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REVIEW

Mechanochemistry's role in non-steroidal anti-inflammatory drugs development: A review

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As a greener method of preparing molecules, mechanochemistry has recently been identified as an ideal strategy for preparing diverse molecules. It is becoming a valuable synthetic tool for multiple fields (e.g., physics, chemistry, and materials science) because it can be performed without solvents or with minimal solvents (catalytic quantities). The use of sustainable methods has been beneficial to several fields of chemistry, including pharmaceuticals, fertilizers, catalysis, organic synthesis, preparation of medicinal solid forms, and synthesis of metal complexes. Pharmaceutical and pharmaceutical chemistry will likely be significantly impacted by these developments in medicinal mechanochemistry. Due to their reactivity and materials, they provide materials that are hard to extract from a solution or are not possible. Nevertheless, these technologies could provide the pharmaceutical sector with safer, cleaner, and more effective synthetic solutions. The importance of mechanochemical processes in the creation of pharmaceutical cocrystals, especially non-steroidal anti-inflammatory drugs (NSAIDs), is discussed in this article.

Keywords: mechanochemistry, solvent-free, cocrystal, NSAIDs, pharmaceutical

1. Introduction

Pharmaceuticals are considered to be a significant environmental problem by environmentalists in the last few years because pharmaceutically active substances (PASs) can negatively impact the chemical and biological processes taking place in land and aquatic habitats and cause pollution (1).

Sulfamethoxazole, naproxen, and sulfasalazine have been documented to persist in the environment for much longer than a year. Clofibric acid has been reported to persist for more than 21 years (2). It is undoubtedly true that the environment and human health may be severely harmed by extremely long lifespans. Recently, mechanochemistry has gained attention as an effective and non-polluting technique that can be used to treat waste (3). The removal of asbestos-containing materials in particular has been so effective that no patent for the transformation of toxic asbestos fibers into non-toxic amorphous asbestos has been granted (4, 5).

In recent years, chemists have become increasingly interested in mechanochemistry (3, 6–11). The two most popular types of milling are mechanical and manual methods for promoting mechanochemistry. A mortar and pestle are used for hand grinding, while planetary mills or mixer/shaker mills are used for mechanical grinding at frequencies of 5−0 Hz. Compared to manual grinding, mechanical milling generates far more energy and is more dependable and complex; this method produces more consistent experimental results. In contrast, hand grinding may yield varying results, depending on grinding strength and speed (12–14).

Sometimes mechanical milling is referred to as grinding in the literature. There are two types of mechanical and chemical methods. It is strongly advised to use the word "grinding," particularly when referring to using a mortar and pestle or anything like a Retsch RM100 mortar grinder.

Only components being milled in a mixer/shaker mill or a planetary mill are covered by the word "milling" (15–17). There are a wide variety of mixers and planetary mills available commercially as well as homemade high-speed vibration mills (HSVM), commercially accessible Fritsch Pulverisette, Retsch mixer mills, Spex CertiPrep mixers and mills planetaries, AGO-2 Planetary Centrifugal Mills, and so on. Since mechanical milling is always carried out using milling balls in a mixer or planetary mill, it is often referred to as ball milling (17–19).

As a green, highly efficient method of producing materials, mechanical synthesis has gained popularity in a variety of fields (e.g., physics, chemistry, and materials science) (20–23). Mechanochemical studies have played an increasingly significant role over the past several decades in many application fields, as shown in **Table 1**.

Over the past three decades, interest in mechanochemistry has increased dramatically, especially as it pertains to pharmaceutical materials. Several independent studies have demonstrated that mechanochemistry is an effective method for gaining access to additional solid forms and is often as effective as other approach materials (61). (62) evaluated mechanochemistry extensively. Tan and Friščić (53) identified numerous other fields where this technology is likely to be used as a screening strategy.

This evaluation focuses especially on the important role of mechanochemistry in the formation, modifications, and development of non-steroidal anti-inflammatory drugs (NSAIDs) as pharmaceutical compounds. Since the apparent equilibrium attained under certain settings frequently does not match the thermodynamic equilibrium but is instead connected to the experimental parameters utilized, mechanochemistry does actually provide favorable conditions for the identification of less stable forms.

TABLE 1 | Potential future applications of mechanochemical synthesis.

Field	Applications	Refs.
Synthetic processes	Pharmaceuticals	(24–28)
	Drug nanocarriers	(29–32)
	Slow/control release fertilizers	(33, 34) "Mechanochemical synthesis of complexes for application as slow-release fertilizer," 2015; (35)
	Organic synthesis	(36–38)
	Nanomaterials	(7, 12, 39–41)
	Mechanochemistry of polymers	(15, 42, 43)
	Storage of hydrogen, heaters, and gas absorbers as a reactive	(11, 24, 44)
	Intermetallic compounds	(13, 17, 18)
	Advanced materials (Superconductors)	(45–47)
	Catalysis	(12, 28)
	Cosmetics	(48)
	Pesticides	(49–51)
Modification processes	Modification of solubility of organic compounds	(52, 53)
	Drugs release	(54, 55)
Treatment process	Waste management	(1, 5, 56)
	Extraction of biologically active compounds from natural resources	(57–60)

2. Mechanochemical aspects

During the 4th century BC, cinnabar and acetic acid were ground together in a copper vessel to produce elements from mercury, according to Takacs (8). Similarly, Aristotle's statement "reaction cannot occur without solvent" (53) also points to a significant early reference point. According to his statement, it is impossible to conduct many solventless mechanochemical reactions (63). Mechanochemistry was developed in the Middle Ages and found use in mining and metallurgy as well, as evidenced by references to various studies (17, 64, 65).

The term mechanochemistry is habitually utilized from a wide perspective, covering any substance response instigated precisely (e.g., by crushing, pounding, and so on) (64). This is the meaning in which it is used in this investigation. It has been argued elsewhere that this widespread use is incorrect and that it should only be used when mechanical energy directly destroys solid bonds (such as in polymers or unquestionably in single molecules) (10). This creates receptive focuses (frequently revolutionaries) that go through additional responses. This more prohibitive utilization of the term would avoid crushing responses that might continue to a great extent because of an expansion in the contact surface region between reactants (as the particles become more modest and all the more personally blended).

A mechanochemical reaction is described by the International Union of Pure and Applied Chemistry (IUPAC) as a "chemical reaction that is induced by the direct absorption of mechanical energy," with the caveat that "shearing, stretching, and grinding are typical methods for the mechanochemical generation of reactive sites, usually macroradicals, in polymer chains that undergo mechanochemical reactions" (64). While the note provides recommendations for its application in the context of polymers, the underlying definition is broad and unrestricted in terms of the atomic scale process. As a result, the term's widespread use appears to be warranted. There may also be some misunderstanding about what is meant by "solvent-free." To begin with, the terms "solvent-free" and "mechanochemistry" are not synonymous because

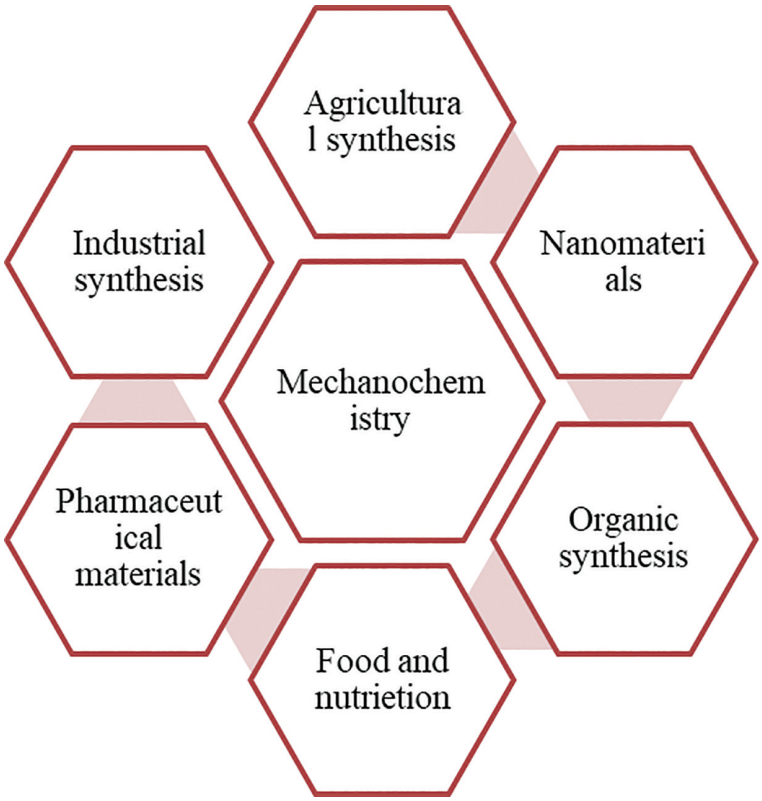

FIGURE 1 | Synthetic fields of mechanochemistry.

mechanochemistry can be performed in the presence of solvents. Nonetheless, the term "solvent-free" has more than one meaning (11, 36, 64). The method emphasizes a practical advantage by not introducing a solvent on purpose into the reaction. While interpreting how these reactions operate mechanistically (especially how fluidity develops), it may be incorrect to view this reaction as solvent-free. Molecular solvates or hydrated metal salts are examples of solid raw materials that can be used as solvents.

There could be (lower) amounts of moisture in non-formally hydrated objects or the environment that help the reaction. Condensates can also produce species such as water and acetic acid. As a result, while the term "solvent-free" is frequently correct in practice, care must be exercised when making mechanical interpretations (6, 66).

As shown in scheme 1, mechanochemistry has recently had a significant impact in a wide range of synthetic fields of chemistry, including agricultural synthesis (34, 67), synthesis of organometallic compounds (68, 69), organic synthesis (38, 70, 71), metal complexes preparation (72), main group elements (73), porous metal-organic frameworks (MOFs) (74), polymers (75, 76), food and nutrition (77, 78), and multicomponent pharmaceutical materials (79, 80).

Mechanical reactions are reactions that are initiated by mechanical methods (milling, grinding, and compression) and are carried out either without solvent or with solvent at levels that are catalytic (20, 21, 34). These techniques have been used since the Stone Age when mortars and pestles were used to prepare foods, medicines, and other items, as shown in **Table 1**. In 1919, Ostwald classified mechanochemistry as the fourth category of chemical processes including thermochemistry, photochemistry, and electrochemistry (8, 13). The mechanochemistry field is coming back, primarily because of the green perspective associated with not requiring any solvents.

3. Mechanochemistry and pharmaceutical materials

Mechanochemistry and pharmaceutical sciences are inextricably linked. The structure of organic molecules must be understood at both the molecular (e.g., the macroscale, such as particle size and shape) and microscopic (such as crystal structure) levels to determine properties such as solubility, dissolving rate, tablet ability, and heat, and moisture stability (21, 53, 81). As a result, solid-state pharmaceutical materials research has primarily focused on influencing API properties in the solid states by altering their molecular arrangement. Examples are amorphization, polymerization, salts, crystalline solutions and, more recently, pharmaceutical cocrystals (25, 73, 82).

However, there are different pharmaceutical applications of mechanochemistry as illustrated in scheme 2 (38, 70, 83, 84).

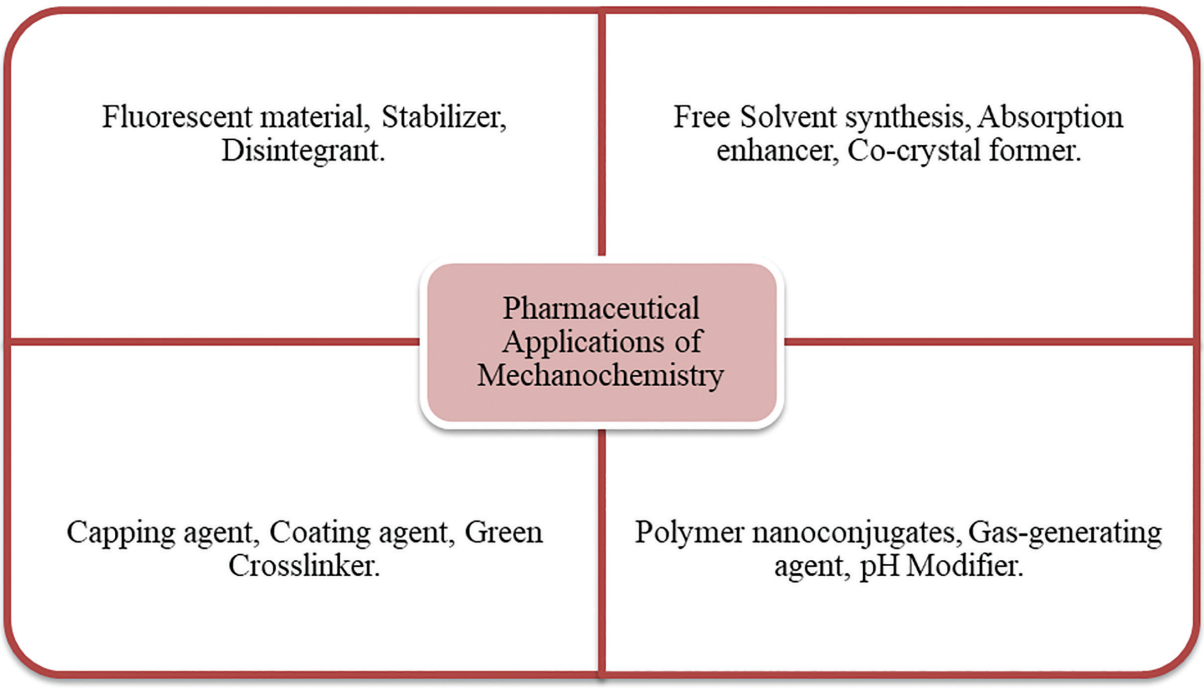

FIGURE 2 | Pharmaceutical applications of mechanochemistry (38, 70, 83, 84).

For the last 15 years, there has been an increased emphasis on solid-state synthesis methods for the exploration and synthesis of active pharmaceutical ingredients API solid forms (81). Mechanochemistry has gained considerable attention, but so has vapor-assisted reactivity (e.g., faster aging and vapor digestion) (16). Solvent-drop grinding, also known as liquid-assisted grinding (LAG), or kneading (19, 36), has been especially successful in identifying novel polymorphs, salts, and cocrystals in the bulk formulation of APIs, in addition to producing large quantities of them (through batch or continuous processing processes, such as twin-screw extrusion [TSE]). By complexing a transition or main group of metal cations (21), this technique has also been extended to the generation of novel API forms and even known metallodrugs.

Cocrystals/multicomponent salts (85) and amorphous (42) are two ways of preparing pharmacological solid forms. Solvent-free solid-state procedures, on the contrary, have recently attracted a lot of attention since they may be carried out without or with very little solvent (catalytic amounts). According to Grant et al., the molecular structure and supramolecular arrangement of a drug influence its intrinsic activity, resulting in mechanochemical activation (73, 86).

For the production of comparable therapeutic molecules, standard chemical procedures involve the use of hazardous solvents and high pressures (87). From both a theoretical and practical standpoint, it is critical and necessary to eliminate these stages. A mechanochemistry technique can be used to create a green chemical process (9, 13). Many recent investigations have demonstrated that mechanochemistry is successful in synthesizing NSAIDs as pharmaceutical molecules, which are the building blocks for more sophisticated organosilicon syntheses (29, 88).

4. Mechanochemistry of non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs are among the most often given medications and delivered medications in the world (89). NSAIDs are used by roughly 30 million individuals every day, accounting for around 5−10% of all drugs administered each year (90). Ibuprofen, indomethacin, meloxicam, and aceclofenac are some of the medications in this class. NSAIDs offer a wide range of benefits and risks, but they are commonly used as analgesics, anti-inflammatory drugs, and antipyretics (90, 91).

According to the Biopharmaceutical Classification System (BCS), several NSAIDs are classified as Class II medicines (poor water solubility and high intestinal permeability) (92). As a result of their limited aqueous solubility, their concentration remains relatively low in stomach and intestine fluids following administration. As a result, even though intestinal permeability is great, the amount of medicine absorbed remains modest (92).

Morozkina et al. (26) were successful in implementing a novel mechanochemistry strategy for improving ketoprofen solubility and efficacy. The methodology's advantages include a reduction in ulcerogenic effects and an improvement in medication absorption and efficacy.

The development of nanocrystalline naproxen (93) is another example of improving solubility and thus bioavailability. Non-steroidal inflammation, swelling, stiffness, and joint pain are among the symptoms of arthritis that are frequently treated with anti-inflammatory medications like naproxen. Two commercially available medications, namely, naprosyn (suspension) and anaprox, were compared to the bioavailability of nanocrystalline naproxen (tablet). According to the findings of a human pharmacokinetic investigation, nanocrystalline dispersion takes about half the time to attain maximal drug concentrations (94).

The field of pharmaceutical materials science uses modern mechanochemistry to a significant extent. The use of neat grinding, liquid-assisted grinding (LAGs), and polymer-assisted grinding (POLAGs) in screening for API polymorphs, solvates, salts, and cocrystals have been extensively investigated (95). As a recent extension of this, mechanochemistry is applied to utilize API molecules themselves, which has given rise to a branch of mechanochemistry called "medicinal mechanochemistry," which strives to produce cleaner, more efficient, and solvent-free alternatives to the solutions-based procedures traditionally used in medicine and pharmacology (53).

The solubility of pure components in classic solvent-based procedures can be a major challenge to cocrystals. In an already complex multicomponent system, the solvent adds more degrees of freedom to the crystallization process. The crystallization of a pure component crystalline product can be achieved with a 1:1 solution composition instead of a 1:1 cocrystal (96).

Using electrically induced techniques such as microwave-enhanced crystallization, ultrasound-assisted procedures, high shear granulation, neat grinding, cry milling, thermal methods, and hot-melt extrusion crystallization, resonant acoustic mixing, and song crystallization yield high-efficiency results (97). It has been discovered that mechanical processes like simple grinding and liquid-assisted grinding have been more effective at producing cocrystals of NSAIDs, as shown in **Table 2**.

As automatic mills have been introduced that control the frequency of milling and energy application during milling, these methods have overcome their limitations on practicality and reproducibility. Extrusion of hot-melt materials is an emerging manufacturing technology (71).

TABLE 2 | Preparation technique of cocrystal NSAIDs (95, 36, 53).

Cocrystal NSAIDs preparation technique	Applications	Refs.
Mechanochemical dispersion	A possible change in drug dissolution rate as well as enhanced bioavailability of drugs.	(98)
	Drugs can be transformed from a liquid to a solid form.	(99)
	Improved wettability.	(87)
Microcapsules	Possible to combine drugs and isolate their components.	(100)
	Medications in liquid form can be solidified.	(100)
	Combining the drugs as well as isolating their active ingredients.	(101)
	Reduction of particle size to enhance solubility.	(102)
Microparticles	Dosage forms are flexible depending on the drug delivery method (parenterally or orally).	(61)
	Enhanced drug stability.	(103)
	Drug release and delivery can be targeted.	(104)
	Combining the drugs as well as isolating their active ingredients.	(105)
Nanoparticles	Greater bioavailability compared to previous types of drug delivery (faster dissolution rate and higher solubility).	(98, 106)
	More homogeneous drug release.	(107)
Microemulsion	Enhanced drug bioavailability.	(44)
	Hydrophilic and lipophilic drugs are easier to dissolve.	(108)
	Long shelf-life.	(109)
	Reversible process.	(110)

5. Conclusion

An overview of current developments in the utilization of mechanochemical methods for the synthesis of pharmaceutical compounds and materials is provided in the following article, with a number of instances of chemical reactions that explain how drugs are transformed using mechanochemistry and mechanistic studies that demonstrate how molecular products are synthesized that are elusive using conventional solution techniques. NSAIDs' mechanochemical role has the following main advantages: enhanced bioavailability and the potential to alter dissolution rates. In addition to facilitating the transformation of drugs from liquid form into solid form and improved wettability.

Author contributions

MA, made contributions to the idea and design of the study, the collection, analysis, interpretation of data, the writing of the manuscript, and the critical revision of the manuscript. Both authors contributed to the article and approved the submitted version.

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