IFPRI Research Project "Crystal Structure Transformation in Milling"

Project presented by the MMT team of the University of Lille (France)
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Milling is mainly used to reduce the size of solid particles. However it is also able to modify the properties of materials. Upon milling, compounds (crystal or amorphous) can transform polymorphically to other crystal phases or amorphize. Sometimes a milled compound does not show a perceptible phase transformation. But the modification of its microstructural characters can be at the origin of later unexpected phase transformations.

The investigation of the effects of milling is a major part of the research activity of our team since the 2000s. Our research area is focused on the physical state of molecular materials composed of "small" molecules and/or of biological molecules. We are particularly involved in the investigation of their physical changes under various stresses: temperature, pressure, milling, dehydration. The main goal is to analyse the situations of metastabilities, the glassy states and the phase transformations and out-of-equilibrium evolutions induced by these stresses. As physicists we are interested in understanding the fundamental mechanisms that are at play in these transformations. Our investigations concern both structural modifications and modifications of molecular mobility, as well as thermodynamic impacts. We conduct these investigations from an experimental point of view. To do this the team has a wide range of experimental techniques covering all these analytical aspects.

It has emerged quite recently that process-induced changes of states play a key role in the formulation of pharmaceuticals and food materials, as well as in the field of cosmetics or molecular materials for energy and electronics. For our studies we have therefore chosen to select model compounds, with representative properties, in the vast array of molecular compounds that may have applications in these fields. Our works have direct implication in the control of the formulation and the stability of these materials with direct consequences, in pharmacy for example, on their bioavailability. Our research in this field is carried out in close collaboration with major companies of pharmacy and agribusiness. They are also integrated into European projects, for which we are responsible, bringing together the activities of companies and large academic laboratories in various European countries.

Our research, on the specific field of milling, has resulted in about 70 publications and 10 PhD theses. We have mainly investigated molecular solids which have several important advantages: They are generally easy to amorphize, their glass transition temperatures are close to room temperature they have a rich polymorphism and are very sensitive to milling effects. They show a particular sensitivity to changes in milling intensity and milling temperature. The latter are very easy to control since they are located in the vicinity of room temperature. Molecular compounds are thus good model system to study the different facets of milling induced transformations in general. We have gained good practice in their response to milling stresses with respect to both amorphization and polymorphic changes. This experience is the basis of the project that we present below.

Administrative situation

The MMT team (Molecular and Therapeutic Materials: 12 permanent researchers, 3 engineers, 6 PhD students presently) is one of the 6 teams of the UMET laboratory of Lille university (France) (UMET: Materials and Transformations Unit: 80 permanent researchers, 40 engineers, 60 PhD students)). UMET is associated to the French national research centre (CNRS).The project will be carried out under the responsibilities of Dr. Jean-François Willart and Pr. Marc Descamps. 2 PhD students will be allocated to the project.

Web page: http://umet.univ-lille1.fr/MMT/index.php?&lang=en

Available Analytical Equipments

In the team: 2 powder X-ray diffractometers. 8 DSC and modulated DSC. 2 TGA. 2 microcalorimeters, 1 Broadband thermodielectric spectrometer, 2 Raman spectrometers (T and P variable. Micro Raman). Solution calorimetry. Thermomicroscopy. Specific equipments to control aging.

+ access to all facilities of the laboratory: TEM, MEB, NMR (solid and liquid), Infra red, Mass spectrometer etc...

The team frequently uses synchrotron and neutron facilities ILL, ESRF, Soleil...

Amorphization/milling relationship

Main problems to solve

Amorphous or defective crystal? Milling a compound can cause its amorphization. There are situations where this is indisputable because of the presence of a glass transition. But it is often difficult to distinguish a true amorphous state from a highly defective crystalline state. This sometimes leads to denying the possibility of amorphizing a compound by milling. It is essential to define analysis strategies to resolve without ambiguity between these two situations.

Nature of the amorphous state: Unlike a polymorphic crystalline variety which is a stable or metastable equilibrium state, a solid amorphous compound, i.e. glassy, is in a state of non-equilibrium which depends on the history of the sample (conditions of preparation, aging etc). Because of this variability of the amorphous state and even the possibility of a polyamorphism, it is essential to find the means to determine the effect of the amorphization by milling on the physical properties of the amorphous end product, in particular its reactivity and its potential for further evolution. It is the same for the modifications induced by milling of an initially amorphous compound. An important point to resolve is to characterize and possibly distinguish the amorphous states (polyamorphism?) resulting from the quenching of a liquid, the application of a high hydrostatic pressure and from milling.

Mechanism of amorphization: The milling causes a modification of the grain sizes, but the process of transformation from crystalline to amorphous state happens inside the grain. The understanding of the amorphization mechanism requires simultaneous investigation of changes in the grain both of its microstructure and on the structural evolutions of ordered and disordered domains that constitute it. One issue is thus the question of whether amorphization is a two-phase process where the amorphous state coexists with a crystalline state residue. The amorphization would then result from an evolution of the proportion of these two phases. The other image would be that of a progressive bulk disorganization of the crystalline state.

Milling characteristics allowing amorphization. The possibility of amorphizing a compound and the kinetics of amorphization depend on the milling conditions and the physical properties of the milled compound. There is a wide variety of possible milling equipments. However, the main relevant parameters are the characteristics of the environment of the sample (temperature, humidity, etc.) and an accurately defined milling intensity. Systematic investigation of theses effects on the nature of the final state are scarce. Our past investigations have shown us that competition between mechanically induced ballistic diffusion effects (athermal) and thermal restoration effects play antagonistic roles. Their competition is undoubtedly paramount in the determination of the final state and the kinetics of the transformation. We have observed therefore that the value of the milling temperature with respect to the glass transition temperature (Tg) is crucial in many cases. We could show that a decrease of the milling temperature yields a higher content of amorphous material, while milling above the Tg favours crystal-to-crystal polymorphic transformations. However, certain compounds can not be amorphized using milling conditions for which amorphization could be expected. It is therefore appropriate to broaden the investigation by integrating these compounds in the cohort of investigated compounds and considering additional effects such as that of elastic constants and nucleation rates. This would help to permit isolation of the disordering phenomenon from its kinetic counterparts.

Some practical details

The Issues briefly underlined above are intimately mixed. To try to solve problems we propose to carry out, on representative compounds, X-ray diffraction structural analyzes, spectroscopic analyzes giving information on the molecular mobility, and calorimetric analyzes giving access to the glass transition and thermodynamic equilibrium level of the phases. If it is useful, additional microscopic analyzes, by SEM and TEM will be done.

The amorphization mechanism will be investigated using both *ex situ* and *in situ*, the latter possibility has been recently developed and uses synchrotron X-ray powder diffraction (at ILL in Grenoble and SOLEIL in Orsay). Diffraction patterns, collected in real time during the milling operation will be analyzed by sequential PDF (pair distribution function) and Rietveld refinements. This allows a simultaneous view of the development of the SRO specific to the amorphous part and to extract crystalline coherent domains attributes (including size as well as stress / strain broadening)

Spectroscopic analyzes will be mainly carried out by dielectric relaxation and Raman scattering. Investigation of the evolution of the relaxations as a function of temperature both above and below the glass transition temperature allows comparing the fragility level of glasses obtained in different ways. It

also allows identifying secondary relaxations which reveal the amorphous character when a calorimetric glass transition is not detected. The ability of dielectric relaxation to detect very low amorphous quantities (resulting from jet- milling process in particular) will be tested.

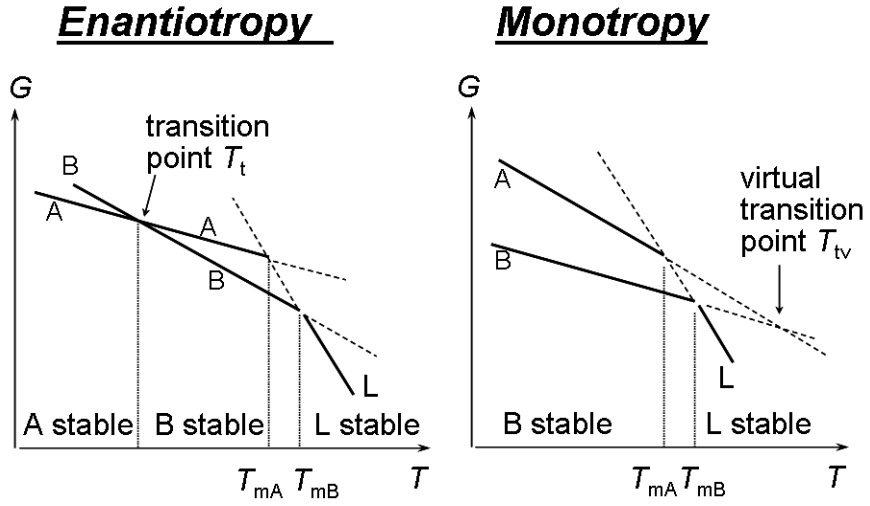
It is possible to follow, by in situ Raman scattering, the effects of the application of a high hydrostatic pressure on a crystal. This will allow comparing the amorphization conditions and the amorphous states (polyamorphism?) that result from the application of a high hydrostatic pressure to those resulting from the application of a shearing during milling.

Calorimetry will be used first to analyze the neighborhood of the glass transition. A fine analysis of the shape of the thermograms provides a great deal of information on the nature of the glass itself. This will determine whether the glass transition (Tg) has similarities to that of a conventionally formed glass. For T <Tg, the presence of an exotherm and a sub-Tg peak reveal the effective formation rate of the amorphized compound whereas an overshoot at Tg is indicative of aging. It gives access to the fictive temperature. This technique will be particularly useful for identifying the potential reactivity level of the amorphous parts and will provide indications on the possibility of manipulating the glassy state by mechanical activation.

Polymorphism/milling relationship

Crystalline polymorphism is the ability for a compound to crystallize in several different forms: same molecule but different crystalline lattices. It may exist intrinsically disordered crystalline polymorphic varieties (such as so called "plastic crystals" or "orientationally disordered crystals". cyclohexane, ethanol or hexagonal ice are examples). But they can always be described by a lattice with long range translational order (LRO), contrary to glasses.

There are two different types of polymorphic behaviors namely monotropic and enantiotropic.



Gibbs free energy as a function of Temperature showing the stability relation between two polymorphs and the liquid phase (L): Enantiotropy (left), Monotropy (right)
Monotropy: One polymorph (B) is stable at all temperatures below the melting point, with other polymorph (A) being metastable. No reversible phase transition between the two forms. Only A --> B can be observed.
Enantiotropy: One polymorph is stable over a temperature range, the other is stable over a different temperature range. Reversible phase transition at T_t

The enantiotropic phase transition at T_t can be a first order transition (with latent heat as in the figure, much more frequent in practice) or second order one (no latent heat, no break in the G(T) diagram, singularity of the specific heat).

To be exhaustive the investigation of the link between milling and polymorphism should consider situations of monotropism and enantiotropism.

Main problems to solve

A number of questions are quite similar to those for amorphization. In addition there are situations where the effects are nested. Amorphization and polymorphic transitions between crystalline varieties could be studied profitably on the same compound when possible.

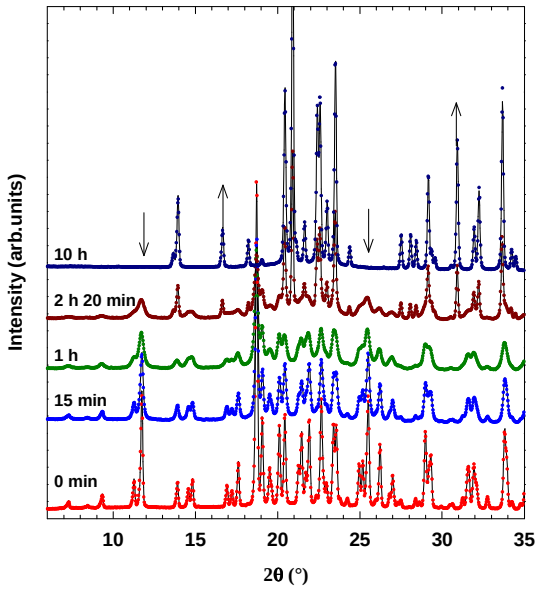
Direction of the transformation: The literature and our own experience show that milling can induce transformations from a stable state to a metastable state. But the opposite situation is also encountered. It is therefore advisable to carry out, on suitably chosen compounds, a systematic investigation of the influence of the milling variables and of the temperature in order to determine if a reversal of behavior can be obtained at some particular value of the milling variables. The role of the

structural proximity of the phases, and their relative densities, should be taken into account. In the case of an enantiotropic situation, the position of the milling temperature with respect to the transition temperature should be considered if this is practically possible.

Influence of the initial state. Uniqueness of the end product? : In the case where a compound has polymorphism and if the different phases can be prepared at the same temperature, it should be determined whether their transformation by milling produces a final state whose nature (single phase or phase mixture) depends only on milling conditions. This study should be expanded to include the glassy state as a starting or finishing variety.

Polymorphic transition or amorphization? : As an extension of the previous question, it would be useful to identify systematic and clear rules concerning the milling variables making it possible to generate phases - or phase mixtures - of different degrees of stability (or/and density).

Crystal to crystal transition mechanism: The transitions between two crystalline forms of the same compound generally involve a drastic change in the crystal lattice (1st order phase transition). In the (very frequent) case of monotropism one can not envisage, by the usual thermal way, transformation of the stable form towards the metastable form. On the other hand, milling very often makes it possible to induce this transition from stable to metastable (example of sorbitol, see figure below). The mechanism of this type of transformation is not understood in detail.



X-Ray diffraction:
Transformation of **sorbitol** during milling from the stable form (red) to the metastable form (Dark blue): the weakening of the Bragg peaks of the stable form is observed, followed by the appearance of the peaks of the metastable form. It may be noted that under milling the crystalline quality of the metastable form improves in the late stage.

The mechanism is not understood.

In a certain number of kinetically favorable cases we have been able to detect the transient development of an amorphous state. It can then be suspected that the transition from the stable crystalline state to the metastable state is mediated by the transient appearance of this amorphous state followed by the recrystallization of the metastable form.

In many cases, as for sorbitol (figure above), such a transient amorphous state is not detectable experimentally under the usual grinding conditions. The question of the mechanism of transformation is therefore totally open:

Two options are a priori possible:

1) *An amorphization* followed by a recrystallization; and, in this case, why recrystallization of a metastable phase? The life time of the amorphous state would become so short that it can not be detected in practice for certain systems and grinding conditions.

2) *A more direct transformation* by which a slip system is activated by shear and provide unit cell distorsions which facilitate the molecular rearrangement and accomplish the interconversion until a stationnary state is reached.

It is also questionable to determine whether the monotropic or enantiotropic nature of the polymorphism, which has a thermodynamic meaning, also has an influence with respect to the transformations induced by grinding.

As for the mecanism of amorphization, an other issue is to determine if the transformation is a two-phase process or results from a progressive bulk disorganization/reorganization of the crystalline state.

Some practical details

The investigation techniques of the polymorphic transitions are largely similar to those specific to amorphization and have been specified above. Moreover, it is clear that an amorphization mechanism can play a transient role in a crystal-to-crystal polymorphic transformation. An amorphization may also compete with a polymorphic transition for some milling conditions.
The first techniques of choice to be used immediately in order to characterize milled samples will be X-ray thermo-diffraction, calorimetry and thermo-Raman scattering. These techniques are available in quantity and quality in the laboratory, and in close proximity to grinding equipments. This allows for parallel investigations without delay. This is an important aspect because of the potential instability of the samples after milling.
X-ray diffraction obviously has a very important role to play in the analysis of structural transformations between crystalline varieties. Investigations will focus on microstructural evolutions by Rietveld refinement of Bragg diffraction lines. This should help to identify the particular roles played by decreases in crystallite sizes at nanoscale and lattice strain increases. It will also be necessary to carry out a meticulous comparison of crystalline structures of the different phases. This should make it possible to determine whether the two forms involved in the transition have a common slip system associated with weak values of the cohesive strength of some crystallographic planes. New in situ monitoring techniques (Simultaneous milling and Synchrotron X-ray diffraction) are expected to improve the perception of transformations and in particular to identify a possible role of an amorphous state or other intermediate crystalline phases.
In general, the possibility of changing the grinding temperature will be very useful to modify the possible lifetimes of intermediate states and increase the possibilities of identifying them. Molecular compounds that are very sensitive to near-ambient temperature variations are particularly interesting from this point of view. The comparison of milling effects for which the shears play an important role to hydrostatic pressure effects that contain no shear components can be followed in detail by Raman scattering because our equipment allows following hydrostatic pressure response up to more of 5GPa.

Kinetics of transformations. After-effects

Kinetics: During milling, the mechanical action is a discontinuous and localized process. A small fraction of the powder is actually processed at each impact. The overall kinetics of a transformation under milling is therefore very dependent on this effect. We have observed that, under milling, amorphization kinetics often have very different behaviors from polymorphic transformation kinetics. We plan to gain a better understanding of this phenomenon, which should help to better understand and control the mechanisms at stake and also to provide predictive tools.

After-effects: Limited millings that do not induce perceptible phase conversions can however have a significant impact on subsequent transformations, especially during heating. For example, a slight grinding of a glass can lead to changes in the nature of the phases which recrystallize. A slight milling of a crystalline phase can induce new kind of phase transformations under heating. Milling thus provides an additional possibility of exploration of physical states that may be useful for screening of polymorphs and their relative stabilities. This effect will be studied during the project.

Milling methods

It is possible to change the impact/shear ratio by changing the type of the instrument or by varying the milling parameters using the same mill (frequency of vibration, rotation rate of the disc, rotation rate of the vial holder etc.). Three mill types with different impact/shear ratios will be used: a Single ball vibration Mill operating at different temperatures, an air Jet Mill, and several Planetary Ball Mills which provide a sizeable shearing contribution. Particular care will be taken to vary and control the surrounding temperature of the mills and the atmosphere inside the milling jars. We will use the possibility of placing the milling instruments in a humidity-controlled cold room where it is also possible to prepare the conditioning of the milled compounds for subsequent analyzes.
Very powerful *in situ* high energy synchrotron powder diffraction during milling is available recently. This new technology should provide very important additional opportunities in the understanding of solid-state processes under milling. We have gained a good experience of this new method for studying both amorphization and transition between crystalline phases. We plan to use it for this project. While powerful, this technology remains underdeveloped. It will be necessary, on the one hand, to contribute to improving the design of containers (X-ray transparent, mechanically durable and thin enough) and, on the other hand, to evaluate the available milling intensities.

It would be interesting to test the response of compounds to millings made in industry (Jet milling in particular) with the help of IFPRI participants.

Compounds to study

To ensure the broadest and most comprehensive investigation, systems will be selected to represent the widest range of responses to milling. As a result of our previous works, we will be able to optimize the choice of representative compounds. In particular it will be taken into account the Tg value of their amorphous form and their ability to develop well-identified surface and volume amorphizations. Carbohydrates, several mono and disaccharides (glucose, trehalose, lactose...) and a lot of pharmaceutical active compounds (indomethacine, carbamazepine, griseofulvine ...) will offer a variety of interesting systems. Saccharides that give hydrates will specifically allow analyzing the effect of moisture content on the amorphization capabilities. Difficult to amorphize compounds will be added to the cohort to clarify the role of elastic constants (e.g. hexamethylenetetramine) or nucleation rate (e.g., caffeine). Polyols (sorbitol, mannitol, arabitol...) have a rich polymorphism and they have glass transition temperatures (Tg) fairly close to room temperature which makes it easy to test the sensitivity of the compounds to the milling temperatures. Caffeine and Chlopropamide will be specifically studied because of their ability to present an enantiotropic phase transition in the solid state.
It will be also possible to consider the study of interesting compounds proposed by members of IFPRI

Brief summary of objectives

- One aim is to clearly define the relative influence of the ballistic (athermal) effects related to mechanical actions on the one hand and the effects of thermal restoration on the other hand for the different types of transformations induced by milling.
- A second aim is to clarify the role of shears and hydrostatic pressure on phase transformations, amorphization capacity and nature of the amorphous state.
- The final goal is to be able to draw a phase diagram which integrates these types of parameters and has a predictive ability.

Many theories compete to describe the physical transformations under milling using arguments founded on thermal equilibrium considerations. They are based on the expression of a "constrained free energy" where the internal energy would be increased by the contribution of stored defects or by the increased effect of surface free energy when nanosizes are reached. However these theories have a lot of shortcomings because transformations under milling do not occur at thermodynamic equilibrium. The proposed experimental study is guided by the fact that it can ultimately help to build a more realistic theoretical approach.

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