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Comminution and Amorphisation of Diaqua-bis(Omeprazolate)-Magnesium Dihydrate: An Analysis of the Energies Involved

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Abstract: Size reduction of Diaqua-bis(Omeprazolate)-Magnesium Dihydrate (DABOMD) crystals, an active pharmaceutical ingredient (API) which inhibits gastric acid secretion and its related disorder in mammals, has been investigated using a planetary ball mill and a single ball mill. The outcome of milling shows that DABOMD undergoes prominent comminution and amorphisation processes that occur parallel to each other, with planetary ball mill causing higher amorphisation rate compared to the single ball mill. To establish a relationship between the degree of comminution and amorphisation, the energies of the planetary ball mill and the single ball mill were quantified using a collision model derived from the literature, and through tracking the milling jar with high speed-camera, respectively. In addition, energies were calculated using the Discrete Element Method (DEM) simulations of both mills. The energy obtained from the DEM simulation of the planetary ball mill is lower than the calculated energies from the literature collision model. This could be due to the fact that the collision model does not consider additional factors affecting the motion of balls, such as friction between the balls and balls and wall. However, the energy calculated from the DEM simulation

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is higher than that generated from high speed video tracking of the milling jar for the single ball, since as shown by the DEM the movement pattern and the velocity magnitude of the ball is different to those of the jar, resulting in higher relative collision velocities than the jar velocity itself. Nevertheless, it was found that the planetary ball mill produces higher energy than the single ball mill which explains the difference in the amorphisation obtained in the two mills. This methodology enables quantification of the changes that arise with the milling of a solid (i.e. comminution and amorphisation) with respect to the energy level involved.

1. Introduction

Ball milling is commonly used in the pharmaceutical industry for the size reduction of pharmaceutical solids. This type of mill has repeatedly been reported for its association with mechanochemistry which refers to the physical and chemical changes (e.g. emergence of an amorphous and or polymorphic) arising with mechanical energy. Examples of studies in the area of mechanochemistry of pharmaceuticals are on Diaqua-bis(Omeprazolate)-Magnesium Dihydrate (DABOMD) [1], Budesonide [2], Indomethacin [3], and Cefalexin [3], [4]. The mechanism of mechanochemistry is not well understood due to the complication and diversity of the reaction types, reaction conditions, as well as the inhomogeneous nature of the solid-solid materials. This is attributed to the difficulty of the direct observation of the material encountering the mechanochemical process at microscopic and molecular levels [5]. Other constraints include the lack of studies and the limited literature covering mechanochemistry, particularly for organic materials and pharmaceuticals. DABOMD is an active pharmaceutical ingredient (API), known as proton pump inhibitor which inhibits gastric acid secretion and its related disorder in mammals. In an attempt to describe the mechanism of mechanochemistry of DABOMD (Figure 1), due to milling, it was found that the underlying structural properties of DABOMD played a significant role in its mechanistic behaviour and mode of breakage, i.e. it was suggested that the extensive hydrogen bonds were responsible for the significant fracture, and the presence of slip system (100) and the existence of water molecules near the slip system were greatly associated with the effective crystalline lattice disorder and the emergence of the amorphous form [1]. As a continuation of the previous work performed on the planetary ball mill to establish a relationship between the underlying material properties of the feed sample and the milling behaviour, it is of paramount importance to evaluate the relationship between different milling energies, the extent of size reduction (comminution) and the level of mechanochemistry (amorphisation). Therefore, this paper compares the milling in

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a vibratory single ball mill (Figure 2) with a planetary ball mill (Figure 3) since in theory, the two mills generate different amounts of energy which can ultimately lead to a variable impact on the milling mechanism of the material [6]. The single ball mill consists of a grinding ball sitting in a milling jar attached to a clamp that vibrates at different frequencies across the x-axis [7]. The vibration of the mill and the movement of the ball contributes to the size reduction of powder through impact and shear stresses [7]. While, in the planetary ball mill, the impact and shear stresses are thought to be more prevailing due to the movement of the grinding chamber with a large centrifugal force [8].

The evaluation of the impact of milling on the physical and chemical properties of DABOMD involves full characterisation of the feed and milled DABOMD to examine its morphology, size, crystalline structure, thermodynamic properties, and intermolecular structure. This is achieved through the implementation of solid-state analytical techniques including SEM, laser diffraction, XRPD, TGA, DSC, and FTIR.

Since the mechanistic behaviour of the milled solid depends on the energy transferred to the powder during milling, it is vital to establish a relationship between the energy of milling and the degree of comminution and amorphisation (mechanochemistry) which has not been widely investigated. The energies of the planetary ball mill, single ball mill were quantified using the available literature methods as well as from using the Discrete Elemental Method (DEM) simulation.

2. Materials and Method

2.1. Material

In this work, two solid-state forms of DABOMD were used, a crystalline and an amorphous powder. The crystalline powder of racemic DABOMD (*R*- and *S*-form) with 98% purity was provided by AstraZeneca.

Amorphous powder of DABOMD was prepared from a DABOMD/methanol solution (approx. 18 g in 0.7 L) followed by rapid evaporation in a rotary evaporator at 40 °C and 20 mbar. Subsequently, the product was further dried in a vacuum (10 mbar). The amorphous form was confirmed by the absence of Braggs peaks in X-ray powder diffraction (XRPD) [1] and used as a standard reference to quantify the amorphousity within the milled sample.

2.2. Method

2.2.1. Milling Experiment

The powder samples of DABOMD were milled in the planetary ball mill PM100 between 1 and 300 min at a speed of 650 rpm in a 250 ml steel jar, using four balls with a diameter equal to 15 mm at a ball to powder ratio (BPR) of 10:1 by weight. The selected BPR allows for increased contacts and better particle breakage and size reduction [9]. The milling jar was filled for up to two-thirds of its volume with the powder and the balls. The mill was set to run for 20 min with periodical breaks to prevent the temperature rise in the system. The lid covering the media was sealed tightly with the aid of a safety clump. The mill was regularly monitored for safety and to prevent a temperature rise of the bulk [1].

For the single ball milling, the powder samples of DABOMD were milled using a MM200 Retsch ball mill from 1 min to 300 min. Approximately 1.3 g of powder with a steel ball of a diameter equal to 15 mm was placed in a steel jar to fill one-third of the jar's volume. The oscillation frequency and the time of milling can be varied depending on the desired experimental setup. The powder and the ball were added to the milling jar which was then securely tightened and attached to the clamp and the oscillation was set to 30 Hz. [1].

2.2.2. Powder Characterization

The non-milled and the milled samples were characterised to determine their morphological, size, crystalline and thermodynamic properties, in addition to the intermolecular characteristics from the crystal structure.

Morphology

Surface and morphological properties of DABOMD were examined using a scanning electron microscope (SEM) in a Carl Zeiss EVO MA15 scanning electron microscope at 20 kV in backscattered imaging mode. Carbon tabs were coated with powder samples and placed on SEM metal stubs. Sample stubs were sputter-coated with a conductive layer of platinum before the analysis to prevent charging.

Particles size analysis

The particle size distribution (PSD) was analyzed by laser diffraction method (in a Malvern 3000) of dry sample powders. The powder was dispersed in the air at a pressure of 2 bars, a feed rate of 50%, and with obscuration ranging from 2 to 10%.

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Thermodynamic properties

Differential scanning calorimetry (DSC) analysis of the non-milled and milled DABOMD was carried out using a Mettler TC 3000 differential scanner calorimeter with purged liquid nitrogen at a rate of 5 °C/min from 25 to 250 °C. Approximately 5-6 mg of powder was placed in an aluminum sealed pan with a small hole in the top. Similarly, thermogravimetric analysis (TGA) was carried out with flowing gaseous nitrogen and at a rate of 5 °C/min from 25 to 250 °C. TA instrument Universal analysis 2000 was used for the analysis step.

Crystalline Properties

The crystalline properties of the milled powder were analyzed using X-ray powder diffraction (XRPD) with a Phillips PW 1710 X-ray diffractometer using a Cu Kα radiation (λ=1.5406 Å operating with 40 kV accelerated voltage and 30 mA current. Scans were collected over a 2θ range from 5° to 55°, scanned in steps of 0.02°, with a dwell time of 0.25 s and a 3° slit in front of the detector.

Intermolecular interactions

Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy measurements were carried out on ATR-FTIR Thermo iS101 to analyze the effect of milling on the intermolecular properties of the sample. FTIR of the non-milled powder, milled samples and amorphous standard powder were carried out at a range from 400 to 4000 cm ^{1}. A background spectrum was obtained for each experimental condition and 37 scans were taken for each sample. Computed IR-spectra was generated for a geometry optimized representative molecular model following [1]. The results are provided in the supplementary information (Figure S2).

Quantification of Solid Phases

A series of XRPD scans were carried out on the crystalline, and the standard amorphous samples of different ratios by weight of (0%, 20%, 40%, 60%, and 80%), and a calibrated curve was plotted from the derived data corresponding to the integrated areas under peaks at 2θ equal to 5.3 and 25.2°. The generated curve has an R-value equal to 0.9949 (Figure 4). The equation derived from the calibration curve is used to quantify the phases formed as a result of milling. This method of quantification was described by [10].

2.2.3 Calculating the Mechanical Energy

Calculating the Energy in Planetary Ball Mill following a literature method

The quantification of the energy in the planetary ball mill using high speed imaging is challenging due to the built-in mill cover in this work which hinders the observations of the milling jar rotating within the mill. Therefore, the energy transferred during the process of milling of DABOMD in the planetary ball mill was calculated following a literature approach referred to as the collision model [11], [12] which was developed based on engineering a transparent mill cover which allows recording the movement of moving parts in the planetary ball mill [13].

The energy transferred during the process of milling of DABOMD is produced as a result of balls-balls and ball-wall collisions and is calculated following the collision model [11], [12]. The collision theory suggests that the energy generated inside the ball mill is a function of the mill variables (i.e. number balls, milling time, mass of powder) and the mill geometry, as shown in Table 1 and Table 2. The collision model methodology is shown in supporting information.

Calculating the Energy in Single Ball Mill Following Empirical Method

High-speed Camera (Imacon 790, Hadlands Photonics) was used to identify the velocity and amplitude of the milling jars in a single ball mill. The high-speed camera records the moving part (milling jar) at 250 frames per second. The experimental setup is shown in Figure 5.

The images from the high-speed camera were processed using Track-Mate plugged in ImageJ software. The generated trajectory of the moving jar with respect to time is displayed in Figure 6, and the mill variables are illustrated in. Table 3

The kinetic energy E_b, in the balls before the hit in the single ball mill is calculated using Equation 1, m_b is mass of the ball. The impact velocity v_b can be assumed from maximum jar velocity obtained from tracking the jar motion as shown in Figure 5 and Figure 6.

$$E_b = \frac{1}{2} m_b v_s{}^2$$ Equation 1b

The power is then calculated by assuming that the ball impacts the jar according to the frequency of vibration, i.e. 60 impacts at 30 Hz.

Calculating the Energy Associated with Compression

In order to mimic the impact stress from the mills and to investigate the type of stress that can lead to the amorphisation of DABOMD, we followed a previously reported method [9] where

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a known amount of compressive energy is applied using the uniaxial compression test. The compression test was conducted at 10 kN using Instron compression test 5566, where approximately 0.4 g of DABOMD powder was placed in a 10 mm die and was compressed up to 10 kN [9].

Calculation of Energy using Simulation

DEM is a powerful tool employed to model the particle interaction; hence it was employed as an additional method for the energy calculations [15]. In principle, in DEM, particles are tracked based on their conditions, including positions, velocity and external forces. In the present study, EDEM 2018® software, provided by Atair, was used. The Hertz-Mindlin no-slip model [14] was employed for the normal and tangential force calculations.

The general governing equations in DEM consider the translational and the rotational motion of particles as expressed in Figure 7 according to Equation 2 and Equation 3 [14].

$$m_i \frac{dV_i}{dt} = \sum_j F_{ij}^c + \sum_k F_{ik}^{nc} + F_i^f + F_i^g \qquad \text{Equation 2}$$

Equation 2 represents the translational motion of particle i in three dimensions, where, m_i and, V_i represent the particle mass and the particle velocity, respectively. F_{ij}^c is the contact force exerted on particle i from particle j or other geometries. F_{ik}^{nc} symbolises the non-direct forces such as van der Walls and electrostatic imposed on particles i and j by particle k or other forces, F_i^f is the particle-fluid interaction force and F_i^g which represents the gravity force, respectively.

$$I_i \frac{dw_i}{dt} = \sum_j M_{ij} \qquad \text{Equation 3}$$

Equation 3 displays the rotational motion of the particle i with I_i and w_i representing the motion of inertia and the angular velocity, respectively. These equations are solved according to a suitable contact model and at small time steps [16].

In addition to the mill's variables (i.e. speed, number and size of balls) and geometrical parameters, other parameters used in the simulation are as follows.

The coefficient of restitution (CoR) is employed in the DEM simulation to account for the presence of the powder within the mills which hinders the ball restitution after each impact. CoR depicts the ratio of the rebound velocity to the impact velocity. CoR depends on various

factors, including the speed of the collision, and the type of material. In this work, CoR was measured using a high-speed camera and the image analytical technique. In this work, the ball was released from a height (approx. 20 cm) and impacted with a surface covered with a layer of DABOMD's powder. The average obtained value (after three experiments) of CoR is 0.16. The quantification of coefficient of restitution for the ball-ball impact is challenging, however, it can be assumed that balls will always be covered in a layer of powder; hence ball-powder CoR can be implemented in the calculation.

Sliding friction

Sliding friction can be obtained by sliding two layers of particles as shown in Figure 8. Simply two flat surfaces are covered by a monolayer of particles that are tilted together until the upper surface slides [16]. This experiment is conducted for particle-particle and particle wall friction. The angle corresponds to the event of sliding is measured from the record taken by a high-speed camera. The obtained sliding friction is equal to 1.53 and 0.73 for powder-powder and powder-steel, respectively. The steel-steel is not applicable since balls are assumed to be covered with powder.

Rolling friction

The rolling friction is used for DEM simulation to account for the effect of the shape irregularity of particles. The default value of a complete sphere is 0; however, it is a common practice to use a value of 0.01 to account for some irregularity in shape [16].

2.2.4 DEM Simulation of the Planetary Ball Mill

In a planetary ball mill, only the balls have been simulated since the number particles to represent the powders would be excessively high leading to very high computational costs. Here the presence if powders is only considered as their effect on the CoR and sliding friction of balls. The kinetic energy (K.E.) is calculated from the related velocity, v_b, of the ball-ball and ball-wall after collisions according to Equation 4. Where m represents the mass of the ball, n is the number of ball and ball-wall collisions occurring in one second. The feed parameters employed for the simulation of the planetary ball mill are shown in Table 1, Table 2, and Table 4.

$$K.E. = \sum_{j=1}^{n} = \frac{1}{2}mv_b^2 \qquad\qquad \text{Equation 4}$$

The kinetic energy simulated using DEM is equivalent to the impact energy ΔE_b derived from the literature. To account for the powder weight, the impact energy is divided by the powder weight (PW).

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2.2.5 DEM Simulation of the Single Ball Mill

The single ball mill was simulated following the same setup used in the planetary ball mill while applying the parameters in Table 3 and Table 5. Here powder was simulated in the single ball mill, but a scale-up particle diameter was employed as the original power diameter would take huge computational time. In our previous studies, we introduced a dimensionless term known as the "cohesion number" which can be used to scale up particle diameter and Young's modulus [17]. Following the approach in the previously published work, the ratio between the scaled properties and the original ones can be determined using Equation 5.

$$\frac{\Gamma_1^5}{E_1^2 D_1^3} = \frac{\Gamma_2^5}{E_2^2 D_2^3} \qquad \text{Equation 5}$$

Where, Γ_1 and Γ_2 are the interfacial energy of DABOMD which is equivalent to the surface energy) can be estimated from Mercury (version 3.9) (CCDC, Cambridge, UK) which is assumed to have a similar value of $0.1\ J/m^2$. E_1 is the Young's modulus of the DABOMD taken from the previously calculated average Young's modulus. E_2 is the scale-up modulus which is equal to $2.5 \times 10^8\ Pa$, a lower Young's modulus value taken practically to reduce the computational time [16]. D_1 is the original particle diameter which is equivalent to the D_{50} of non-milled DABOMD and D_2 is the scaled-up diameter.

3. Results and Discussion

3.1 Powder Characterisation of DABOMD

Particle Morphology

Representative SEM images of the non-milled and 300 min milled powders of DABOMD in planetary ball mill and single ball mill are shown in Figure 9 (See Figure S1 from supportive information for SEM from 1 min to 300min single ball-milled samples). The particles of DABOMD depict irregular sizes with agglomerated surfaces which tend to become smoother with milling similar to that of samples milled using planetary ball mill. Yet agglomerates are more prevailing in the single ball-milled samples due to significant amounts of fines adhering to the surfaces, particularly at longer milling times as observed in Figure 9c (See Figure S1for higher magnifications).

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Particle Size Distribution

The Particle size distribution (PSD), the cumulative distribution and the characteristic sizes of the non-milled and the milled powders of DABOMD using the planetary ball mill and single ball mill are shown in Figure 10a and b, Figure 11 and Table 6. It can be seen that the particle size distribution (PSD) profile of the single ball-milled in Figure 10b and planetary ball mill in Figure 10a [1] that the PSD profile changes from a broad trimodal to a monomodal profile in planetary ball mill and bimodal profile in the single ball mill. This implies that the two mills generate sufficient energy to cause a significant fracture to DABOMD. When comparing the characteristic sizes of the two mills (Table 6), it is evident that the single ball mill generates smaller particles in the first 30 min of milling as opposed to the planetary ball mill. The mechanism of milling in a single ball mill is suggested to be dominated by impact stress, whereas that in planetary ball mill occurs by impact and shear stresses. This indicates that the prevailing impact stress associated with single ball mill is an effective route for rapid particle fracture. However, milling over 30 min shows that the process of particle size reduction declines in the single ball mill, which indicates that the agglomeration is taking over. Agglomeration is less apparent in the planetary ball mill compared to the single ball mill (observed at 30 min, 60 min, 180 min and 300 min). This can be explained by the fact that progressive milling leads to the formation of fines (not shown due to the low resolution of dry system in detecting fines) which tend to adhere to the surfaces and form large particles with the aid of van der Walls forces. The greater energy dissipated in the planetary ball mill (probably from the aggressive shear stress) breaks the bonds of agglomerates and eventually leads to the formation of smaller particles (D_{90}). Thus, the planetary ball mill yields smaller particles with a longer milling time. This is seen for example, in the sample milled for 300 min in the single ball mill which depicts a larger size ($D_{90} = 48.2\ um$) compared to that milled with

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a planetary ball mill (D_{90} =35.3 um). Furthermore, it is evident that single ball mill has slightly

a higher impact on the fines as seen by the comparison of D_{10}.

Crystalline Properties of DABOMD

XRPD is used to determine the effect of milling on the crystalline properties of DABOMD (Figure 12). With progressive milling, the XRPD patterns change rapidly with both a reduction in intensity as well as broadening of the Bragg peaks which indicates a solid transition from crystalline to amorphous in the two mills. A distinction can be observed in the rate of crystalline disorder, where single ball-milled samples experience a slower rate of amorphisation. The sharp Braggs peaks characteristics for a crystalline are absent (a typical scattering pattern for amorphous) beyond 60 min of milling in planetary ball mill and beyond 120 min milling in the single ball mill. This suggested that the planetary ball mill caused a rapid amorphisation as opposed to the single ball mill, which further stresses that the planetary ball mill could generate more milling energy compared to the single ball mill.

Thermodynamic Properties

TGA and DSC techniques are employed to evaluate the effect of milling on the thermochemical properties of DABOMD (see Figure 13 and Figure 14). The TGA shows that two events of water loss (DABOMD exhibits four water molecules, two with stronger interactions, and the other two with weaker interactions) occurs in the single ball-milled samples which is similar to the planetary ball-milled samples. This was demonstrated to be as an underlying factor for the amorphisation of DABOMD as discussed in our previous paper [1]. The results displayed in Table 7 suggest that the single ball-milled samples have slightly less water loss compared to the planetary ball milled ones elucidating the difference reported in XRPD peaks. Similarly, the DSC results in Figure 14 shows the exothermic peaks at 109 ℃ and 173 ℃ (represent the weakly bonded waters and the strongly bonded waters respectively) and the endothermic peak at 197.8℃ (represents the decomposition) reduce in intensity and shift to a lower temperature consistent with loss of water and crystallinity in single ball milled sample. The slight difference is observed in higher intensity and stability within single ball-milled samples indicating lower amorphisation.

Intermolecular properties of DABOMD

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The phase transformation occurs as a result of a change in the molecular interactions manifested in the change in the FTIR peaks. It is evident that the samples milled using the single ball mill exhibit similar FTIR spectra as those milled with the planetary ball mill (see S2 a and S2 b in supporting information) with a significant change in the O-H region (3070-3660 cm^{-1} and 3130 cm^{-1}) which further stresses that single ball mill leads to the amorphisation of DABOMD driven by the process of dehydration. Slight variation in FTIR spectra (reported in Table 8) is analogous to the XRPD, TGA, and DSC outcome.

3.2. Kinetic of Comminution and Amorphisation in Single Ball Mill

Prolonged milling of DABOMD in the single ball mill (Figure 15) follows an exponential decay pattern for the change in D_{90} (for details please see [1]) similar to that seen with the planetary ball mill which reflects that the same mechanism is occurring in both mills following the same sequential events. The comminution process involves two phases; a rapid phase driven by the slip of planes ((100) system) which accounts for the majority of size reduction, and a slower steady-state phase which accounts for the remaining size reduction. Similarly, the change in the amorphous content of DABOMD (AAC, for details please see [1]), shown in Figure 16, involves two phases a rapid phase driven by the rapid water loss and plastic deformation and a slower phase driven by slower water loss [1].

In our previous paper [1] we discussed the details of a model fit for the kinetics of the comminution and amorphisation of DABOMD milled with a planetary ball mill and the single ball mill to identify parameters (α_{rpd_com} for comminution and α_{rpd_amp} for amorphisation) and time constants for rapid and slow comminution (τ_{rpd_com} and τ_{slw_com}, respectively) and amorphisation (τ_{rpd_amp} and α τ_{slw_amp}, respectively). From the results summarised in Table 9, the following points can be concluded:

1) Based on the model fitted to the comminution data from D_{90} of single ball-milled samples as shown in Figure 15, $\alpha_{rpd\_com} = 88\%$, $\tau_{rpd\_com} = 2.2\ min$ and $\tau_{slw\_com} = 25\ min$. This indicates that the comminution process is more rapid in the single ball mill and accounts for an additional 7% size reduction as opposed to the planetary ball-milled samples where, $\alpha_{rpd\_com} = 81\%$. This is postulated to be associated with the prevailing impact stress mode in the single ball mill which promotes particle fracture. Interestingly, the first and the second

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phases of comminution in the single ball-milled samples seem to occur at a faster rate compared to the planetary ball milled one where $\tau_{\text{rpd\_com}} = 3.6\ min$ and $\tau_{\text{slw\_com}} = 88.3\ min$.

2) The model fitted to the amorphisation data of single ball-milled samples (Figure 16, modelled) shows; a rapid amorphisation accounting for approximately 80% of the formed amorphous which occurs in the first few minutes as follows; $\tau_{rpd\_amp} = 5.9$ which indicates that amorphisation occurs at a slower rate in the single ball mill as opposed to the planetary ball mill (where, $\tau_{rpd\_amp} = 5.6$) which is associated with the larger energy available in the planetary ball mill that promotes amorphisation (including shear of planes, hydrogen bonds distortion and higher kinetics of water molecules). The second slower amorphisation phase in the single ball mill occurs at $\tau_{slw\_amp} = 100\ min$ which is slower compared to the planetary ball mill where, $\tau_{slw\_amp} = 52.3\ min$. This is postulated to the prevailing shear mode in the planetary ball mill which promotes rapid amorphisation through extensive shearing of planes and plastic deformation.

3) The model fitted to the water content data of single ball-milled samples (Figure 17,) shows that at $\tau_{rpd\_amp} = 6.3\ min$ (slightly longer than planetary ball mill), the $\%\ water$=12 as opposed to 15% water loss in the planetary ball. This further enhances the slightly lower rate of amorphisation observed in XRPD, DSC, TGA and FTIR data.

3.3. Quantification of the Milling Energy

3.3.1 Calculating the Energy in Planetary Ball Mill using an empirical method

The total energy calculated for the mill at different times is shown in Table 10, and Figure 18. It can be seen that the planetary ball mill provides a collision power of about 20.3 J/g.s. Hence the energy to mill DABOMD in 2 min is equal to 2.43 kJ/g which is in the range of the energy needed to mill cellulose for 2 min (6.29 kJ/g) in [11].

From Figure 18, it can be seen that approximately 93% of amorphous was formed at an energy input of 48.6 kJ/g which is about 20% of the total energy input to the system and, 97% of amorphous was generated at 60% of the total energy input to the system. This implies that a significant amount of energy is required to distort the remaining crystalline lattice. It also provides guidance on the most cost-effective route that can be followed to generate amorphous material.

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3.3.2 Calculating the Energy Transferred to the Single Ball Mill

The deduced impact energy from the high-speed camera measurements is equal to 0.028 J/g from which single ball mill power can be calculated as 1.68 J/g.s. The power is significantly less than that of PBM, but seems reasonable due to the lower mechanical energy produced from a single ball vibrating in the axial direction as opposed to four larger balls moving in the radial direction with additional centrifugal forces in the planetary ball mill.

3.3.3 Calculating the Compression Energy

The load versus displacement curve produced from the compression test is illustrated in Figure 19. The generated energy from the compression test can be calculated using the trapezoid rule of the area under the curve. The calculated energy is equal to 2.21 J, which is equivalent to 5.52 J/g (Table 10).

The derived energy of compression is analogous to milling for approximately 3.3s in the in a single ball and less than a second in PBM.

However, the XRPD analysis shows that the compression of DABOMD leads to a reduction in its crystallinity which is indicated by its lower peaks intensity as compared to the non-milled sample (Figure 20). The fact that that DABOMD experiences some degree of crystalline disorder with compression suggests that the slip of the plane (100) is sensitive to the compression stress.

3.3.4 Calculating the Energy in Planetary Ball Mill using DEM Simulation

DEM simulation of the planetary ball mill is shown in Figure 21. The total collision energy of the balls is shown in Figure 22. It is evident that the energy rises initially then drops after one second of simulation, this represents the increase in the kinetics of the ball as they are pushed hard at the start of milling then they stabilise shortly. However, the system has reached a steady state after 2s of simulation. The calculated impact energy normalised to the powder weight is shown in Table 10. The power of the mill obtained from DEM simulation is equal to 9.33 J/g.s which is less than that calculated using the collision model from the literature. This is presumably due to the assumptions that has been used in the collision model and lack of consideration of ball-ball and ball-wall friction which would lead to energy dissipation within the jar, while this is considered in the DEM model.

Snapshots from DEM simulation of the single ball mill at different times are shown in Figure 23. Figure 24 shows velocities of ball and jar at different times during vibration. Relative velocities of ball and jar can be observed in Figure 25. It can be seen after the start of vibration, the first collision occurs with the relatively stationary ball, then the ball accelerates within 6 ms and moves with nearly a constant velocity of about 1.99 m/s for almost 8 ms, where it collides with the jar moving with an opposite direction with the velocity of about 1.67 m/s. This results in a relative collision velocity of about 3.66 m/s, leading to a collision energy of about 0.072 J/g. This is significantly higher than the collision energy estimated from high speed camera recording of the jar as the ball impacts with a relative velocity to the moving jar in opposite direction. This pattern of collision repeats throughout vibration as can be observed from Figures 24 and 25 (here we show 0.2 seconds of vibration for the clarity purpose).

The calculated impact power of in SBM using DEM simulation is equal to 3.42 J/g.s (Table 10) which is higher (approx. 50% lower energy) than the calculated energy from the trajectory of the milling jar recorded by the high-speed camera (1.68 J/g.s) this was anticipated, as DEM simulation tracks the movement of ball as opposed to high speed tracks the movement of the milling jar. The milling jar and milling ball have different dynamics; where, the ball and powder could move with the opposite direction to the jar motion. This implies that a higher relative velocity of impact can be achieved than that estimated from the jar motion (see Figure 26).

In summary, a relationship can be established between the comminution and amorphisation of DABOMD, and the energy associated with these two processes during milling. The hypothesis was that the two mills generate different levels of energy; with the planetary ball anticipated to produce more substantial energy due to the multiple wall/media impacts and collisions compared to the single ball mill, which was supported by the experimental outcome. This work allows a straightforward quantitative comparison of the processes of comminution, amorphisation and the amount of energy generated with different mills as shown in Table 11 which can help to address the questions of what, when, and how much change occurs with milling. It is evident that a lower amount of energy is sufficient to induce a remarkable change in DABOMD, which is mainly associated with its material properties. For instance, DABOMD experienced a 20% size reduction and lost 30% of its crystallinity with a milling energy as little as 0.21 kJ/g in SBM. Higher energy transferred to the crystals from planetary ball mill leads to

a rapid phase transformation due to increased slip and shearing of planes and the generated heat caused by the prevailing stress, for instance, it can be seen that the planetary ball mill after 15 min yields 78 % amorphisation (at 8.4 kJ/g in PBM), while single ball mill results in 62.4% amorphisation (at 3.08 kJ/g in SBM). Nonetheless, the energy profile for the two mills remarkably follows a unified correlation in amorphisation which is evident from Figure 27. The plot in Figure 27, provides the correlation between the extend of amorphisation of DABOMD for given level of milling energy, regardless of mill type.

4. Conclusion

DABOMD was milled using a planetary and a single ball mill at 1 min to 300 min. In this work, special attention was paid to the comminution and amorphisation behaviour of DABOMD and the energy associated with these processes. It was found that the milling of DABOMD resulted in significant comminution and amorphisation with a slightly higher extent of comminution and amorphisation obtained with the planetary ball mill.

The energy levels involved within the planetary ball mill and the single ball mill were quantified using a collision model and jar motion analysis using a high-speed camera, respectively. It was found that the energy level generated within the planetary ball mill is higher than that of the single ball mill which agrees with the milling results in terms of rate of amorphisation. The energy quantification was also checked using DEM simulations which resulted in a lower value than that calculated for the planetary ball. In contrast, the energy obtained from DEM simulation for single ball mill is higher than that calculated from the jar motion analysis due to the fact that the jar and ball have different motion patterns and can collide with a relative velocity higher than the velocity of jar itself.

The compression test was also carried out which revealed that DABOMD experienced some degree of crystalline disorder at a low level of energy, equivalent to that generated within 3.3s in a single ball mill, which suggests that the slip of the plane (100) is also sensitive to the compression stress.

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This work provides a study of the comminution and amorphisation in ball mills which could help the development of mechanochemistry for pharmaceuticals. The implementation of this approach in the pharmaceutical industry could be useful for the optimisation and process control, which could eventually help to reduce the amount of time and costs associated with the empirical work required for each API.

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