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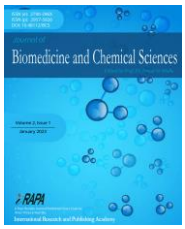

Mechanochemical Synthesis of Host-Guest Inclusion Complexes of Cyclodextrin: A Review

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ABSTRACT

Mechanochemical activation by grinding appears to be the preferred method for the solid-state synthesis of the cyclodextrin inclusion complex because it is fast, highly effective, convenient, and versatile. It is also sustainable and eco-friendly since it uses no solvents. As a result of this review, we will highlight both the advantages and shortcomings of such an approach. Furthermore, we will review the current data in this area systematically. Several possible mechanisms have been illustrated to explain complex formation in the solid state as a result of grinding. We examined the process variables associated with each type of milling instrument applied, as well as the features of the resulting products. We also discussed the physio-chemical properties of the drug as well as cyclodextrin. As a result of the critical process parameters, a rational selection of conditions for the efficient preparation of inclusion complexes by grinding has been demonstrated, with the ultimate objective of increasing the use of this solvent-free process for preparing cyclodextrin inclusion complexes in solids.

1. Introduction

Recently, the field of mechanochemical synthesis has witnessed explosive growth, generating a variety of review articles a monograph, and several journal-themed issues (Alrbaihat, et al., 2022; Alrbaihat, 2022; Takacs, 2013; Zhang & Saito, 2012). The combination of its effects with other strategies that achieve better synthetic efficiency and reduce 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 combining the advantages of both approaches. Often, mechanochemical activation of mechanochemical reactions (MCRs) results in increased yields, reduced reaction times, and other advantages (Virieux, et al., 2021; Baláž, et al., 2006; Friščić, et al., 2020; Morozkina, et al., 2019; Baláž & Baláž, 2008; Tan, & Friščić, 2018; Cross & McAinsh, 2014). Chemical reactions were divided into four subcategories including mechanical, thermochemical, photochemical, and electrochemical reactions (Solares-Briones, et al., 2021). Due partly to the fact that mechanical chemistry does not require solvents, it has made a comeback after being out of favor for two to three years.

Mechanochemistry and pharmaceutical sciences are inextricably linked (Virieux, et al., 2021; Solares-Briones, et al., 2021; Tan, et al., 2016). Several solid-state properties of organic molecules, including solubility, dissolving rate, tablet ability, heat and moisture stability, and so on, are vitally dependent on their structure at both the molecular (e.g., crystalline structure) and macroscopic (e.g., size of the particles and morphology) levels. Significant work in solid-state pharmaceutical materials has thus been directed toward finding ways to influence the solid-state properties of active pharmaceutical ingredients (APIs) by affecting their

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molecular arrangement in solids, such as amorphization, the production of polymorphs, solid solutions, salts, and, more recently, pharmaceutical co-crystals (Tan, et al., 2016).

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 enhancements in stability, solubility, half-life period, and dissolution rate. over the last two decades (Kavanagh, et al., 2019). There has been a fascination with cyclodextrins in research and industry for more than 130 years (Gregório, 2014; Matencio, et al., 2020; Stella, & He, 2008). Cage molecules are composed of a hydrophobic cavity at the core of their structure, which can enclose other substances with a hydrophobic moiety through host-guest interactions (Figure 1).

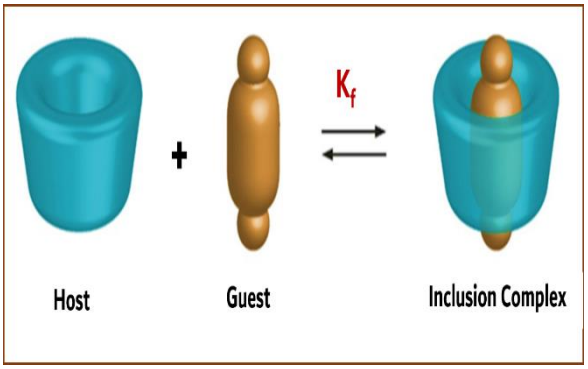

Fig. 1. Schematic diagram for the formation of inclusion complexes from cyclodextrin molecules with guests

Cyclodextrins and their derivatives have found use in many fields, including the chemical and pharmaceutical industries, biology, medicine, and biomedicine, as well as the food and beverage industry, hygiene, electrochemistry, and catalysis (Stella, & He, 2008; Crini, et al., 2018; Jansook, et al., 2018). In this review, we will summarize the data that are currently available in this field in a systematic way. In this study, we aim to investigate the ability of ball mills to synthesize CD complexes without solvents.

2. Chemistry of Cyclodextrins

As a result of the degradation of starch, cyclodextrins (CDs) are derived from the α -(1,4)- linked D-anhydroglucopyranose units. As demonstrated in Fig. 2, the α-, β-, and γ-CDs (each consisting of 6, 7, and 8 glucose units) can create host-guest inclusion complexes with a variety of configurations, that make hydrophobic substances more soluble, chemically stable, bioavailable, and dissolvable when these enhancing properties are present. CD inclusion complexes and their capacity to entrap molecules through reversible non-covalent interactions have found use in a variety of fields, including the nutrition, cosmetics, and pharmaceutical industries (Cravotto, et al., 2006).

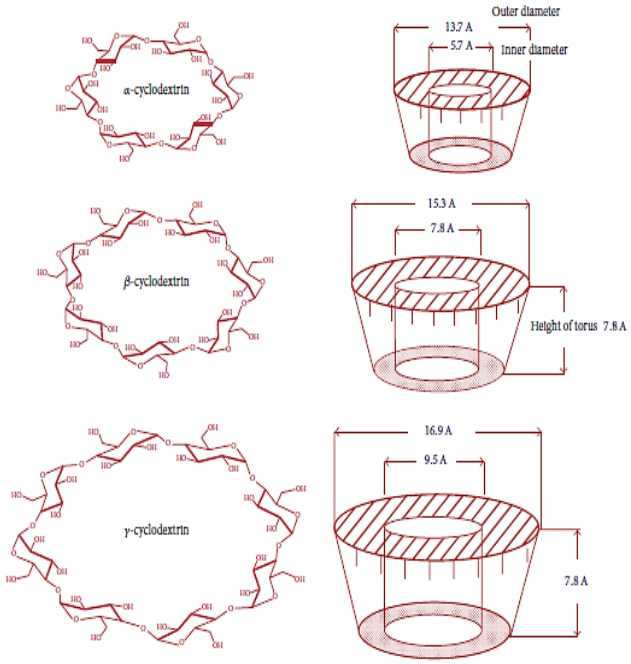

Fig. 2. Structure and conformation of natural cyclodextrins (Davis & Brewster, 2004).

The quantity of glucose units affects the size of a cyclodextrin cavity (Sikder, et al., (2019; Nury, et al., 2015; Su, et al., 2021). In contrast to the oxygen atoms in the glycosidic bonds and the hydrogen atoms within the cavity, which give the hydrophobic character, the free hydroxyl groups outside of the CDs are in charge of the hydrophilicity. This allows for the dissolution of substances with low solubility in an aqueous medium. Inclusion complexes with substances that are poorly soluble can also form due to the area inside the cyclodextrin molecule (Kurkov, & Loftsson, 2013; Gandhi & Shende, 2021).

Through the inclusion of complex formation, cyclodextrins (CDs) are recognized as multifunctional excipients capable of increasing drug solubility, dissolution rate, chemical stability, and bioavailability (Colombo, et al., 2009; Friscic, & Jones, 2009). CD encapsulation may also help reduce or prevent irritants and other side effects, increase drug penetration across biological membranes, reduce drug-excipient interactions, modify the organoleptic characteristics of molecules embedded within, and convert liquids and volatile compounds into powders that are technically more acceptable (Wu, et al., 2018; Khoushabi, et al., 2015; Zeeshan, et al., 2018; Yu, et al., 2017). Various sophisticated drug delivery methods include monolithic, micro- to nanoparticulate, and CD-based approaches to target and control the drug release kinetics based on therapeutic requirements (Jug, et al., 2018).

3. Mechanochemical Synthesis Of Cyclodextrin

In chemical reactions, mechanical means (milling, grinding, and compression) are used to induce reactions, which occur in a solvent-free environment or with solvents in catalytic amounts (MCRs) (Alrbaihat, et al., 2021). It is believed that mortars and pestles were used to prepare food

and medicine during the Stone Age (Alrbaihat, 2022).

By using the grinding method, metal-ligand coordination bonds and non-covalent interactions such as hydrogen bonds, halogen bonds, and arene stacking can be built by a mechanochemical process (Friščić, et al., 2020; Solares-Briones, et al., 2021; Štrukil, 2018; Zhao, et al., 2016; Dong, et al., 2008; Delori, et al., 2012). A detailed analysis of these nanoparticles provides evidence as to how grinding plays a role in the creation of pharmaceutically relevant cocrystals, porous metal-organic nanoparticles, framework polymorphs, polymeric dispersions, as well as inclusion complexes (Friščić, 2010; Tole, et al., 2019; Pladevall, et al., 2021).

Hydrophobic medicines with low aqueous solubility can form molecular inclusion complexes with cyclodextrins and a few of their derivatives (Braga, 2019). These cyclodextrin molecules are advantageous because the exterior of the host molecule is largely hydrophilic, while the hydrophobic cavity inside is large enough to house the lipophilic medicines as guests (Jansook, et al. 2018; Sadaquat, et al., 2021). As a result, the molecularly encapsulated drug's water solubility and dissolution rate have significantly increased (Promzeleva, et al., 2018; Jablan, et al., 2012; Ahmadian, et al., 2021; Cao et al., 2019; Mennini, et al., 2014; Maestrelli, et al., 2009). Among the nine methods mentioned above, the preparation of inclusion complexes with cyclodextrins is of particular interest.

The CD complexation is conducted by overheating in a sealed container, which is known as the sealed-heating technique (SH), by microwave irradiation (MWI), or by physio-chemically grinding a mixture of cyclodextrin and medication using several types of mills (Maestrelli, et al., 2009; Cirri, et al., 2009; Cugovčan, et al., 2017). There is currently no known mechanism for how complex formation happens when drug-cyclodextrin combinations are ground, but researchers suggest a possible scenario, shown in Figure 3 (Hasa & Jones, 2017). According to this mechanism, mechanochemical reactions occur in three steps, and additional processes may be involved during mechanochemical drug activation (Colombo, et al., 2009; Friscic & Jones, 2009).

Hasa and Jones (2017) proposed a three-step mechanism to understand the mechanochemical reactions that occur by grinding, whereas during the first step particle size reduction, formation of defects in the crystal structure, and mechanochemical activation of the surfaces of the reactants occur. During the next step, the inclusion of complex formation at the surface of the reactants takes place. During the third step, detachment of the formed complexes from the reactant surfaces during the milling, the formation of the product particles, as shown in Fig. 3.

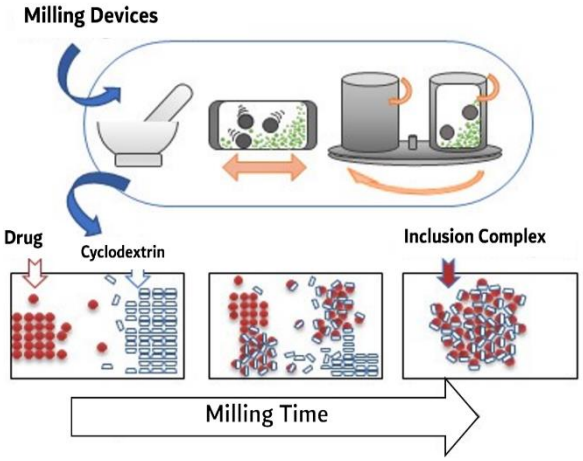

Fig. 3. Solid-state inclusion complex formation by grinding (Jug & Mura, 2018).

Fast solvent-free mechanochemical treatments in PBM have the potential to facilitate the efficient synthesis of steroid-CD inclusion complexes. Moreover, the interaction between steroids and CDs has been strengthened, and the solid inclusion complex forms obtained can be used directly as pharmaceuticals, dietary supplements, and cosmetics (Nury, et al., 2015).

Through mechanochemistry, Hoti et al. (2021) developed cyclodextrin nanosponges that were environmentally friendly and efficient. Chemical reactions are controlled and driven by mechanical forces, which transfer energy from one bond to another. A twin-screw extruder is used in the mechanochemical approach. It allows fine temperature control as well as an ongoing process, which makes this chemical reactor ideal for continuous organic synthesis [58]. Nanosponges made from cyclodextrin have made significant contributions in the past 20 years to the environment (for instance as an adsorbent), pharmaceutical (for instance, as a drug delivery system), and food (for example, to remove target substances) due to their three-dimensional nanostructured network with controlled properties. The eco-designed nature of such nanomaterials provides for a wide range of applications (El Achkar, et al., 2020; Crini, et al., 2018; Řezanka, 2019).

A mechanical ball milling method was successfully used by Wenjing et al, 2021, to prepare astaxanthin inclusion complexes AST IC, which was able to improve astaxanthin solubility and bioavailability. The results exhibited that AST entered the HP-CD cavity and that the host-guest complex was created throughout the grinding process. After being ground, the AST IC's solubility improved as compared to astaxanthin. The AST IC may self-assemble into micelles with a homogeneous particle size distribution, spherical shape, and drug release qualities in vitro when it is dissolved in water. The antioxidant activity of AST may be enhanced by oral administration of the AST IC. Our study offers a significant advancement in the creation of self-assembled micelles and demonstrates a novel technique for mechanically ball-milling AST IC (Su, et al., 2021).

Based on the theory, activated solids cannot be affected by slowing down their relaxation time (Zhao, et al., 2016; Cao, et al., 2019; Aleksandrov, et al., 2021; Kang, et al., 2021; Yong, et al., 2021; AlShamaileh, et al., 2018).

However, some long-living states (such as surface area) might not be affected by mechanical activation techniques, requiring the use of mechanical methods to determine their influence. Various relaxation processes have been documented [66]–[68], including melting, aggregation, recombination, adsorption, defects, and chemical reactions between neighboring particles (Boldyrev, 1986; Suryanarayana, & An, 2006; Al-Rawajfeh, et al., 2020). During these relaxation processes, the rate of occurrence can be dramatically different, and the processes can shift from one mode to another. As a result, mechanically activated (MA) can be viewed as a multi-stage process, with each stage involving changes to energy parameters and solid energy accumulations. Mechanical activation is the formation of metastable polymorphous structures through a combination of four processes: defect build-up, amorphization, chemical reaction, and metastable polymerization (Baláž & Baláž, 2008; Wei, et al., 2017; Boldyrev, 2006; Watabe, et al., 2021; Mucsi, 2019; McCormick & Froes, 1998; Rudmin, et al., 2019).

4. 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 host-guest inclusion complexes, highlighting cyclodextrin synthesis. The key benefits of a solid-state mechanochemical role for CD inclusion complexes are improved drug solubility and the ability to boost drug dissolving rate, chemical stability, and bioavailability by the inclusion of complex formation. To reduce solvent consumption, avoid solubilities, and safeguard the environment up till now, mechanical chemistry has been extensively employed in a wide range of industrial and scientific settings. It will continue to play a significant role in research in the future.

Competing Interests

The authors have declared that no competing interests exist.

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