Mechanochemistry vs Conventional Solid-State Synthesis: A Sustainable Development Pathway

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Abstract. The shift to sustainable chemical manufacturing highlights the need for solid-state synthesis methods that minimize solvent use, energy consumption and environmental impact. This review summarizes mechanochemistry and cocrystal-assisted strategies as alternatives to conventional high temperature solid-state synthesis routes. Mechanochemical activation enable rapid, selective and solvent free transformations by creating highly reactive local environments, while cocrystal engineering improves molecular organization, lower activation barriers and enhances polymorph control. These methods together access the reaction pathways, metastable phases and product selectivity that are often difficult to obtain by thermal or solution methods. A comparison shows clear differences from mechanochemical and conventional solid-state synthesis from energy input, reaction kinetics, phase selectivity and sustainability. In recent years, many advances including continuous manufacturing such as liquid-assisted grinding (LAG), in-situ mechanism research and twin-screw extrusion, show that mechanochemistry has increasing scalability and industrial importance. However, there are still challenges in mechanistic understanding, equipment dependence and specific system kinetic limitations. Overall, mechanochemical and cocrystal-assisted synthesis provide a selective, efficient and sustainable method that can complement conventional solid-state synthesis methods. In some cases, it partly replace conventional methods. The continued development of these technologies may influence future materials discovery, pharmaceutical solid form design and industrial scale sustainable manufacturing.

1. Introduction

As people pay increasing attention to environmental impact, energy consumption and economic benefits, the development of sustainable synthesis methods has become the core goal of chemical and materials science [1, 2]. Previous studies have demonstrated that, conventional solution and thermal synthesis methods usually require large amounts of solvents and long time heating, resulting in a large amount of experimental waste and extremely high costs [1]. Therefore, sustainable synthesis aims to minimize the use of solvent, reduce energy demands and achieve safer and more efficient chemical production through

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more economical methods. This is consistent with the concept of green chemistry and the trend of gradual shift to more environmentally friendly and efficient technologies [2].

Under this background, solid-state synthesis plays an important role in materials that cannot be stably prepared through conventional liquid phase synthesis [3, 4]. This method is used in many important fields, including battery materials, nanomaterials, ceramic oxides, catalyst, adsorbent materials and pharmaceuticals, because solid-state synthesis is still necessary due to solubility restrictions or temperature requirements [4, 5]. Solid-state synthesis cannot only prepare relatively complex and high temperature materials, but also form metastable intermediates which plays an important role in the research and development of functional materials [4]. In pharmaceutical science, the engineering design of solid-state forms directly affects many key properties such as solubility, bioavailability, and stability [5, 6]. Therefore, improving the solid-state synthesis methods is important to both materials and pharmaceutical development.

However, the conventional solid-state synthesis methods still face some challenges. The reaction usually requires high temperature heating for long times and repeated grinding to overcome the slow diffusion in the solid-state [3]. These conditions consume a lot of energy and may lead to incomplete transformation, impurity phases or metastable intermediates which could affect the purity. Furthermore, due to the complex interaction between thermodynamics and kinetics, the reaction pathways are usually difficult to predict, so the conditions of solid-state synthesis largely depend on experiments rather than theoretical calculations [3, 4]. Although the solution based crystallization method is widely used, it usually requires a large amount of solvents and often produces unwanted phases because the solubility of different components are difficult to match [7-9].

To overcome these issues, mechanochemistry and cocrystallization provide a practical alternative approach. Mechanical force replaces heating and bulk solvents, allowing fast transformations with minimal environmental impact and energy consumption [5, 7]. Cocrystallization further improves efficiency by arranging reactants into favourable arrangements before reaction start, which lowering the activation energy and improving both selectivity and efficiency [7]. Comparative studies show that, when solvent use or phase stability limits conventional slurry or solution methods, mechanochemistry can provide cleaner, more selective and sustainable outcomes [9]. Several reviews highlight that, these methods make mechanochemistry especially cocrystal assisted methods as an important route for achieving highly selective and efficient sustainable solid-state synthesis [2, 3, 7, 9].

This study focuses on mechanochemical cocrystallization as a sustainable solid-state synthesis method. Reactants can be converted into pre-reactive cocrystals or intermediates by applying mechanical forces through grinding or milling, which can modulate reactivity, enhance selectivity, or alter reaction pathways [5, 7]. Mechanochemical method uses very little or no solvents, and has demonstrated high efficiency and wide applicability in the discovery and production of cocrystals [5, 9]. The aim of this study is to summarize the feasibility of this method, identify the factors that determine the success of cocrystallization mediated transformation, and compare its sustainability and performance with conventional solid-state methods [5, 6, 7, 9].

2. Conventional solid-state synthesis

Conventional solid-state synthesis is a high temperature process driven by diffusion, in which inorganic precursors (typically oxides, carbonates or salts) are mixed, pressed and heated to trigger reactions through interfacial diffusion and phase transformation. Because the reaction is limited by both thermodynamic stability and slow solid-solid diffusion, the system typically produces the most energetically stable phase. Only deliberate changes to heating conditions or precursor design can shift the reaction away from this fixed pathway [3, 4].

Classic examples include the synthesis of layered transition metal oxides for battery materials, which requires repeated grinding-heat cycles to achieve uniform diffusion and phase purity [3]. Solid-state metathesis reactions are also used to generate metal nitrides or chalcogenides under highly exothermic conditions [6].

The conventional solid-state synthesis has several advantages. It has simple concepts, compatible with a wide range of inorganic chemistry, and easy to scale up to industrial scale. Many functional materials, including ceramic oxides, phosphates, superconductors and cathode materials are still mainly produced through conventional solid-state routes because this method provides excellent thermal control and long term phase stability [3, 4, 8]. These processes are also well established in industrial practice, allow reliable production at the ton scale thus having practical application value in the manufacturing industry.

However, although the conventional synthesis has been widely adopted, it also has several limitations. As reported in several studies, high temperatures and long reaction times lead to significant energy consumption, and slow solid-solid diffusion reactions often requiring multiple grinding and reheating steps to obtain a homogeneous product [3, 4]. Due to limited control over intermediate formation, these issues not only limit the phase selectivity but also do not meet modern sustainability requirements such as E-factor and solvent free processing standards [2, 3, 4]. These challenges shows the necessity of alternative synthesis that can reduce energy consumption, improve mixing efficiency, and more easily obtain metastable phases. These factors have prompted an increasing interest in mechanochemistry as a sustainable and efficient solid-state approach [1, 2, 10].

3. Mechanochemistry

3.1 Definition and principles

Mechanochemical synthesis refers to a chemical reaction process driven by mechanical energy rather than thermal energy or a large amount of solvents. As shown in figure 1, processes such as impact, shear, and compression can disrupt the crystal lattice, increase the surface area, and create a highly reactive local environment that promote bond formation under solvent free conditions or with minimal solvents [1]. Because the mechanical energy acts directly on solids, this method can also open up a reaction pathway that is completely different from the observed reaction routes, thus enabling production of unstable or complex products that are difficult to obtain by other methods [10, 11]. The International Union of Pure and Applied Chemistry (IUPAC) also considers this method to be a transformative technology because it can provide a new reaction environment that achieve fast, selective, and cleaner chemical transformation reactions [10].

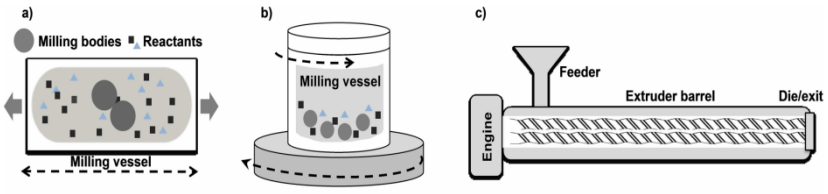

Fig. 1. Mechanochemical techniques and equipment. Source from: Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. ChemSusChem. 14, 2145–2162 (2021).

3.2 Reaction mechanisms in mechanochemical processes

Mechanochemical reactions are usually carried out using grinding based techniques, including manual grinding, shaker mills and planetary ball mills [10]. During the ball milling process, the reactants and the grinding medium repeatedly collide in a sealed container, creating a short term high pressure and high temperature microenvironment. These conditions enhance the contact between solids and produce defects that reduce the activation energy barrier. Researchers used advanced in-situ characterization techniques, such as powder X-ray diffraction (PXRD) and Raman spectroscopy to observe transient short-lived crystals or intermediates formed during grinding directly. These experiments show that without solvents, some intermediate structures can remain stable long enough for detection, and they usually transformed immediately in solutions [11]. Mechanical chemistry can directly observe the transient intermediate structures that could not be observed in solution based systems before, demonstrating the unique reaction pathways brought by mechanochemistry.

3.3 Liquid assisted grinding

Liquid-assisted grinding (LAG) is a very widely used method, which improves reaction control by adding a small amount of solvent. The amount of solvent is described by the parameter η, and typically between 0 and 2 $\mu L mg^{-1}$ [7]. It had been shown that, even a small change in η can significantly affect the reaction kinetics, nucleation behavior, and polymorphous selectivity. Changing the η value during the cocrystallization process can change the reaction results, which indicates that small changes in the local microenvironment have a significant impact on outcomes [7]. Therefore, LAG can control the reactivity of reaction while maintaining the sustainability advantages of mechanochemical synthesis.

3.4 Applications of mechanochemical synthesis

Mechanochemistry has been successfully applied in pharmaceuticals, organic reactions, and materials chemistry. In pharmaceutical solid-state design, mechanical grinding is used to prepare cocrystals selectively with better solubility or stability compared to conventional methods. For example, several drug cocrystals prepared by mechanochemistry have higher purity and fewer by-products compared to the slurry method. This is due to the absence of solubility competition between crystallization pathways [5]. In materials chemistry, mechanochemical route has enabled the solvent free synthesis of many functional nanomaterials. For example, noble metal nanoparticles such as Au or Ag can be produced directly with controlled sizes and good catalytic properties [12]. In addition, antibacterial silver nanoparticles can be generated in a single solid-state process by natural reducing agents [13]. These examples demonstrate that mechanochemical synthesis can access highly reactive or energy rich materials through a simple, flexible and sustainable process.

3.5 Scalability of mechanochemical synthesis

Importantly, mechanochemistry is no longer limited to laboratory operations. Twin-screw extrusion (TSE) has become a powerful continuous flow mechanochemistry technique that can produce milligrams to quantites of solid products without requiring large amounts of solvents [14]. Pharmaceutical research shows that TSE can stably produce high quality cocrystals and precisely control the shear force, temperature and residence time. This scalability makes TSE a promising way to transform laboratory scale mechanical synthesis

into industrial production, effectively bridging the gap between experimental innovation and real industry application [14].

4. Comparison, challenges and future directions

4.1 Efficiency and energy input differences

Conventional solid-state synthesis and mechanical chemistry are two completely different methods to drive solid-state reactions. Conventional methods rely on high temperatures to overcome diffusion restrictions, which leads to long reaction time and high energy consumption [3, 4]. In contrast, mechanical chemistry achieves mixing, activation and bond rearrangement by mechanical forces, which allow reaction to proceed quickly under solvent free or low solvent conditions [1, 5, 10]. This difference directly affects the efficiency: comparative investigations indicate that, mechanochemical reactions are usually completed in a few minutes to hours, while conventional methods may require repeated grinding - heating cycles to achieve phase purity [3]. Mechanochemistry can enable rapid and selective transformation under minimal solvent or solvent free conditions.

4.2 Selectivity and sustainability comparison

Their selectivity is also different. High temperature solid phase usually follow thermodynamically favoured pathways, which limits the formation of metastable intermediates or alternative polymorphous types [4]. By controlling the local environment, mechanochemistry can form specific cocrystals, selective polymorphs and even metastable phase that cannot be achieved by solution or heating alone [7, 11, 14]. Sustainability standards further highlight these differences. The mechanochemical method itself can minimize solvent use, and the E-factor and PMI values are significantly lower than those of solution crystallization or high temperature solid-state processing [1, 2]. This strategy is particular important in the pharmaceutical field, several reports show that it can reliably and environmentally friendly produce specific cocrystal polymorphous products [14]. Cocrystal assisted mechanochemistry further improves efficiency by pre arranging reactants, reduce activation energy barriers and improving control over polymorphism.

4.3 Scalability and industrial applicability

In terms of scalability, both methods show industrial application value. Conventional solid-state synthesis is still the main method of ceramics, oxides and battery cathode materials [3, 8]. However, progress in twin-screw extrusion (TSE) and continuous mechanochemical processing shows that the large scale production of cocrystals, metal-organic frameworks (MOFs) and inorganic materials is feasible, thus connecting laboratory grinding with industrial production [14]. These advances show that mechanical chemistry can combine sustainability with actual industrial development to provide a complementary alternative to conventional high temperature routes.

4.4 Current challenges in mechanochemical synthesis

Despite significant progress in mechanochemical and cocrystal assisted synthesis, still several challenges need to be addressed before these methods can completely replace conventional methods. First, the fundamental mechanisms controlling the reactivity of mechanochemical reactions, particularly the formation of short lived intermediates and local

temperature/pressure fluctuations, remain difficult to characterize in real time [11]. Limited mechanical understanding makes it still difficult to precisely control reaction pathways compared to more established thermal processes. Secondly, mechanical activation can be highly sensitive to grinding parameters such as the ball to powder ratio, solvent amount (η value), frequency and container material, all of which can affect selectivity, polymorphous products or reaction kinetics [7, 9]. Differences in grinding equipment also lead to reproducibility issues, especially when translating lab scale reactions into industrial platforms.

4.5 System limitations of mechanochemical synthesis

Although mechanochemistry greatly enhances mixing and activation, it cannot fully replace thermal energy for all systems. For many complex oxides, the reaction pathway is still limited by intrinsic kinetic barriers, which means heating is still required to enable long range diffusion and complete phase formation [3, 4]. In some cases, mechanochemistry is not fully applicable and may still require thermal input for certain materials to complete phase formation. Therefore, a mixed strategy of combining mechanical activation with controlled heating (such as thermal assisted mechanochemistry) may become increasingly important. Similarly, for the synthesis of MOFs and nanoparticles generation, controlling particle size, defect density, and surface chemistry remains a challenge that requires further development to improve in-situ monitoring and predictive models [12, 13].

4.6 Future directions for mechanochemical synthesis

Looking forward, there are three key directions for future developments. First, data driven predictive synthesis will become increasingly important, as computational models can identify feasible reaction pathways and guide precursor selection, which can improve efficiency and rationality [15]. Second, continuous mechanochemical manufacturing which includes TSE and large scale grinding reactors will provide a route toward solvent free, energy efficient production of pharmaceuticals, specialty chemicals, and MOFs [14]. Finally, access to metastable and functionally unique phases will remain a key advantage of mechanochemistry, enabling materials that are difficult to obtain through high temperature conventional routes and supporting advances in energy storage and catalysis [6, 11, 15]. Overall, mechanochemistry and cocrystal-assisted synthesis provide a sustainable, selective, and scalable alternative to conventional solid-state synthesis, which have significant potential to guide the future development of inorganic and materials chemistry.

5. Conclusion

This study shows that mechanochemical and cocrystal assisted routes represent a completely different and increasingly important sustainable solid-state synthesis. Several key insights are obtained by examining the principles, reaction mechanisms, applications and industrial scalability.

Compared with conventional solid-state synthesis, mechanochemistry is not only a simple alternative method, but also a complementary route with unique advantages. It can access a new reaction pathway, produce cleaner phase products and reduce environmental impact, benefiting both materials and pharmaceutical solid preparation design.

Looking forward, future development will likely focus on three main areas: improving understanding through real time characterization, building predictive data driven models to guide reaction design, and expanding continuous manufacturing technologies such as twin-screw extrusion. These advances will improve repeatability, scalability and form metastable

or functionally unique materials that cannot be obtained by conventional high temperature methods. Overall, mechanochemical and cocrystal assisted synthesis provide a powerful and sustainable platform that is expected to influence future material discovery, pharmaceutical development and industrial solid-state manufacturing.

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