusion.

References

Bento O. et al., 2022. Sustainable Mechanosynthesis of Biologically Active Molecules. Eur.J. Org. Chem. 21, e202101516. https://doi.org/10.1002/ejoc.202101516

Cugovčan M., 2017. Biopharmaceutical characterization of praziquantel cocrystals and cyclodextrin complexes prepared by grinding. J Pharm. Biomed. Anal. 137, 42-53. https://doi.org/10.1016/j.jpba.2017.01.025

D'Abbrunzo I. et al., 2024. Praziquantel Fifty Years on: A Comprehensive Overview of Its Solid State. Pharmaceutics 16, 27. https://doi.org/10.3390/pharmaceutics16010027

Jablan J. et al., 2024. Product contamination during mechanochemical synthesis of praziquantel co-crystal, polymeric dispersion and cyclodextrin complex. J. Pharm. Biomed. Anal. 238, 115855. https://doi.org/10.1016/j.jpba.2023.115855

Tan D. et al., 2016. Toward medicinal mechanochemistry: evolution of milling from pharmaceutical solid form screening to the synthesis of active pharmaceutical ingredients (APIs). Chem. Commun. 52, 7760–7781. https://doi.org/10.1039/C6CC02015A

Šagud I. et al., 2018. Identification of degradation products of praziquantel during the mechanochemical activation. J. Pharm. Biomed. Anal. 159, 291-295. https://doi.org/10.1016/j.jpba.2018.07.002