Crystal Structure Transformation in Milling

Dr Jerry Heng, Chemical Engineering, Imperial College London

Milling of crystalline materials is a common top-down approach to achieve a desired particle size during industrial processing and development. It is well known that in doing so, a whole range of bulk and surface changes can occur in crystalline solids which can subsequently affect further processes. However, it should be noted that the degree of milling induced changes in crystal lattice is material specific and depends on several processing parameters. Moreover, the driving forces and mechanisms for the transformation of crystalline particles during and post milling are still poorly understood and difficult to predict. This project seeks to develop a scientific understanding of these complex transformation mechanisms and address the key gaps in the existing knowledge.

Overview into current state of art on milling induced transformation

The current state of research on milling of solids revolves around two main aspects namely, particle breakage and induced physicochemical transformation/s. Crystalline solids subjected to mechanical processing, like milling, are expected to generate structural disorder and deformed states. Although a size reduction operation, it can cause a wide range of secondary and sometimes unwanted physicochemical changes in particle properties, in particular, introduction of defects, amorphisation and polymorphic transformations. These changes ensuing bulk and/or surface of the solids. Some of these significant changes in crystalline solids are depicted in Fig. 1.

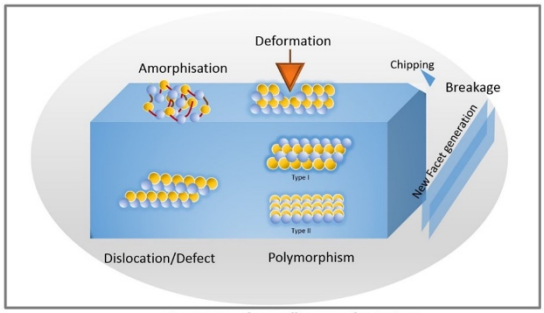

Fig. 1 Types of crystalline transformations

The most commonly observed adjunct change in milled crystalline materials is the occurrence of small degree of amorphisation, especially on the vicinity of the surface stress event [1,2]. Luisi et al. (2012), have also suggested that certain intermediate phases coexist in milled materials instead of two distinct crystalline and amorphous phases [3]. Another phenomenon which has intrigued researchers over the years is the milling prompted polymorphic transformation in the crystalline solids. Descamps and co-workers from their work have reported such polymorphic conversions in a wide variety of crystalline materials [4,5].

In addition, the mechanical stresses imparted could result in abrupt changes in surface textural and energetic properties of particles [6–11]. Often, milled material also has the most active surface, making it more interactive with other surfaces. Further insight provided on such milling induced surface evolution put forward a heterogeneous surface energy landscape that can affect interparticle interaction [12,13].

Although crystalline forms are preferred in industries due to the reasons of stability, it is in common knowledge that mechanical treatments such as milling could result in a stability problem by increasing the level of defects or disorder and phase transformations. Researchers have found that often the solid-state stability appears to correspond to the crystallinity or contrarily, to the extent of disorder in that material [14]. The mechanical treatment exposes the solids to a large variety of perturbations in the physicochemical properties and the associated thermodynamic vulnerability of the activated solids can result in the spontaneous recrystallization with time. Furthermore, altered interfacial interactions (adhesion/cohesion) in milled particles could result in problems like processing delays, increased cost and lower yield.Studies have also proposed that anhydrous forms of crystalline solids are more prone to amorphisation as compared to their hydrate forms [15]. Moreover, scientists have also reported alterations in the magnetic, electrical and electronic properties of inorganic materials like alloys due to high mechanical deformations induced from the milling treatment [16]. Besides, it has been reported that high mechanical stresses could also lead to release of bound water in some cases.

When it comes to the predictive approaches, the majority of research work in milling is focused around utilisation of energy input-size reduction relationship. As a result, early attempts have led to development of several empirical size reduction laws (Rittinger's, Kick's and Bond's law) correlating energy input with the particle size parameters. However, seldom these laws apply well in practical situations. From a molecular perspective, researchers have also tried to explore the

use of crystal inter-planar d-spacings and slip-plane interaction energies for predicting and characterising mechanical properties of crystalline solids [9]. Sun and Kiang (2008) proposed that precautions in the selection of appropriate force field must be taken while using attachment energy calculations for identifying the slip planes or cleavage planes in organic crystals on milling [17]. Heng et al. (2006), investigated the milling of paracetamol crystals and observed an increase in the dispersive component of surface energy upon milling. It was argued that upon milling, crystals fracture along the weakest attachment energy planes, which is known to be the most hydrophobic and have high a dispersive component of surface energy [18]. Moreover, the importance of crystal habit and crystal anisotropy in milling and breakage cannot be understated [19].

Overall, it is clear from the literature that not a lot of work has been done on understanding the milling induced changes from surface properties perspective of the milled crystalline solids. Also, there is a vast scope for understanding the localised deformation and the associated residual stresses in different milled crystalline solids from the material properties and processing conditions viewpoint. As far as process optimisation and prediction capabilities with regards to crystal structure transformation in milling are concerned, the present methodologies lack systematic understanding of the process as well as the materials involved. The intrinsic difficulty in predicting the complex nature of the properties of the resulting solids post-milling again lies in uncertainty and poor understanding of mechanisms creating the vast spectrum of crystalline disorders. Thus, it becomes imperative to develop an efficient integrated analysis framework for an in-depth understanding of the properties of disordered crystalline solids.

Current practices in advanced physicochemical characterisation of milled crystalline solids

To discern the milling promoted transformations in crystalline solids, several recent efforts have concentrated on developing methods to follow in situ bulk and surface alterations. Particularly, powder X-ray diffraction (PXRD) is the go-to analytical technique in most studies, when it comes to elucidating crystalline disorder [20]. Once the solid phase and structure identification is established, spectral methods like Fourier transform spectroscopy (FTIR), UV-Vis spectroscopy can be used for further examining the nature of crystalline disorder. Thermal methods also play a significant role in characterising the crystalline transformations and these include differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and hot stage microscopy (HSM). However, these techniques are not always adequate to quantify low levels of disorder or amorphous content and focused predominately on the bulk aspect of the crystalline material. Advanced techniques like solid-state NMR (ssNMR) has shown usefulness for quantitative amorphous characterisation of milled solids. Similarly, Raman spectroscopy, for quantifying the density of lattice defects and identifying the surface amorphous domains, is another potent tool to aid solid state characterisation.

On the other hand, for the characterisation of structural or physical properties, several microscopic and spectroscopic techniques are employed. Thus, imaging techniques like SEM, polarised light microscopy, TEM, usually coupled with other complimentary techniques, are used to elucidate the surface features and damage of milled crystalline materials. Single particle analysis tools such as Atomic Force Microscopy (AFM) are mostly employed for the study of defects in crystalline materials. The technique allows for very accurate studies, both in dry or wet conditions. Besides, optical scanning technique like profilometry can be used to image the surface texture of the milled and deformed surfaces. Likewise, to gain information on the mechanical properties of crystalline particles from their fracture mechanics and breakage behaviour, single particle impact loading tests using nano-indentation technique are frequently performed [21]. However, owing to the anisotropy in crystalline properties, due considerations should be given to the crystallographic structure and crystalline planes during analysis [22]. Another drawback of these analytical tools could be their inability to assess large amount of material, representative of the sample, often leading to bias.

Moreover, adsorption-based techniques, such as inverse gas chromatography (IGC) and dynamic vapour sorption (DVS), appear to have found the potential to provide quantitative data on the number of surface defects present in crystalline materials, along with the surface energies associated with them.

Engineering the analysis for crystalline transformations

Experimental and modelling works done previously have not decoupled the surface effects from the bulk body breakage properly. Moreover, organised study at different length scales and/or in different time domains (eg rates/kinetics vs equilibrium) is missing. Hence, before commencing a systematic investigation to establish facts and reach new conclusions on physico-chemical transformations of milled crystalline materials, it is imperative to break down the overall methodology to the following aspects.

1. Understanding the extent of crystalline transformations

In milling processes of crystalline solids, the disruption or transformation of crystalline structure often leads to varying degrees of disorder. From a practical viewpoint, the different levels of disorders could be classified as below.

- ***Minor disorder***: This disorder includes small perturbation of crystalline order like lattice defects and dislocations, including exposure of new crystalline facets. In one of our earlier works demonstrating the anisotropic properties of milled crystalline materials, Heng et al. (2006), reported that on milling of paracetamol, the dispersive component of surface energy increased with decreasing particle size and it was attributed to the surface energy of the weakest attachment energy plane exposed during milling.
- ***Major disorder***: This degree of disorder corresponds to a marked departure from the existing crystalline order, eg. phase transformation (polymorphism, hydrate formation and amorphisation) of materials. Moreover, it is important to state that both the above degree of disorders and the intermediate states can also occur simultaneously.

2. Decoupling surface and bulk changes

The ability to decouple contributions of surface vs bulk will be key in developing understanding of the respective transformations in milled crystalline solids. Reduction of particle size by milling cause increase in surface area and surface energy of particles, which consequently promotes adhesion of particles. In one of our recently reported works on powder cohesion, we decoupled the effects of milling on surface energy from surface area. Normalisation of surface energy of milled mefenamic acid crystals using silanisation approach was achieved to decouple the surface energy and surface area effects on powder bulk behaviour [23]approach was successful in decoupling the role of surface energy and surface area, other surface alterations like textural changes (roughness and deformation) as well as surface amorphous regions could be targeted. Likewise, the influence of transformational effects in particle shape, crystalline facets, surface chemistry (acid-base properties) could be elucidated.

3. Interplay between environment and multiple length-time scales in crystalline transformations

Milling can cause numerous changes in a crystalline solid, as mentioned previously, and the majority of these begin at the surface, which may later propagate to the bulk of the particle. The length scales and domains over which such order and disorder persist is also important. As it can be conceived, even in amorphous materials, a short-range order exists due to chemical constraints. Milling can thus induce disorder in the crystalline form but induce order in its amorphous form. Also, the surface chemical environment becomes important during milling.

Moreover, the external environment can either assist or resist the process related material transformation. Many of these transformations can result from an interaction of stresses in material and the environment. These effects can be physical, principally irreversible plastic deformation, or chemical such as phase change due to the adsorption of vapours in the disordered domains. In one of our previous works, we reported that milling temperature may affect the particle mechanical properties (elasticity/ brittleness) resulting in significantly higher surface area for cryogenic temperatures compared to room temperature milling conditions (Shah et al., 2015).

Certainly, in order to investigate the milling induced transformations in crystalline solids at different levels, comprehensive strategies to carefully control the disorder and employing suitable technique/s to probe milled solids is needed. Thus, designing the methods and selecting the conditions that create different degrees of disorder and/or in different domains as well as analysing them at this level is important.

Hypothesis and critical unknowns

The abrupt and complex nature of changes in milled solids pose a serious challenge in predicting the outcome from the operation. Thus, it becomes essential to develop a better framework for understanding the bulk and surface transformations in milled crystalline materials from molecular level perspective.

1. Generation of new surfaces

It is observed that milling results in the generation of new surfaces exposing different crystal facets varying in facet specific surface energy, defects, generation of high energy amorphous regions or a combination of any of these. As far as cleavage planes are concerned, it is often argued crystals fracture along weakest attachment energy planes, which are known to be the most hydrophobic. However, the importance of crystal habit and crystal anisotropy in milling and breakage also cannot be understated. ***Unknowns:*** Crystal slip planes, attachment energy predictions, influence of crystal habit, anisotropic mechanical and chemical properties of crystals.

2. Generation of metastable regions

The disorders created due to the mechanically intensive processes like milling provides the required space and energy for solid state transitions. For example, a small amount of amorphous content or surface cracks/defects in the crystalline solid is likely to be exacerbated through processes like milling. At the molecular level however, the mechanisms by which milling creates low levels of amorphicity remains unclear. Investigators believe that molecular level disorder generated during milling is the main source of free energy storage, considered as a driving force for phase transition to amorphous nature. Recently, researchers have also indicated that the milling prompted transition from crystalline to partial amorphous nature could occur through intermediate crystalline mesophases [24]. The presence of such metastable regions often prompts stability issues and pose a concern post milling operations. ***Unknowns*:** Critical material attributes, methods applied and extrinsic conditions that create localised disorder/s or damage. Sensitivity of tools and techniques to capture these alterations.

3. Non-equilibrium nature of materials/ Dynamic behaviour of processed materials

Milling induces an extensive disruption of the local arrangement of the molecules and different levels of energy are transferred to the particle in the impaction processes. These changes beginning at the surfaces, often in the form of lattice defects, then propagate or migrate to the bulk of the particle. The molecular level changes occurring are exhibited as a form of relaxation behaviour and thermodynamically speaking, the system fluctuates from moment to moment. Moreover, materials can transform or heal over a period post milling, sometimes aided by external environmental conditions. Such dynamic behaviour, in the form of disordering and reordering of materials over a period of time or due to extrinsic factors, involves complex mechanisms and pose a great challenge for the study and understanding of processed solids. ***Unknowns:*** How these materials evolve and transform? The rate of transformation or time dependent changes. Difficulty in predicting change, e.g., size, phase change etc.

Research Objectives: The overall research objectives of this project are i) to develop an integrated framework for identifying and characterising the nature of disorder in milled crystalline solids, ii) to gain a mechanistic understanding of the molecular level events initiating the transformations for predicting the outcome of milling operation and iii) to investigate the non-equilibrium/dynamic nature of processed materials.

Project Planning (Work packages)

WP1: Identification of materials

Selection of possible crystalline materials will be done following consultation with IFPRI members covering the industries of interest. The materials will be screened for different particulate attributes like crystalline habit or shape, size (particle or granule), chemistry (organic or inorganic), susceptibility for polymorphic transition and tensile properties (elasticity and plasticity) etc. The idea is to undertake comprehensive characterisation of the feed materials (pre-milling) in order to tease out the differences in these samples post-milling.

WP2: Processing of the selected materials

Keeping in mind the objectives of this work, considerable efforts will be invested in pre-processing or pre-treatment of crystalline materials. This preparative component of the work will include selection of specific feed material and impact mills like ball mill or fluid energy mill to introduce controlled disorders caused by the mechanical shocks of the collisional impact. The sample preparation process will be optimised by modulating different material and process parameters like particle size, shape, energy input and time of milling as well as through external processing conditions like temperature and humidity. Also, commonly known empirical models will be used to examine the performance of the operation and for generalizability of these findings to a range of conditions used in other mills.

WP3: Analysis of the type and extent of milling induced transformations

An extensive study on the complex nature of surface and sub-surface properties of the crystalline solids post milling operation is planned. In this multi-tier evaluation proposed (Fig.2), the first step would involve crystal structure determination using microscopy and diffraction techniques. Microscopy (optical and electron) will be used for crystal habit, size and surface texture investigation and PXRD for crystalline nature, degree of crystallinity, polymorph identification and stability analysis. Moreover, these techniques will thus provide the first hint about the type/s of crystalline disorder. The next step will involve understanding the nature of crystalline disorders like defects, polymorphic form, amorphisation, dehydration or hydrate formation. This will be done employing a combination of different spectroscopic techniques like IR, Raman and ssNMR alongside the thermal methods like DSC and TGA. For comprehensive elucidation, the third-tier of analysis (depicted in Fig. 2) will predominantly focus on surface properties and damage caused in milled crystalline solids, which will be covered under WP4.

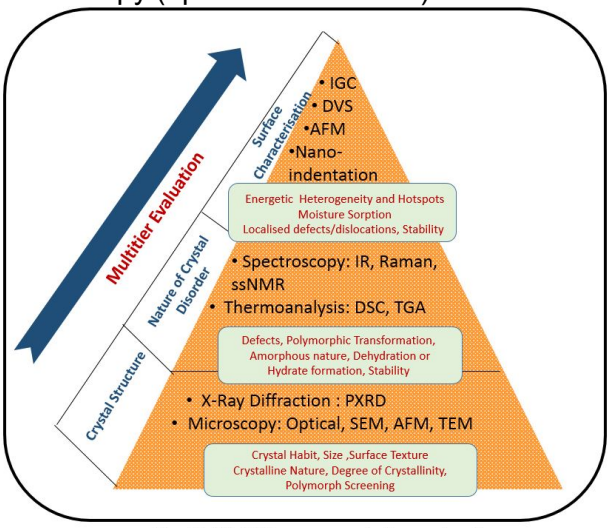

Fig. 2. Multitier approach for evaluation

WP4: Characterisation of mechanically induced surface changes

As mentioned earlier, this WP primarily focuses on the milling induced surface transformations in selected crystalline materials. In addition to the conventional analytical techniques several advanced probing tools will be employed to investigate the surface properties of milled solids.

- Surface energy evolution: Inverse Gas chromatography (IGC) to characterise energetic hotspots and heterogeneity of the damaged/disordered surfaces. These hotspots might be a consequence of crystalline disorders, like localised defects, phase change and surface stress. Finite dilution IGC (FDIGC) approach will provide the heterogeneity of the processed surfaces alongside the acid-base properties from the exposed chemical moieties which will be determined using polar probes. Measurements on milled samples with normalised surface energies, achieved through surface modification, will uncover the localised energetic domains generated.
- Surface amorphous regions: Dynamic Vapour Sorption (DVS), in combination with in-situ Raman spectroscopy and/or AFM morphological imaging, will be used to identify the surface amorphous domains. (Note: Both IGC and DVS tools will enable us to analyse the representative sample of the large population of particles produced after milling.)
- Facet specific studies: To study the deformation characteristics of crystalline material, nano-indentation experiments on different facets of single crystals will be performed. Similarly, these facets will also be probed for regions of localised density of defects or dislocations using AFM.

Some of the data generated and information gained in WP3 and WP4 will be incorporated in the subsequent WP's to facilitate design of experiments (DOE).

WP5: Investigating dynamic behaviour of thermodynamically activated solids

This work package will primarily focus on the time dependent evolution of milled materials with the influence of environmental conditions on its behaviour. The fresh surfaces of the milled solids will be exposed to varying moisture and temperature conditions to examine critical conditions for dynamic behaviour like spontaneous annealing or recrystallisation of the surfaces. To achieve dynamic measurements, multiple samples will be exposed to the pre-set conditions and analysis will be done at different time points in order to establish repeatability and accuracy of measurements. Investigations will be performed on multiple samples under both accelerated (ramped) and long-term (sustained) conditions. In addition to such continuous conditioning profiles, inspections under cyclic conditions of temperature and humidity are planned.

WP6: Studying influence of processing conditions

The milling experiments will be performed at ambient and cryo conditions, to compare the effect of processing temperatures on the nature of crystalline transformations. Additionally, experiments under humid conditions or in presence of other grinding media are also planned with selected crystalline materials. Subsequently, whenever relevant, studies with varying processing parameters like feed rate, mass of feed, milling time and milling speed will be covered.

Existing programs and infrastructure to leverage impact

The work packages are proposed for a dedicated PhD student in Years 1-3 with a second PhD student in Years 4-6 (see Appendix for Work Plan). This project will be leveraged with the following existing projects and PhD studentships at Imperial College London (ICL).

- EPSRC funded project (EP/N025261/1) *Virtual Formulation Laboratory (VFL)* for prediction and optimisation of manufacturability of advanced solids-based formulations. The project involves a dedicated post-doctoral research associate (PDRA) at Imperial College London and 4 additional PDRAs based at University of Leicester, University of Leeds and University of Greenwich.
- Two EPSRC iCASE Studentships with two pharmaceutical companies looking at the manufacturability of powders focusing on the powder surface properties related to the mixing and sticking of pharmaceutical solids.

Our laboratory at ICL has a well- established infrastructure and proven track record of research in the area of surface chemistry, particle engineering and interfacial phenomena. Research activities include studying the influence of particle engineering operations like milling, crystallisation on surface properties of solids, employ modelling tools for the predictions and control of these operations and the development of inverse gas chromatographic techniques to determine surface energy characteristics of powders.

References

1. Otte A, Zhang Y, Carvajal MT, Pinal R. CrystEngComm. 2012;14:2560–70.
2. Trasi NS, Boerrigter SXM, Byrn SR. Pharm Res. 2010;27:1377–89.
3. Luisi BS, Medek A, Liu Z, Mudunuri P, Moulton B. J Pharm Sci. 2012;101:1475–85.
4. Descamps M, Willart JF, Dudognon E, Caron V. J Pharm Sci. 2007;96:1398–407.
5. Gusseme A De, Neves C, Willart JF, Rameau A, Descamps M. J Pharm Sci. 2008;97:5000–12.
6. Guoxian L, Erde W, Zhongren W. J Mater Process Technol. 1995;51:122–30.
7. Ohta M, Buckton G. Int J Pharm. 2004;269:81–8.
8. Kwan CC, Ghadiri M, Papadopoulos DG, Bentham AC. Chem Eng Technol. 2003;26:185–90.
9. Shariare MH, Leusen FJJ, de Matas M, York P, Anwar J. Pharm Res. 2012; 29:319–31.
10. Shah U V, Wang Z, Olusanmi D, Narang AS, Hussain MA, et al. Int J Pharm. 2015;495:234–40.
11. Luner PE, Zhang Y, Abramov YA, Carvajal MT. Cryst Growth Des. 2012;12:5271–82.
12. Gamble JF, Leane M, Olusanmi D, Tobyn M, Supuk E, Khoo J, et al. Int J Pharm. 2012;422:238–44.
13. Thielmann F, Burnett DJ, Heng JYY. Drug Dev Ind Pharm. 2007;33:1240–53.
14. Otsuka M, Kaneniwa N. Int J Pharm. 1990;62:65–73.
15. Willart JF, Dujardin N, Dudognon E, Danède F, Descamps M. Carbohydr Res. 2010;345:1613–6.
16. Sánchez-Alarcos V, Recarte V, Pérez-Landazábal JI, et al.J Alloys Compd. 2016;689:983–91.
17. Sun CC, Kiang YH.J Pharm Sci. 2008;97:3456–61.
18. Heng JYY, Thielmann F, Williams DR. Pharm Res. 2006;23:1918–27.
19. Ho R, Naderi M, Heng JYY, Williams DR, Thielmann F, Bouza P, et al. Pharm Res. 2012;29:2806–16.
20. Bates S, Zografi G, Engers D, M, et al. Pharm Res. 2006;23:2333–49.
21. Taylor, L.J., Papadopoulos, D.G., Dunn, P.J., et al. 2004. Org. Process Res. Dev. 8, 674–679.
22. Olusanmi D, Roberts KJ, Ghadiri M, Ding Y.Int J Pharm. 2011;411:49–63.
23. Shah U V, Olusanmi D, Narang AS, Hussain MA, Tobyn MJ, Hinder SJ, et al. Pharm Res. 2014;32:1–12.
24. Shalaev E, Wu K, Shamblin S, Krzyzaniak JF, Descamps M. Adv Drug Deliv Rev. 2016;100:194–211.

Proposed Workplan