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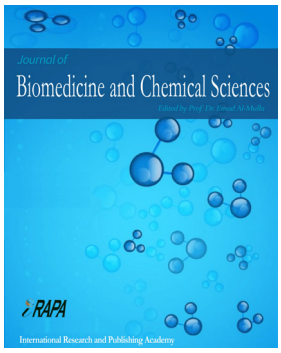

Mechanochemistry's Role in the Synthesis of Solid Form of Olanzapine Drug: A Review

Mohammad R. Alrbaihat*

Teacher Training Institute, Ministry of Education, Dubai, United Arab Emirates

*Corresponding author: Mohammad R. Alrbaihat | e-mail: moh.irbeihat83@hotmail.com

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ABSTRACT

Mechanochemistry has recently been identified as an attractive greener method of preparing diverse molecules and has become an imperative synthetic tool in multiple fields (e.g., physics, chemistry, and materials science) because it can be performed without solvents or with minimal quantities of solvent (catalytic quantities). A variety of chemistry fields have benefited from using sustainable methods, including drug synthesis, catalysis, organic synthesis, preparation of medicinal solid forms, metal complex synthesis, etc. This review highlights the hallmarks of using mechanochemical methods to prepare multicomponent solid forms, particularly those focused on the Olanzapine drug. As a result, Olanzapine -multicomponent solid forms prepared by mechanochemical methods have many advantages over their liquid-phase counterparts in terms of yield, selectivity, short reaction times, a simpler work-up procedure, and eliminating harmful organic solvents.

INTRODUCTION

A mechanical chemical reaction (MCR) is a reaction that occurs through physical action (milling, grinding, compression) in a free-solvent environment or containing catalysts and solvents in catalytic amounts (Alrbaihat, et al., 2021; Alrbaihat, 2022). Mechanical reactions are classified as the fourth subcategory of chemical reactions along with thermochemistry, photochemistry, and electrochemistry (Solares-Briones, et al., 2021). After being in the background for 5 to 10 years, mechano-chemistry is making a comeback partly due to the green aspect associated with the absence of solvents (Solares-Briones, et al., 2021; Alrbaihat, et al., 2022). Mechanochemistry and pharmaceutical sciences are inextricably linked. The structure of organic molecules at both the molecular (such as the crystal structure) and macroscopic (such as the particle size and morphology) levels must determine several solid-state properties of organic molecules, including solubility, dissolving rate, tablet ability, heat and moisture stability, and so on. In solid-state pharmaceutical materials, considerable research has focused on modifying the molecular arrangement of active pharmaceutical ingredients (APIs) to influence their solid-state properties. Amorphization, polymorph production, amorphous solutions, salts, and pharmaceutical co-crystals are examples of amorphization, polymorph production, and salt production (Tan, et al., 2016).

It is also possible to prepare multicomponent co-crystals using mechanochemical processes. Takuria and colleagues prepared solid multi-component pharma-drug and pharma-nutritional products. The conversion was incomplete after neat grinding (NG), which resulted in the formation of the amorphous phase. The amorphous olanzapine enateglinide, salts, and salt hydrates of olanzapine are synthesized via liquid-

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assisted grinding (LAG) with remaining conformers (Sarmah, et al., 2020). In a recent investigation, Roex and coworkers fabricated nine novel multi-component crystalline materials from three antimalarial triazoles, seven-chloroquinolines, and two carboxylic acids. In the study, they showed that coformers can modify some chemical characteristics of drug molecules (Surampudi, et al., 2020; McNaught & Wilkinson (2007) describe mechanical synthesis as a chemical transformation using mechanical energy, which is widely used for preparing valuable products, such as alloys and organic compounds. Through the encouragement of such studies. In recent years, innovations in green chemistry, supramolecular chemistry, pharmaceutical chemistry, organic synthesis, catalysis, inorganic chemistry, and metal-organic frameworks (MOFs) have been widely reported (Tan & Friščić, 2018). Figure 1 shows the most frequently used application areas.

Fig. 1. Applications of Mechanochemistry (Ozer, 2021)

Pharmaceutical materials are a relatively new area of mechanochemistry, which has seen explosive growth in interest over the past three decades. The study of mechanochemistry has been independently confirmed as a method of discovering additional solid forms that are effective and often superior to other approaches. Indeed, Tan et al. have recently released an extensive overview of how effective it is as a screening method as well as several other fields where it is likely to be employed in the future (Ozer, 2021; Hasa & Jones, 2017). Over the last three decades, interest in mechanochemistry has grown significantly in organic compounds, especially organic compounds with mechanochemical reactions. Mechanochemistry is successful and sometimes superior to other approaches in discovering additional solid forms, although studies have been quite recent. According to (Tan et al., 2016), mechanochemistry as a screening method has exceptionally high efficiency, and there are several other areas where it will likely be successful.

Despite the focus of research during the last 5 years on the applications of mechanochemistry in the development of materials in various fields, including pharmaceuticals, lack of favorable physicochemical properties that would accommodate Olanzapine pharmaceutical applications (Gong, et al., 2021; Hossain Mithu, et al., 2021; Paczkowska, et al., 2020; da Costa, et al., 2022; Souza, et al., 2018; Steed, 2018). According to Thakuria and Sarma, in a recent review, drug-drug cocrystals and drug-nutritional cocrystals are important and many examples have been documented. (Sarmah, et al., 2018). This review has a particular focus on the major role of mechanochemistry in the formation, modifications, and development of Multicomponent Solid, particularly Olanzapine Drug as pharmaceutical compounds, as a result, mechanochemistry is well suited for discovering fewer stable forms, as it offers conditions where equilibrium is not necessarily related to thermodynamic equilibrium, but is rather related to the experimental procedure.

Hallmarks of Mechanochemistry

In his definition of mechanochemistry, (Butyagin, 1994) described it as the stabilization of a solid structure, which increases its reaction ability. The role of structural relaxation in mechanical activation is significant. The concept of slowly changing states after mechanical action is interrupted is a concept (Baláž, et al., 2013). Among their results was the creation of a generalized relaxation curve for activated solids, which corresponds to different relaxation times for different processes. Activated solids cannot be influenced by slowing down their relaxation time during states which are shorter than their characteristic reactions,

according to the theory (Tan, et al., 2016; Gonnet, et al., 2021). Some long-living states (such as surface area) may, on the other hand, be considered constant throughout the reaction, in which case mechanical activation techniques would be necessary to determine their influence. Heating, surface formation, aggregation, recombination, adsorption, defects, chemical interactions between adjacent particles, and other relaxation phenomena have all been described (Boldyrev, 1986; Suryanarayana, 2001; Al-Rawajfeh, et al., 2020).

The rate at which these relaxation processes occur can vary dramatically, and the processes can shift from one mode of relaxation to another. Due to this, mechanically activated (MA) can be viewed as a multi-stage process, with each stage involving some change in energetic parameters as well as the amount of accumulated energy in the solid. The phrase mechanical activation refers to the combination of four processes: defect buildup, amorphization, development of metastable polymorphous structures, and chemical reaction (Tan & Friščić, 2018; Szabó-Révész, 2018; Nangare, et al., 2021). Mechanically activated processes have been categorized into main and secondary processes, according to researchers. When a fundamental process occurs (e.g., the increase of surface area, surface energy, or a decline in a solid's coherence energy), the substance becomes more reactive. Secondary processes (such as aggregation, adsorption, and recrystallization) occur spontaneously in active systems and can occur during or after milling (Borges, et al., 2015; Frost, et al., 2001).

Mechanochemical of Multicomponent Solids

Recently, the field of mechanochemical synthesis has witnessed explosive growth, generating a variety of review articles, a monograph, and several journal-themed issues (Leonardi, et al., 2018). Leyssens & ter Horst, 2017). The combination of its effects with other strategies that achieve better synthetic efficiency and reduced solvent waste has been relatively overlooked and ignored until now. The present Perspective article explores a type of combination that permits green synthetic methodologies to become one of the forefronts shortly. This is done by way of combining the advantages of both approaches. Often, mechanochemical activation of mechanochemical reactions MCRs results in increased yields, reduced reaction times, and other advantages, as will be discussed in Section 1. As an alternative approach to the traditional process of incorporating substituent groups into a drug, pharmaceutical cocrystallization/ salt preparation can improve the physicochemical properties of the drug (Cherukuvada, et al., 2016). The pharmaceutical multicomponent solids industry has tested numerous formulations for enhancement in stability, solubility, half-life period, and dissolution rate. over the last two decades (Kavanagh, et al., 2019).

Recent years have witnessed the development of nutraceuticals and flavonoids that positively impact health with minimal side effects as coformers rather than GRAS molecules (Sarmah, et al., 2017). Additionally, coformers incorporating two drug molecules have been synthesized to deal with multiple diseases in the same manner. The target-specific nature of targeted therapy still prevails over combination therapy even though it has several advantages over the latter, such as reduced drug load, cost-effectivity, clinical effectiveness, etc. (Žegarac, et al., 2014). The reason for the relatively lower level of crystals/salts between drug-drug compounds compared to an exponential database of multicomponent pharmaceutical solids is because of this factor.

Behavioural Pharmacology of Olanzapine

Olanzapine crystallizes as multiple solvates/ or hydrates as a single-component system, when these soluble forms are stored, they compete with anhydrous stable forms I and II to crystallize, resulting in phase transitions (Sun, et al., 2018; Askin, et al., 2020). Solvent/hydrate molecules can be incorporated into the dimer structures generated by olanzapine dimers (Reutzel-Edens & Bhardwaj, 2020; Cavallari, et al., 2013). Because supramolecular hosts for solvate inclusions have received limited attention, multi-component systems play a critical role, the mechanochemical approach is thought to be one of the best approaches for this process [8]. In Figure 2, an olanzapine derivative is an antipsychotic drug that is derived from thienobenzodiazepines (Moore, 1993). This class of antipsychotics has been described as demonstrating: (i) a wider efficacy, especially in treating patients suffering from mental illness; (ii) a lower prevalence of extrapyramidal symptoms; and (iii) minimal prolactin perturbation (Callaghan, et al., 1999). Fuller & Snoddy, 1992).

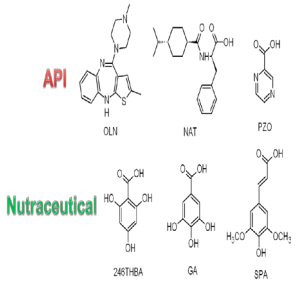

Fig. 2. Molecular structure of olanzapine (OLN) (Sun, et al., 2018).

Olanzapine shows a wide range of receptor affinities in brain cell homogenates or cell lines expressing cloned receptors, including 5-$HT_{2A/C}$ serotonergic, D_{1-4} dopaminergic, histamine H_1, α_1 adrenergic, and muscarinic M_{1-5} receptors as described in (Fuller & Snoddy, 1992; Bymaster, et al., 1996). There is strong evidence that olanzapine acts through a glutaminergic mechanism. For instance, phencyclidine and MK-801 antagonize olanzapine's effect on phencyclidine- and MK-801-induced behaviors that model schizophrenia (Corbett, et al., 1995). There is a great deal of evidence that olanzapine may be an effective treatment for schizophrenia and psychosis associated with schizophrenia (Callaghan, et al., 1999). Beasley Jr, et al., 1997). Antipsychotic medication olanzapine (OLN) is used to treat schizophrenia and bipolar disorder (Faden, et al., 2022). There are many forms of OLN documented in the literature, including cocrystals, salts, solvates, and hydrates, as well as polymorphic forms Although it is one of the most frequently prescribed antipsychotics, OLN has a few metabolic side effects. These include weight gain, impotence, and high blood glucose levels associated with type 2 diabetes. Metformin, glyburide, nateglinide (NAT), and other type 2 diabetes medications are prescribed to patients when taking OLN, to prevent metabolic side effects. As a coformer, nateglinide produces OLN drug-drug multicomponent solids with improved efficacy and fewer side effects (Sarmah, et al., 2020).

Sarmah et al., 2018 were successful in synthesizing a series of olanzapine (OLN) dicarboxylic acid salts, which included previous reports on olanzapine malonate (1:1) and maleate (1:1 and 1:2) that were prepared mechanochemically utilizing liquid assisted grinding (LAG) to investigate their hydration stability. They proposed that, in addition to the stronger hydrogen bond synthon (N+–HO– in OLN salts vs. O–HN in OLN hydrates), the entire crystal packing plays an essential role in developing OLN salts with superior hydration stability. In the study by Sarmah et al. (2020), they prepared amorphous and crystalline multicomponent solids of OLN using mechanochemistry to add nutraceuticals and drugs as coformers. Despite this, it was observed that NG always leads to amorphous materials, whereas LAG shows completion of the reaction process for salt formation. Furthermore, they reported the occurrence of a two-step crystallization process with an amorphous phase as a key intermediate for several OLN salts using mechanochemical synthesis and concluded that drug formulations as combination drugs would be a novel approach to treating targeted diseases with reduced cost and smaller dosage forms simultaneously (Sarmah, et al., 2020).

Microbial Behavioural of Olanzapine

Olanzapine has been found to affect the gut microbiome, which is the community of microorganisms that inhabit the human gastrointestinal tract. Studies have shown that treatment with Olanzapine can alter the composition and diversity of the gut microbiome, leading to changes in the metabolism of the microorganisms and potentially affecting the host's health (Zheng, et al., 2019). For example, A study published in 2019 on bipolar disorder patients found that olanzapine treatment was associated with an increase in the relative abundance of the genus Streptococcus in the gut microbiome, as well as a decrease in the relative abundance of Bacteroidetes (Leprun & Clarke, 2019). This research suggests that Olanzapine may have a significant impact on the gut microbiome and that further research is needed to understand the mechanisms by which Olanzapine affects the gut microbiome and its potential effects on health.

Another study from 2020 published on Schizophrenia patients found that Olanzapine treatment was associated with the increased relative abundance of Enterobacteriaceae and reduced relative abundance of Bacteroidetes (Li, et al., 2020). It is important to consider that the gut microbiome has a bidirectional interaction with host, which means that not only medications may affect the gut microbiome but also the gut microbiome itself may affect the drug efficacy and side effects. Further studies are needed to fully understand the potential effects of Olanzapine on the gut microbiome, as well as the potential implications for the treatment of schizophrenia and bipolar disorder.

CONCLUSIONS

Mechanochemical synthesis is an environmentally friendly, more time-saving, highly efficient, time-saving, and economical synthesis technique for creating new and efficient functional materials. This review provides a brief of recent advances in the use of mechanochemical techniques for the synthesis of pharmaceutical molecules and materials, highlighting olanzapine synthesis. The main advantages of the mechanochemical role of multicomponent solids of OLN have enhanced drug bioavailability and the possibility of a change in dissolution rate. As a result of mechanical chemistry's use in industry and science up until now, solvent usage has been reduced, solubilities are prevented, and the environment is protected.

Competing Interest

The authors had no competing interests.

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