molecular pharmaceutics

Solid State Amorphization of Pharmaceuticals

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Abstract: Amorphous solids are conventionally formed by supercooling liquids or by concentrating noncrystallizing solutes (spray-drying and freeze-drying). However, a lot of pharmaceutical processes may also directly convert compounds from crystal to noncrystal which may have desired or undesired consequences for their stability. The purpose of this short review paper is (i) to illustrate the possibility to amorphize one compound by several different routes (supercooling, dehydration of hydrate, milling, annealing of metastable crystalline forms), (ii) to examine factors that favor crystal to glass rather than crystal to crystal transformations, (iii) to discuss the role of possible amorphous intermediates in solid−solid conversions induced by milling, (iv) to address the issue of chemical stability in the course of solid state amorphization, (v) to discuss the nature of the amorphous state obtained by the nonconventional routes, (vi) to show the effect of milling conditions on glasses properties, and (vii) to attempt to rationalize the observed transformations using the concepts of effective temperature introduced in nonequilibrium physics.

Keywords: Disordered solids; glasses; thermal properties of amorphous solids and glasses; machining; milling

1. Introduction: Conventional and Less Conventional Routes of Amorphization

Glasses are classically prepared by the rapid cooling of the melt, bypassing crystallization. Below the melting temperature the liquid becomes metastable. This is due to the existence of a thermodynamic barrier which controls the nucleation of supercritical clusters of the stable crystalline phase. The possibility to get a glass strongly depends on the persistence of the metastable liquid state in the quenching process.[1−4] This is schematically illustrated in Figure 1a, which shows the time taken for a given amount of crystalline phase to emerge as a function of temperature. The main feature of this time−temperature transformation (TTT) diagram is that the crystallization rate reaches a maximum at a given "nose" temperature T_n. This nose results from the competition between the thermodynamic driving force for the transformation, which increases with decreasing temperature, and the molecular mobility. For molecular glass formers the latter usually follows in temperature an even more rapid slowing down than that for Arrhenius evolution (the so-called super-Arrhenius behavior of fragile glass

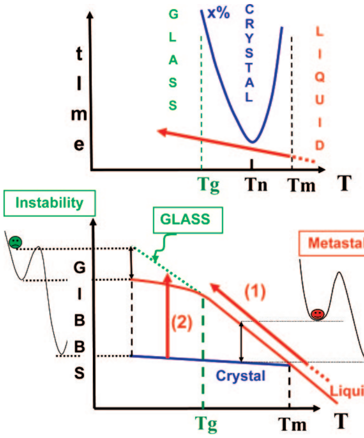

Figure 1. (a, left) Schematic TTT diagram for crystallization in an undercooled melt and conventional vitrification path. (b) Gibbs free enthalpy curve for crystal, liquid (stable and metastable) and glass. Paths 1 and 2 correspond to conventional and solid state vitrification paths respectively.

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formers[5−7]). During this conventional vitrification process the optimum quenching rate which eventually leads the metastable liquid to enter the glassy state is fixed by the necessity to quickly pass the nose of most rapid crystallization. At the temperature position of this nose we would expect an exotherm of recrystallization in the course of a DSC cooling scan performed at a too low rate. At the glass transition temperature (T_g)—which is revealed by a heat capacity drop in a DSC scan—the liquid falls out of equilibrium. The disordered molecular configuration of the liquid state is frozen-in or largely so. Atoms in the glass vibrate about the now frozen positions. T_g does not mark a transition in the thermodynamic meaning. In particular T_g is not associated with any structural signature detectable in X-ray scattering patterns. Passing T_g, only a slight change can be observed in the rate of the temperature evolution of the X-ray diffusion pattern of amorphous materials. It is more a "cross-over" temperature below which the typical time for equilibration of the liquid—of its enthalpy, its volume...—becomes longer than our experimental time. The position of T_g depends on the intrinsic time scale of the measurement. For a DSC scan performed at 10 °C/min, this time is of 10^2-10^3 s. $T_g$thus depends slightly on the scan rate of the measurement. It is a kinetic indicator for the change of the liquid from an ergodic state at high temperature to a non equilibrium state below T_g.

During its formation, the glassy material is trapped in a local minimum of the potential energy landscape whose topology characterizes the amorphous system. Its physical state may strongly vary with the history of the sample: preparation process and aging. When using the conventional thermal quench of the liquid to prepare a glass, the energy level where the end product is trapped depends on the cooling rate itself. Upon further aging, the measured enthalpy of the system relaxes. Annealing below T_g or changing the cooling rate modify relaxation times in glass and have a strong impact on its stabilization properties.

The previous description of the glass formation allows to emphasize the sharp "viscous slowing down" leading to the universal $\eta \approx 10^{13}$ P value measured at the calorimetric T_g. Below T_g the compound has the rigidity of a solid and the structure of a liquid without any long-range crystallographic order. From the point of view of the physical stability, the situations of the crystal, liquid (stable and undercooled), and glass state of a compound are displayed in the Gibbs energy diagram of Figure 1b. Conventional glass formation corresponds to path (1). Between T_m and T_g the undercooled liquid is really in a metastable equilibrium with respect to the crystal. Below T_g, there is no defined state function characterizing the glass which is unstable. Operationally it is possible to calculate a value for $G = H - TS$ (H, enthalpy; S, entropy) in the glassy state, using the measured values of $C_p(T)$. However the latter is history dependent. Strictly speaking the values of $G(T)$ thus obtained (dotted line in Figure 1b) cannot be used as a really defined thermodynamic state function: to evaluate "solubility" for example. Relations used to compare dissolution capabilities of different polymorphic varieties of a solid were however extended to compare "solubilities" of glasses and crystals.[8] Such a relation shows that, in usual conditions, a glassy form being of higher G value is more soluble than any crystalline form of the same compound at the same temperature. Solids may thus be either crystalline or glassy with, in this latter case, desired (more soluble) or undesired (less stable) consequences on the properties of the compound[9] (i.e., reactivity,[10] solubility, hygroscopicity or mechanical properties[11]).

It is known that a lot of industrial processes which do not impose quench cooling to a compound may however lead to a noncrystalline solid state. That may for example result from fast desolvatation as is employed in spray-drying techniques. For practical formulation reasons, the pharmaceutical industry has frequent recourse to milling operations in order to reduce the size of the particles. Milling is also used for more specific applications such as preparation of cocrystals[12,13] or to produce enhanced surface properties by comilling active pharmaceutical ingredients with silicates for

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example.[14] These millings can however induce changes of the physical state of the product which may have harmful consequences for their stability: a partial amorphization is often detected which is a factor of subsequent instability of the drug. Pharmaceutical literature describes numerous examples of organic compounds like piroxicam,[15] budesonide,[16] sucrose,[17,18] lactose,[19,20] trehalose,[21] and so on which become partially or totally amorphous when they are submitted to mechanical treatments. Solid state amorphization will be the main topic addressed in this paper. In nonliquid related preparation techniques, the trajectory followed by the system in the Gibbs representation is depicted by the path (2) in Figure 1b. Many researchers hesitate—even refuse—to apply the term "glassy" to noncrystalline solids whose origin is not the liquid state. Of course we may fear confusion between an assembly of more or less defective nanocrystals and a true amorphous solid similar to that obtained by cooling of the liquid. Considering the definitions of the glassy state and "glass transition" given above it seems natural to admit that we are facing a total or partial conversion to glassy solid if the two following points are satisfied: evidence of an amorphous X-ray pattern and, upon heating, presence of a calorimetric glass transition with a T_g close to that of the corresponding liquid. Since a glass is a frozen-in liquid state, the question is in fact simply to detect if one has a progressive "super-Arrhenius" unjamming of the molecular mobility rather than a melting of nanocrystals. Evidently, the solid state route to prepare the glass may give rise to an effective trapping in very specific zones of the landscape, perhaps not accessible to glasses conventionally prepared with usual cooling rates. This may lead to unusual fictive temperatures, with their corresponding signatures around the C_p jump at T_g. The pharmaceutical literature reveals that milling crystals may just as well induce amorphization or transformations to other crystal polymorphs. We will briefly present some published results of milling experiments carried out on pharmaceutical compounds. These results reveal some interesting tendencies in the way molecular compounds transform.

The first example is the investigation of the effect of milling on the two polymorphic varieties of sulfamerazine by Grant et al.[22] It has been shown that milling the metastable form II only produces an intensity decrease and a broadening of the X-ray diffraction Bragg lines without any indication of a change of the crystalline structure. On the contrary, form I of sulfamerazine is completely converted into the metastable form II in two hours of milling. Form II thus appears to be the result of milling whatever the initial crystalline state product with no apparent sign of amorphization. Partial investigations carried out on the pharmaceutical compound indomethacin bring further information about the behavior under milling which also demonstrates the identity of the end product irrespective of the starting state but depending only on the milling conditions. Otsuka et al.[23] carried out milling experiments with the polymorphic forms γ (stable) and α (metastable) of indomethacin at 30 and 4 °C (i.e., close to the glass transition, which is $T_g \approx 42$ °C). At 30 °C milling each of the two forms leads in less than 10 h to a mixed state composed of approximately 50% of amorphous state and 50% of α phase. At 4 °C milling each of the two forms leads within 2 to 4 h to a completely amorphous final state in both cases. Milling experiments realized at nitrogen temperature by Crowley and Zographi[24] lead in less than twenty minutes to an amorphous state independently of the starting crystalline state. It should be noted that the amorphous states obtained in all the cases are really glassy states—homogeneous at the molecular level and not only nanocrystalline—since a calorimetric glass transition is detected upon a DSC heating experiment. It is also interesting to notice that the glass transition temperature ($T_g \sim 42$ °C) is located slightly above the ambient temperature so that the milling operations were carried out below T_g. The formation of disordered states is thus favored by milling at lower temperature. It must be noted that any of these observations seems to contradict the proposal frequently put forward that the amorphization induced by milling results simply from a succession of real local melting due to hot spots generated by the mechanical shocks. Moreover this latter approach is unable to predict the occurrence of crystal to crystal

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transitions. On the other side approaches only appealing to the concept of induced disorder are no more able to predict the whole pattern of behaviors briefly evoked above.[25] A recent study of the factors influencing the complexation of ursodeoxycholic acid with phenanthrene or with anthrone has clearly revealed the influence of the temperature of grinding.[26] The results indicate that complexation is only possible above some grinding temperature while milling at temperature much lower than room temperature prevent the complexation process and results in the amorphization of the ursodeoxycholic acid.

It is difficult to explain the crystal−crystal polymorphic transition observed when milling the γ form of indomethacine at the highest temperature since polymorphs form a monotropic set. It is thus not possible to "explain" the conversion induced by milling by the argument that milling brings the compound to a temperature higher than that of an equilibrium transition. For all similar cases it is thus highly questionable if a transient stage of amorphization could mediate between polymorphs. This issue is also found in the case of crystal−crystal conversions induced by milling to produce cocrystals.[27]

The purpose of the present paper is to exemplify the low temperature process induced amorphizations of pharmaceuticals, and to examine the factors that favor crystal to glass transformation rather than crystal to crystal transformations.

Using mainly examples studied in our group, we will address questions such as these: (1) Is it really possible to amorphize a crystal by milling? And the connected question: Does the amorphous-like compound obtained that way undergo a calorimetric glass transition upon heating? (2) Is the apparent amorphization simply the result of a local heating and quenching (hot point interpretation)? (3) What is the possible role of amorphous intermediates in solid−solid conversions induced mechanically (also questionable for cocrystals formation)? (4) What about the chemical stability in the course of solid state amorphization for a compound which undergoes chemical degradation at high temperature? (5) What about modifying a glassy compound by milling it? This issue is closely related to that of knowing if different amorphous states, or even situations of polyamorphism, can be reached. (6) How can a heuristic rationalization of the observed transformations be given?

2. An example: The Various Routes To Amorphize Trehalose

Trehalose is a very illustrative example of a compound which can be amorphized by several different routes. In addition to the usual quench of the melt, spray and foam drying, lyophilization, this disaccharide—in its anhydrous form—has been found to reach a glassy amorphous state by at least three independent solid state routes. These routes are the milling of its crystalline anhydrous form β,[21] the dehydration of its dihydrate form T_{2H_2O}[28] and the sub T_g annealing of its crystalline metastable polymorphic form α.[29] These latter routes are the archetype of really low temperature solid state vitrification processes. Furthermore the milling of the dihydrated form of trehalose (T_{2H_2O}) gives some insights of the conditions which are necessary to achieve the vitrification of a compound by high energy milling.

Experimental Details. The ball milling was performed in a high energy planetary mill (Pulverisette 7, Fritsch) at room temperature (RT) and under a dry nitrogen atmosphere. We used ZrO_2 milling jars of 45 cm^3 with seven balls (Ø = 15 mm) of the same material. One gram of material was placed in the planetary mill corresponding to a ball/sample weight ratio of 75:1. The rotation speed of the solar disk was set to 400 rpm which corresponds to an average acceleration of the milling balls of 5 g. The crystalline compounds (β form or $T_{2H_2}O$) were submitted to mechanical treatment during several hours alternating milling periods of 20 min with pause periods of 10 min in order to limit the warm-up of the powder in the jars. The experimental details are available in ref 21.

Milling and Vitrification of Anhydrous Trehalose. Figure 2 shows the X-ray diffraction patterns of the stable crystalline form β before and after a 30 h milling process. After milling the Bragg peaks characterizing the crystalline state have clearly disappeared and the X-ray diffraction pattern is found to be fully similar to that of the quenched liquid suggesting an amorphization of the milled sample. Figure 3 shows the DSC heating scan (run 3) of the milled sample. It exhibits clearly a C_p jump characteristic of a glass transition which occurs exactly at the same temperature as that of the quenched liquid, followed at higher temperature by an exothermic recrystallization. This recrystallization is an indirect signature of the amorphization which has occurred during the milling process, and the C_p jump indicates that the amorphous material has a glassy character. Such a thermal behavior reveals that the milling has given rise to a real glassy state, and not to a mere nanocrystalline material resulting from a strong size reduction of the crystallites. The T_g value is similar to that obtained upon heating the quenched

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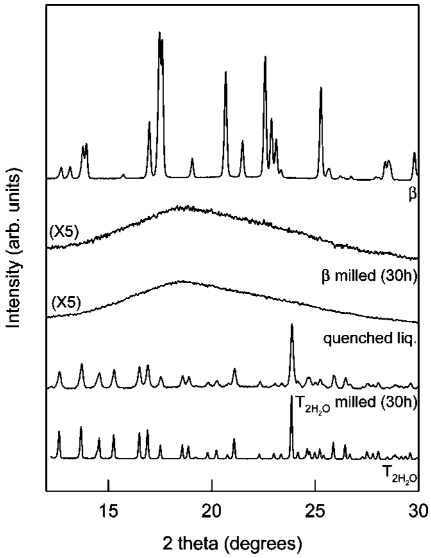

Figure 2. X-ray diffraction patterns of trehalose recorded at RT. From top to bottom: nonmilled form β, form β after a 30 h milling process, quenched liquid trehalose, T_{2H_2O} after a 30 h milling process, nonmilled T_{2H_2O}.

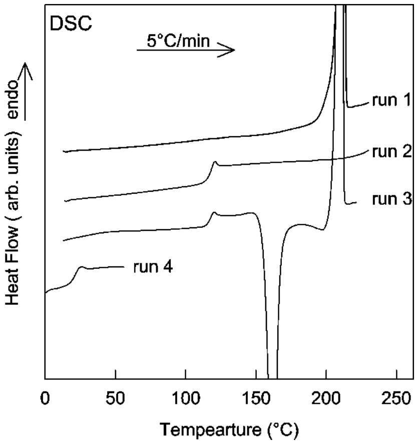

Figure 3. DSC scans recorded upon heating (5 °C/min). Run 1: nonmilled form β. Run 2: quenched liquid trehalose. Run 3: form β after a 30 h milling process. Run 4: T_{2H_2O} melted and quenched in a hermetic pan.

melt (run 2). However, while the quenched liquid does not recrystallize upon heating, the glassy state obtained upon milling recrystallizes totally for the same heating rate. This difference is generally attributed to the existence, in the milled sample, of residual nuclei of the starting crystalline phase which have survived to the milling and which trigger the crystallization upon heating. These remaining nuclei disappear for further milling of the apparently amorphous sample. After a 100 h milling process any trace of crystallization could be detected upon heating while the C_p jump at T_g persists. This indicates that fully amorphous trehalose with thermal properties similar to those of the quenched liquid can be reached through a long enough milling process.

Milling of the Dihydrate Form of Trehalose (T_{2H_2O}). A most interesting point is that the dihydrate form of trehalose (T_{2H_2O}) has a totally different behavior upon milling. Figure 2 shows the X-ray diffraction pattern of crystalline T_{2H_2O} before and after a 30 h milling process. Contrary to the case of the anhydrous crystal, the Bragg peaks broaden but do not disappear. This indicates that the milling has only for effect to reduce the size of the crystallites but does not induce the solid state vitrification of the sample.

The conditions required to amorphize a crystal remain largely a challenging issue. However the present experiment appears to confirm what we have shown in a previous paper,[30] i.e. amorphization is all the more easier as milling is performed deeply below the glass transition temperature (T_g) of the corresponding liquid state. In the case of trehalose, the glass transition of the anhydrous compound is located at T_g (anhydrous) = 120 °C, i.e., far above the milling temperature (RT). On the contrary, because of the plasticizing effect of its structural water molecules, the glass transition of the dihydrate form is expected to occur at a much lower temperature, which is confirmed by the DSC run 4 of Figure 3. This run has been recorded upon heating, and after melting and quench of a T_{2H_2O} sample in a hermetic pan. It clearly reveals a C_p jump at T_g (T_{2H_2O}) = 20 °C corresponding to the glass transition of an amorphous trehalose/water mixture having the stoichiometric composition of trehalose dihydrate. The forms β and T_{2H_2O} have thus their glass transition temperature respectively above and below the milling temperature, which suggests strongly that passing T_g may have a considerable effect on the capability to amorphize a sample. On the one hand, it is thus probable that when milling is performed above the glass transition temperature of the corresponding liquid state, the lifetime of the fractions amorphized during milling is short. As a consequence rapid recrystallization occurs either toward the initial crystalline form as in the case of trehalose or toward a different polymorphic form as seen for several other molecular crystals.[23,31−34] On the other hand, if milling is performed well below T_g, the lifetime of the amorphized fraction is long with regard to amorphization kinetics upon milling. For a long enough milling a fully amorphous sample can thus be obtained which is durably reluctant to crystallization. It is to be reminded that “fragile” molecular glass formers show a sharp decrease of the structural relaxation times above T_g.

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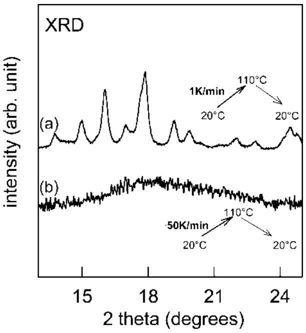

Figure 4. X-ray diffraction patterns recorded at RT for two anhydrous trehalose samples obtained by heating previously T_{2H_2O} up to 110 °C at 1 °C/min (a) and at 50 °C/min (b).

We may think intuitively that, in those conditions, temperature is able to efficiently thwart mechanically induced disordering.

Vitrification by Dehydration of the Dihydrate Form T_{2H_2O}. As for the mechanical milling, the dehydration of hydrated molecular crystals often induces solid state transformations.[35−37] Despite many recent investigations, the understanding and the control of these transformations remain empirical. For dehydration, the perturbation is no longer extrinsic to the sample as in the case of milling. On the contrary, the perturbation is intrinsic to the sample since the destabilization of the crystalline lattice is due to the removal of the water molecules and to the breaking of the hydrogen bonds that they often develop with the other molecules. As a result, a structural reorganization of the sample occurs, either toward a crystalline anhydrous form (stable or metastable) or toward an amorphous state. Since trehalose has a dihydrate form, we have investigated in detail its transformations upon dehydration in order to check if this process could provide another solid state vitrification route in addition to the milling route.

Our results have clearly revealed a duality between an amorphization process and a polymorphic transformation in this compound during the stage of water removal. This duality appears to be very sensitive to the thermal treatment used to dehydrate the sample. Figures 4 and 5 show respectively the X-ray diffraction patterns and the heating DSC scans of two T_{2H_2O} samples which have been previously dehydrated rapidly and slowly by heating them up to 110 °C respectively at 50 °C/min and 1 °C/min. After the fast dehydration the X-ray diffraction pattern is that of an amorphous state and the DSC scan (run 3) reveals a C_p jump at T_g fully similar to that of the quenched liquid. It thus appears clearly that upon a fast dehydration T_{2H_2O} undergoes a direct transformation from crystal to glass. On the other hand, after a slow dehydration the X-ray diffraction pattern is clearly that of a crystalline form which is different from the well-known stable crystalline form β (X-ray diffraction pattern shown in Figure 2). Moreover the DSC scan (run 1) shows that the melting peak of the dehydrated sample is located at about 125 °C, i.e. far below that of form β. A slow dehydration of T_{2H_2O} thus induces clearly a transformation toward a metastable polymorph of anhydrous trehalose which is called form α.[28] For intermediate dehydration rates, a mixture made of glassy amorphous trehalose and crystalline polymorphic form α is obtained in proportion fixed by the heating rate used to dehydrate the sample. For instance, the DSC run 2 of Figure 5 recorded after a dehydration performed at 10 °C/min shows clearly the thermodynamic signatures of both the glass transition of amorphous trehalose and the melting of form α. As a result, the nature of the transformation of T_{2H_2O} induced by dehydration appears to be governed by the rate of water removal. This suggests that the transformation of T_{2H_2O} upon dehydration results from a dynamic forcing mechanism similar to that of mechanical milling or irradiation.[38]

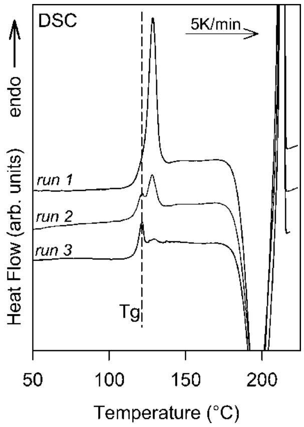

Figure 5. Heating DSC scans (5 °C/min) of three anhydrous trehalose samples obtained previously by heating T_{2H_2O} up to 110 °C at 1 °C/min (run 1), at 10 °C/min (run 2) and at 50 °C/min (run 3).

Vitrification by Isothermal Annealing of the Polymorphic Form α. The melting of the polymorphic form α shown in the previous section occurs just above the glass transition temperature. Such a close to T_g melting is very unusual and suggests that the polymorphic form α is in fact unstable with respect to the amorphous state, and thus transforms toward this amorphous state as soon as the molecular mobility is high enough, i.e., just above T_g. To characterize further this instability of phase α we have followed the structural and thermodynamic evolutions of this phase during long iso-

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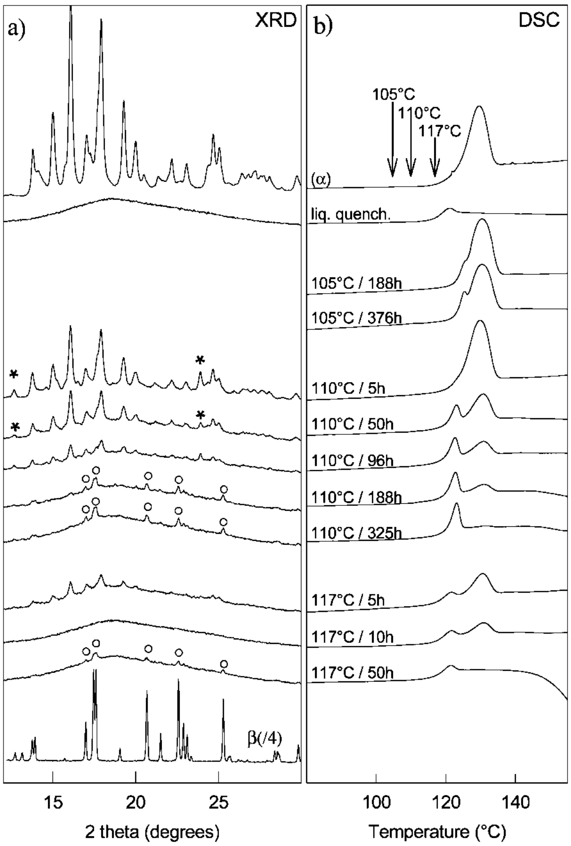

Figure 6. X-ray diffraction patterns (a) and heating (5 °C/min) DSC scans (b) of phase α of trehalose recorded after different annealing times at 105 °C, 110 °C and 117 °C. The annealing times are reported on the left-hand side of the thermograms. Data for some pure forms of trehalose (α, *β*, and quenched liquid) are also reported for comparison. Stars and open circles mark respectively the main Bragg peaks of T_{2H_2O} and form *β*.

thermal annealing below the glass transition temperature, and thus below its apparent melting temperature.

Figure 6 shows the DSC heating scans of the samples after increasing annealing times at 105 °C, 110 °C and 117 °C. We can see that for increasing annealing time at 110 °C, the melting peak of form α progressively drops while the C_p jump characteristic of the glass transition develops. This behavior clearly reveals a slow isothermal vitrification of the material. After 325 h of annealing the melting peak has totally disappeared, indicating that the vitrification process is completed. In this view, the kinetic of vitrification is directly related to the molecular mobility so that it is very sensitive to the annealing temperature. It is, for instance, much slower at 105 °C where after 188 h of annealing the glass transition only starts to be detectable through a shouldering in the left-hand wing of the melting peak (Figure 6b). On the other hand, the kinetics of amorphization is much more rapid at 117 °C since the overall sample is vitrified in less than 50 h.

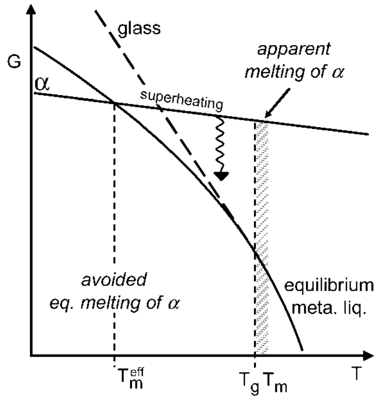

Figure 7. Schematic free enthalpy diagram illustrating the superheating condition of polymorphic form α between its equilibrium melting temperature and the glass transition point.

Figure 6a shows the evolutions of the X-ray diffraction pattern of phase α during the annealing at 110 °C and 117 °C. The progressive disappearance of the Bragg peaks confirms the isothermal amorphization process. It must also be noted that some X-ray diffraction patterns show additional Bragg peaks revealing traces of T_{2H_2O} and form *β*. The traces of T_{2H_2O} mainly appear for short annealing times when a large amount of phase α is still remaining. Since this phase is very hygroscopic,[39−41] some reversion toward the T_{2H_2O} form cannot be fully avoided during the management of the X-ray diffraction experiments which follow the annealing stages. On the other hand, the traces of form *β* mainly appear for the longest annealing times. They reveal a very slow nucleation of the most stable crystalline form in the amorphized fraction of the sample during the sub-T_g annealing.

As a conclusion, the spontaneous vitrification of form α upon isothermal annealing below T_g implies that this phase has a free enthalpy higher than that of the amorphous state. This indicates that phase α is in fact in the original situation of a superheated crystalline state as schematically shown in Figure 7. The metastability breaking of this phase then occurs through a slow but spontaneous vitrification of the material below T_g. It is exactly the inverse of the usual nucleation and growth process by which an undercooled liquid escapes from metastability. Here, we expect the nucleation and growth of liquid droplets, but this mechanism is made very slow by the very high viscosity of the liquid below T_g. This exceptional situation is due to the fact that the melting temperature of phase α is likely to be located far below the glass transition temperature of the corresponding liquid. The phase α thus appears to be a very convenient system to study in detail the mechanism which governs the metastability breaking of a crystalline phase with respect to the liquid phase.

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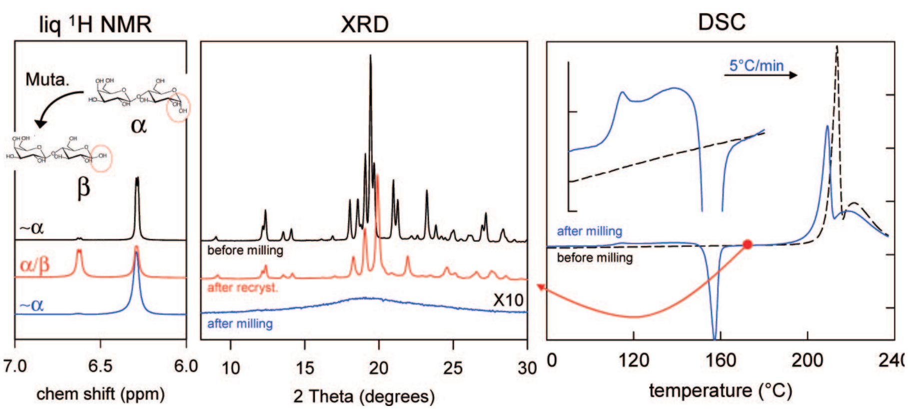

Figure 8. Liquid state NMR spectra of lactose powder dissolved in DMSO-d_6 and X-ray diffraction (XRD) patterns recorded at room temperature for crystalline αL (top), crystalline αL milled during 23 h (bottom) and recrystallized at 170 °C after amorphization by milling. C_p curve obtained upon heating (2 °C/min) for unmilled and milled (23 h) crystalline αL. The inset shows the glass transition region in an enlarged scale.

3. Amorphization by Milling and Chemical Stability: The Examples of Lactose and Glucose

Milling of Crystalline Anhydrous α Lactose. Much interesting information concerning the solid state amorphization process upon milling could be obtained through the study of lactose. Anhydrous lactose presents at the molecular level two isomeric forms (α and β). A conversion (mutarotation) from α to β is known to occur in a variety of liquid solvents.[42] This results in a rich variety of crystalline forms:[43] anhydrous α[44,45] and β[46] pure forms and several α/β defined molecular compounds.[47−49] However it has been reported that the mutarotation is not observed when heating the stable anhydrous α crystalline form.[50] We showed[19] that—similarly to trehalose—a quasi pure α-anomeric form of lactose in an amorphous state can be obtained by ball milling of the α crystalline form under a dry nitrogen atmosphere. Figure 8 demonstrates that the milled compound is X-ray amorphous and has also a real glassy character since a glass transition at $T_g \cong 110$ °C is revealed by the heating DSC scan (heating rate = 5 °C/min) of the milled material.

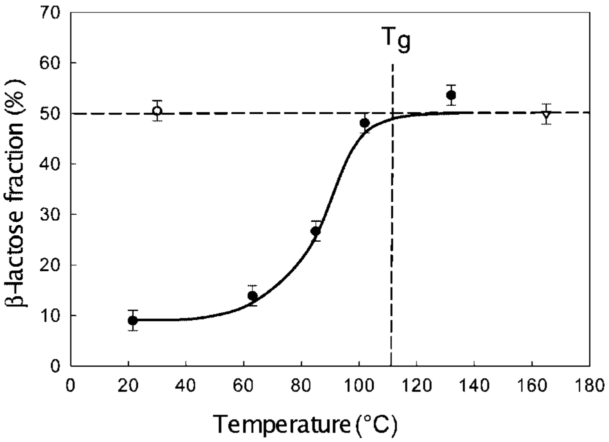

Figure 9. Temperature evolution of the fraction of β lactose after amorphization of α lactose by milling.

The mutarotation reaction of lactose in the solid state after amorphization by milling could be quantitatively measured in situ by solid state ^{13}C NMR and by liquid state NMR of the powder dissolved in DMSO-d_6. This allowed to characterize finely the nature of the amorphous state and also to get an indication about the temperature which has been really reached upon milling. It thus offers the opportunity to test the hypothesis that the amorphization would be the result of local melting. After milling, the amorphized anhydrous lactose is still in the α-anomeric form (96%). As shown in Figure 9 the mutarotation is only seen to occur progressively upon heating. The β lactose fraction increases with temperature to reach the value of 50% at about 132 °C (just above T_g). This value remains unchanged with further heating and also when cooling down the sample before recrystallization could occur. In this case, an amorphous α/β lactose is obtained. Important information emerges from this set of experiments:

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(42) Haase, G.; Nickerson, T. A. Kinetic reactions of alpha and beta lactose. I. Mutarotation. *J. Dairy Sci.* **1966**, *49* (2), 127–132.

(43) Kirk, J. H.; Dann, S. E.; Blatchford, C. G. Lactose: A Definitive Guide to Polymorph Determination. *Int. J. Pharm.*, in press.

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(45) Platteau, C.; Lefebvre, J.; Affouard, F.; Derollez, P. Ab initio structure determination of the hygroscopic anhydrous form of α-lactose by powder X-ray diffraction. *Acta Crystallogr., Sect. B: Struct. Sci.* **2004**, *60*, 453–460.

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(47) Drapier Beche, N.; Fanni, J.; Parmentier, M. Kinetics of the synthesis of lactose molecular compounds. *J. Dairy Sci.* **1998**, *81*, 2826–2832.

(48) Lefebvre, J.; Willart, J. F.; Caron, V.; Lefort, R.; Affouard, F.; Danede, F. Structure determination of the 1/1 α/β mixed lactose by powder X-ray diffraction. *Acta Crystallogr. B* **2005**, *B61*, 455–63.

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(50) Lefort, R.; Caron, V.; Willart, J.-F.; Descamps, M. Mutarotational kinetics and glass transition of lactose. *Solid State Commun.* **2006**, *140* (7−8), 329–334.

(i) It is possible to amorphize (to vitrify) lactose directly at low temperature by a dynamical shearing process.

(ii) The glass which is obtained by this route is in a pure α anomeric form. It thus differs chemically from those which are obtained by cooling the metastable liquid below T_g, by lyophilization or also by spray drying, which all give rise to a nearly equimolar amorphous mixture of α and β lactose. It must be noticed that quenching the liquid itself could only produce a caramelized black sample. Milling is the only process able to produce amorphous α lactose which has the appearance of a white powder of a non-chemically damaged compound.

(iii) Importantly, the anomeric purity of the glass obtained by milling indicates that the amorphization is not associated to a local heating/quenching process as it is often invoked to explain this kind of amorphization. Neither the melting point nor the glass transition temperature was reached during the milling process since temperature higher than T_g would have triggered unavoidably the mutarotational kinetics in solid state lactose. The mutarotation which is a local chemical process is thus expected to be strongly coupled to the cooperative structural relaxations in the amorphous state. The latter relaxation which becomes more rapid on heating up to T_g was however never fast enough to trigger the chemical process. The structural modification was thus really generated by dynamical shearing occurring far below the melting point. The process appears to be able to generate an amorphous glass which differs from that obtained by a thermal quench. This glass is also strongly out of equilibrium since it cannot be recovered after a thermal excursion at a higher temperature.

Milling of Crystalline Anhydrous Glucose. D-Glucose ($C_6H_{12}O_6$) can be easily vitrified by cooling the melt, and T_g is less than 20 °C above RT. No chemical degradation occurs during a short excursion just above the melting point, but a strong mutarotation process leads to a nearly equimolar mixture of the two anomeric form of glucose (G_α and G_β). It is thus an excellent system both to test the capability to amorphize by milling and to check the relation between vitrification and mutarotation. Raman scattering (see the wavenumber range 730−950 cm^{-1} in Figure 11) is very convenient to discriminate easily the two anomeric forms directly in the solid state. The two spectra show some specific modes as already reported by Araujo-Andrade et al.[51]

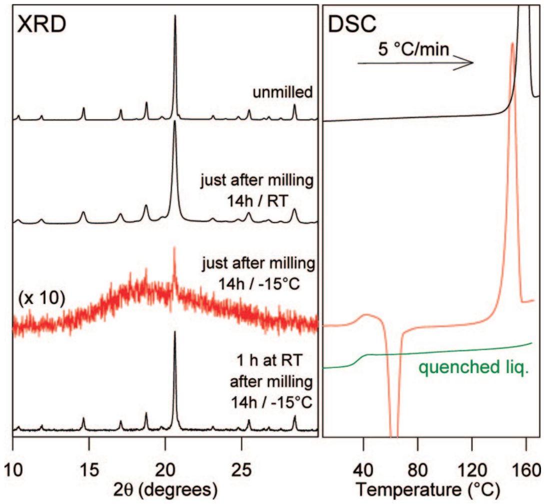

Figure 10. (a, left) Powder X-ray diffraction patterns recorded at RT. Top to bottom: unmilled crystalline α-D-glucose (G_α); initially crystalline G_α milled for 14 h at RT; initially crystalline G_α milled for 14 h at −15 °C; initially crystalline G_α milled for 14 h at −15 °C and then annealed 1 h at RT. (b, right) DSC scans obtained upon heating at 5 °C/min. Top to bottom: initially crystalline α-D-glucose (G_α); same sample, after milling at −15 °C for 14 h; amorphous glucose obtained by cooling of the liquid state.

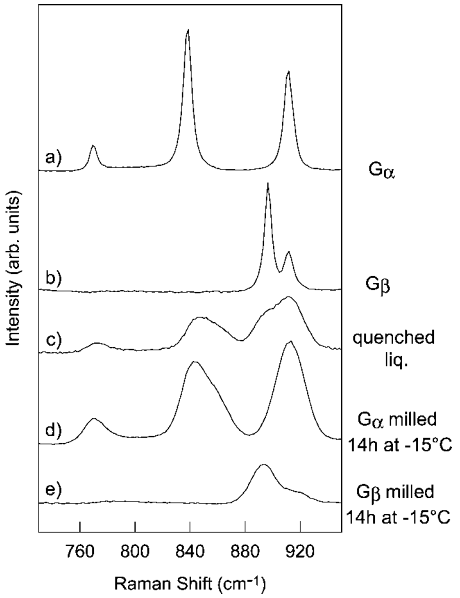

Figure 11. Raman spectra recorded at RT for: (a) unmilled crystalline α-D-glucose (G_α), (b) unmilled crystalline β-D-glucose (G_β), (c) amorphous glucose obtained by quench of the liquid, (d) initially crystalline G_α milled for 14 h at −15 °C, and (e) initially crystalline G_β milled for 14 h at −15 °C.

It has been shown by Suga et al.[52,53] that no sign of amorphization of G_α could be detected after long milling of crystals performed at RT, i.e. 13 °C below the glass transition temperature (T_g = 38 °C). It has however been found[54] that solid state amorphization is possible when milling is performed at a slightly lower temperature (−15 °C) and in very dry atmosphere. Figure 10a shows the XRPD patterns recorded at RT of (1) the crystalline phase of anhydrous G_α, (2) the same sample after a long (14 h) milling at RT, (3) after a long (14 h) milling at −15 °C and (4) one hour after

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the end of the milling at −15 °C. After milling at RT the Bragg peaks are much broader but there is no trace of amorphization or any sign of polymorphic transformation toward a metastable state. On the contrary, after the low temperature milling, the Bragg peaks have nearly totally disappeared to give place to a large diffusion bump. This indicates that a large part of the initial crystalline G_α has been amorphized. However this amorphized sample rapidly recrystallizes at RT after the end of the LT milling process.

The DSC heating scans shown in Figure 10b demonstrate that the G_α sample milled 14 h at −15 °C exhibits a glass transition at 38 ± 1 °C similar to that of the quenched liquid followed by a recrystallization exotherm at 85 °C. Melting is then observed at 150 °C as usual for crystalline G_α. This indicates that a real, 100% glassy amorphous state has been produced upon milling about 55 °C below T_g. After short milling times ($t_{mill} < 5$ h) the recrystallization starts before the end of the C_p-jump making the glass transition difficult to observe. For increasing milling times, the recrystallization peak progressively shifts toward higher temperatures. This reveals an increasing stability of the amorphous state and the increasing scarcity of the remaining crystallites of G_α.

The behavior of crystalline G_β upon milling at −15 °C has been found very similar to that of G_α.The crystal of G_β is totally converted to glass after a 14 h milling process, and the glass transition is seen at 39 °C.

Raman spectra of Figure 11 show that the vibrational modes of the quenched liquid wrap those of both crystalline G_α and G_β, indicating that the quenched liquid is a mixture of the two anomers. On the contrary the milled samples have not undergone any mutarotation and show an anomeric purity which cannot be reached by the traditional quench of the liquid.

All these results are coherent with our general observation that amorphization is all the more successful as milling temperature is lower than T_g (the latter could be decreased by plastization in the presence of humidity). Furthermore, as was found for lactose, the absence of mutarotation induced by milling is a strong indication that temperature did not reached the melting point. The nature of the thermal and milling routes of vitrification is different, and the glasses are different.

4. The Issue of Crystal to Crystal Transitions and the Possible Role of Amorphous Intermediates

Pharmaceutical literature also reports a lot of observations about crystal−crystal transformations between different polymorphic forms resulting from milling. It is for example the case of modafinil[55] chloramphenicol,[56] cimetidine,[32] sulfamerazine,[22] indomethacin,[23] phenylbutazone,[31] sorbitol,[34] mannitol[57,58] and so on, for which a conversion from the stable phase to a metastable phase is observed. The inverse situation is described for caffeine for which a quick conversion from the metastable phase I to the stable form II is reported.[59] In the case of mannitol we could demonstrate that, in the case of polymorphic transformations, the final crystalline state is independent of the initial physical state. Mannitol presents a complex polymorphism with three polymorphic forms whose increasing stability order at room temperature is δ, α, β. The milling at room temperature of the most stable form β and that of the less stable form δ both induce—for the same milling conditions (temperature and intensity)—a transformation toward form α of intermediate stability.[30] After stopping milling, it is noticed that the metastable phase α quickly transforms toward the more stable phase β, indicating that the metastable form α is stabilized by the milling itself.

A similar crystal−crystal transformation was observed when grinding another polyol: the sorbitol.[34] Milling the Γ crystalline form of D-sorbitol during 10 h at room temperature (i.e., above T_g which is ∼ 0 °C) promotes a progressive conversion to the metastable crystalline form A. The X-ray analysis of the nanostructure evolution upon milling has shown a clear reconstruction of the ultimate crystallites. In the first stage of milling ($t_{mill} < 1$ h) a broadening of the diffraction peaks reveals a stage of nanostructuration of the crystallites. This is confirmed by the decrease of the melting temperature of the Γ phase according to the Gibbs−Thomson law. Then the peaks of the new polymorph appear ($t_{mill} >$ 2 h) and are also broad. After a long enough milling, the Bragg peaks of the appearing new form progressively become very sharp. This shows that, this time, milling is able to promote a total reconstruction of the new long-range order on a large microstructural scale. It must be noted that sorbitol and mannitol can be obtained in the amorphous state by the melting/quenching process and have their glass transition

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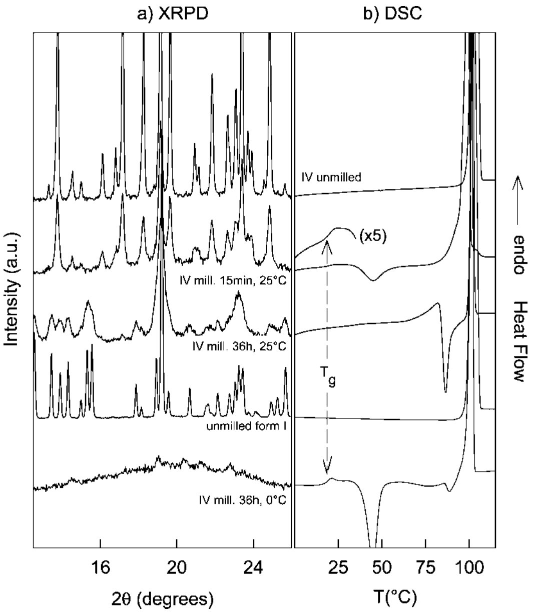

Figure 12. (a) X-ray diffraction patterns of fananserine form IV recorded at room temperature after different milling times at different milling temperatures. (b) Corresponding DSC heating curves (5 °C/min). A close-up view of the glass transition temperature underlines a transient amorphization.

temperature T_g below the milling temperature ($T_{g\ \mathrm{sorbitol}} \approx 0$ °C,[60] $T_{g\ \mathrm{mannitol}} \approx 12$ °C[61]).

The previous results suggest that a low milling temperature or more exactly a milling temperature lower than the glass transition temperature favors the amorphization of the compounds. Recent milling experiments performed at different temperatures with fananserine clearly show this point.[62] Fananserine is a pharmaceutical compound which presents a complex polymorphism with at least four crystalline forms. The milling at room temperature of the most stable forms III and IV induces for both a polymorphic transformation toward the least stable form I. Decreasing the milling temperature of only 25 °C is sufficient for the milling to induce an amorphization of the fananserine rather than a polymorphic transformation. This result is illustrated in the Figure 12. We can see on the XRPD pattern the diffusion halo which characterizes amorphous compounds and on the DSC scan the C_p jump which proves the vitrification. The glass transition temperature of fananserine is $T_g = 19$ °C (heating at 5 °C min^{-1}). The change in the nature of the transformation for millings performed in a small temperature range on either side of T_g reveals a large sensibility of the response at a dynamic perturbation in a temperature zone where the structural relaxation characteristic times evolve quickly. Indeed, the dynamic characterization of metastable liquid of the fananserine showed that this glass former is fragile.[63]

Amorphous Intermediates. The X-ray diffraction patterns recorded for different times of milling of form IV of fananserine at room temperature reveal an intermediate amorphization stage which precedes the transformation toward the metastable crystalline phase I.[62] This is clearly shown by the existence of a transient amorphous halo underlying the Bragg peaks. Moreover, the DSC scans of these different intermediate states recorded upon heating reveal a small C_p jump immediately followed by a small recrystallization peak confirming the vitrification of the material.

For sorbitol, the phase conversion is generated by milling at a temperature higher than T_g, where molecular mobility in the amorphous state is high. It is not totally clear from the direct observation of the X-ray diffraction patterns if the transformation between the two polymorphs involves or not a transient amorphization stage. An amorphization is however suggested by the fact that some transport of matter is necessary for the crystalline reconstruction to operate. This mass transport is indirectly demonstrated by a peak profile analysis which provides the evolution of the microstructure at different times of grinding. Figure 13 shows that during the first 15 min of milling the average size of the crystallites decreases in the *a* and *b* crystalline directions. Size however transiently increases by about 35% in the *c* direction. Transient amorphization has also been detected during the milling process which leads to growing carbamazepine–nicotinamide cocrystals.[64] The amorphous state serves as a medium where inherent molecular mobility can lead to molecular associations between different components such that a single crystalline phase of multiple components is formed. The mobility which is high above T_g but much more limited just below T_g is most probably the reason why transient amorphization can be detected in real time on the XRPD patterns for the fananserine conversion and not for the sorbitol conversion. Above T_g the lifetime of the fraction amorphized by milling is short as a result of a rapid recrystallization either toward the initial crystalline form (e.g., trehalose dehydrate or glucose) or toward a different polymorphic form (e.g., sorbitol or mannitol). Below T_g but not far, the competition between crystallization and amorphization can be observed in real time (e.g., fananserine, in-

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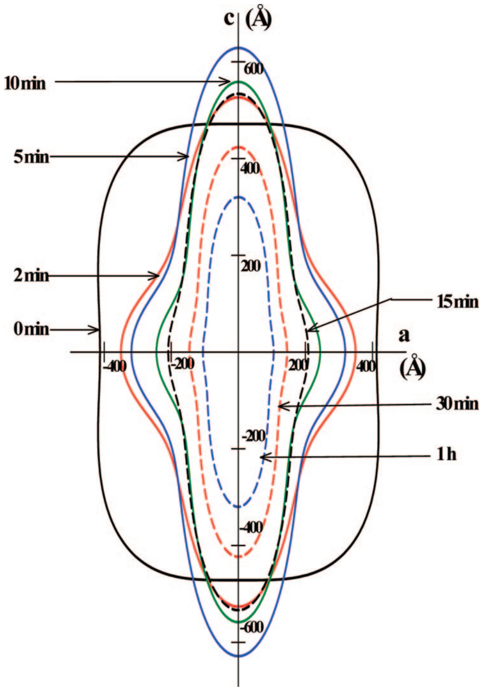

Figure 13. Milling of sorbitol: evolution of the crystallite size along *a* and *c* crystallographic directions after different milling times (obtained from analysis of the shape of the Bragg diffraction lines).

domethacin). Well below T_g the kinetics of recrystallization is too slow to compensate the amorphization.

At this level it may be interesting to mention that it is possible to manipulate the glassy state by comilling compounds which have respectively values of T_g lower and higher than the milling temperature (for example mannitol and lactose[57]). Glass solutions which are not affected by mutarotation and caramelization could be produced for all concentrations where the T_g of the mix is higher than the milling temperature.

5. Heuristic Rationalization: Effective Temperature under Milling

How To Describe Amorphization? The results which have been reported above all emphasize that the amorphization efficiency upon milling increases as the milling temperature decreases. Besides, there are clear indications that, during milling, the temperature of the samples does not reach the melting temperature. This is evident for all cases where a crystal−crystal transformation is observed, this is also demonstrated by the absence of mutarotation for lactose and glucose. Consequently when amorphization is observed, it is directly induced by default accumulation created by shearing. The physical state created this way is stabilized by milling. Generally, when milling is stopped, irreversible evolutions to more ordered crystalline states are observed. It looks as if, during milling, the temperature could not counterbalance the mechanically generated disorder. The increasing amorphization efficiency of milling for decreasing milling temperatures is well taken into account by the "driven material concept" developed by Martin and Bellon.[65] This model was initially proposed to describe transformations under irradiation. According to this model, the compound can be viewed as exploring its configuration space under the effect of two distinct mechanisms which act in parallel: the usual thermally activated molecular motions which operate in the absence of the external forcing and ballistic jumps which are generated by the external forcing. The originality of this approach is to take into account the overall physical state itself. According to this model, the competition between, on the one hand, the disorder induced by milling and, on the other hand, the diffusion effects—which tend to restore the system to lower energy configurational states—is modelized for the configuration of the whole system and not only locally. It is to be noticed that diffusion itself can be accelerated by the mechanical shocks. We will go back to that point later when discussing the effect of activating a glass itself.

We start considering the model of a structural phase transition. The kinetics of evolution of a macroscopic order parameter (Q) describing the phase—after a temperature change for example—is conveniently written in the form

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = -D(T)\frac{\partial G}{\partial Q} \qquad (1)$$

where $\partial G/\partial Q$ is the driving force, G the free enthalpy of the system, and $D(T)$ the temperature dependent rate of thermal jump. This is compatible with the fact that thermodynamic equilibrium is defined by $\partial G/\partial Q = 0$.

Closely following Martin's approach, the rate equation of the macroscopic order parameter describing the dynamically disrupted phase is obtained by adding a term which reflects the disordering influence of the perturbation.

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = -D'(T)\frac{\partial G}{\partial Q} - D_B Q \qquad (2)$$

In this expression the rate of thermal jump D' may be enhanced because external forcing modifies the noise level and may also generates extra defects. The second term describes the effect of disordering with a "ballistic" jump frequency D_B (rate of ballistic jump), independent of the temperature but which dependent on the milling intensity. In the course of a ball milling experiment the specific milling intensity is—depending on the authors[65−67]—either the momentum or the kinetic energy transferred by the ball to the unit mass of powder per unit time. This intensity thus depends on the mass and number of balls, as well as frequency of shocks (quantity related to the rotation speed of the vials which contain the powder and the balls).

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This concept can be simply illustrated using a kinetic Ising model.[68,69] For the simple case of a relaxation of the order parameter Q and for a second order transition occurring at T_c with no milling, the equation of relaxation in the presence of milling can be written (in the range of temperature where, upon milling, Q is infinitely small)

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = D'\left(-Q + \left(\frac{T_c}{T}\right)Q\right) - D_B Q \qquad (3)$$

The first term of the right member is that of the equation of motion in the molecular field approximation (after linearization of the hyperbolic tangent). (See for example ref 69, pp 284, 285.)

In stationary regime ($\mathrm{d}Q/\mathrm{d}t = 0$), eq (1) possesses nonzero solutions only for temperatures below a critical temperature under milling:

$$T_c' = \frac{T_c}{\left(1 + \frac{D_B}{D'}\right)} \qquad (4)$$

This is obviously equivalent to a rescaling of the physical interactions J:

$$J_{\mathrm{eff}} = \frac{J}{\left(1 + \frac{D_B}{D'}\right)} \qquad (5)$$

That can be extended to situations which need to express the exchange integral J in the reciprocal space.[70]

Otherwise stated, the physical state of the system which is ground at the real temperature T is that of the system in absence of milling at an effective temperature:

$$T_{\mathrm{eff}} = T\left(1 + \frac{D_B}{D'}\right) \qquad (6)$$

The rate of thermal jump D' decreases when the temperature decreases. Figure 14 represents typical variations of T_{eff} as a function of T. At high temperature thermal jumps are efficient enough to restore an equilibrium so that $T \cong T_{\mathrm{eff}}$. It means that milling has no practical influence on the physical state. However at low temperature thermal restoration becomes less efficient and T_{eff} eventually increases. It may thus overcome the equilibrium phase transition temperature. Even if the kinetics of melting are less simple to modelize, such an approach can explain amorphization. It occurs at low enough milling temperature or (and) rather high milling intensity when T_{eff} overcomes the value of the melting temperature. It also reproduces consistently what has been experimentally observed to make amorphization easier, i.e., a decrease of the milling temperature.

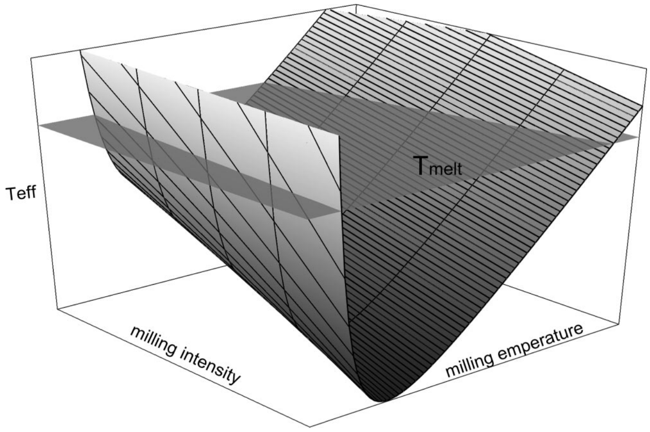

Figure 14. Temperature evolution of the effective temperature T_{eff} under milling.

How To Understand Crystal to Crystal Transformation? It is impossible to explain the observed crystal−crystal polymorphic transitions described above (fananserine, sorbitol, and indomethacin) using a simple effective temperature concept since polymorphs in those cases form monotropic sets. No equilibrium transition temperature between the different polymorphs is thus expected that an effective temperature under milling could overtake. It is also to be noticed that there is no group to subgroup symmetry relation between these phases. The transitions are totally reconstructive. Furthermore the conversion is sometimes observed from a metastable to a more stable state (case of mannitol). That would certainly need to admit some decrease of T_{eff} upon milling which is not predicted by eq 6. It is to be remembered that such milling induced crystal conversions are correlated to the fact that milling is performed at temperatures higher than the glass transition of the compound, or very close to it. For the milling experiments which could be performed at temperatures very close to T_g—as for fananserine and indomethacin—we have observed some transient stages of amorphization preceding the polymorphic crystalline transformation. The formation of a noncrystalline solid in the initial stage of formation of phase I was also observed during the ball milling of sulfathiazole form III.[33,71] The mechanisms of transformation during grinding of other drugs,[72] cephalexin, chloramphenicol palmitate and indomethacin were found to proceed by going through amorphous states of the material followed by transformation to another polymorph. As already mentioned, such a transient amorphization could hardly be detected in the cases of sorbitol[34] and mannitol[30] which were ground several tens of degrees above their T_g's. We can suspect that the extreme slowing down of the structural relaxations near T_g is responsible for

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the amorphous state to have a longer lifetime and thus being experimentally detectable. These observations suggest that the crystal structure change is mediated by the amorphization. The simplest mechanism which comes to mind is that of a nucleation and growth process of the new form inside the amorphized fraction. An interesting proof of this is given by investigations of the effect of milling on the cimetidine[32] which has a complex polymorphism made of four crystalline forms. Form A was found to transform in 84 h of grinding into form D after a transient amorphization if 0.1% of phase D is admixed during the grinding process. The kinetics of phase transformation could be significantly accelerated by increasing the amount of added phase D. A 1:1 mixture of modifications A and D transformed completely to D within 6 h. This supports the idea that nucleation out of the amorphous content was essential for the path of phase transformation.[73] The transformation would thus involve a two step process:

(1) The first is an amorphization according to the driven material concept described above.

(2) The second is the milling assisted crystallization out of the amorphized part of the compound. An effective temperature argument cannot justify such a transformation in the same way as the initial amorphization. We may imagine that milling effectively pushes the compound to a higher effective temperature T_{eff}. But that time we must admit that the system does not transform because it is displaced with regard to an equilibrium crystal-to-crystal transition. However it is reasonable to assume that milling effectively pushes the amorphized system up to effective temperatures where nucleation becomes more favorable. This temperature is situated between T_g and the equilibrium melting temperature. This second part of the process does not come out directly from a milling-modified relaxation equation of an order parameter as described by eqs 2 and 3. However milling the glass after it has been formed is likely to help the glass exploring more of its phase space. The driven activation concept of Barrat et al.,[74] to be evoked below, may be that time relevant. It is worth noticing that a modification of the activation energy is still foreseen in the Martin's like expression (eq 2) through the modified $D'(T)$ rate of thermal jump.

6. Driven Dynamics of Glassy State under Milling

The issue of the effect of milling the glass follows from the observations which have been made above. Intuitively, mechanical milling may induce transitions between states of the glass structure in addition to those induced by temperature alone which are rather infrequent in the nonergodic glass state. This point becomes clear if we remind ourselves of the case of granular matter. In that case the energy needed to move a macroscopic grain by a distance commensurable with its size is much larger than the thermal energy, k_BT. For granular systems, thermal activation is totally irrelevant. Blocked configurations of granular systems can only be unjammed if external driving is applied in the form of shearing, vibrations etc. Once externally driven, granular matter can relax to states of lower energy as glass does under the effect of temperature. External driving provides an effective temperature to granular matter. We can expect that driving externally a glass—by milling for example—will have the same effect as increasing real temperature.

Milling a sample which has been first prepared in the glassy state by quench cooling offers an original nonequilibrium situation to search evidence of an effective temperature for the driven material. The pharmaceutical ingredient indomethacin is a very good glass former which offers an interesting opportunity to explore the effects of driven dynamics. This is due to its specific recrystallization properties which are rather well documented.[72] Systematic investigations of the effects of milling the glassy state of indomethacin have been reported in ref 75. They consisted in performing milling of the quench-cooled glass, at room temperature (i.e., about 30 °C below T_g), with various grinding intensities (by varying the rotation speed Ω of the planetary mill). Steady states were reached upon milling which were found to depend on the rotation speed Ω as follows (Figure 15): (1) For low Ω value (150 rpm), the steady state is that of a sample partially crystallized in the stable form γ. (2) For medium Ω value (200 rpm), the steady state is that of a sample entirely crystallized in the metastable form α. (3) For high Ω values (300−400 rpm), ball milling maintains the sample in a fully amorphous state.

It is interesting to notice that for the two lower milling energies we observe a crystallization of the amorphous state under milling. There is further a correlation between the nature of the recrystallized phases, the intensity of grinding, and the temperatures where these phases have their maximum of recrystallization rate in the absence of milling. The stable phase γ whose recrystallization is enhanced at lower milling intensity has also its maximum rate of recrystallization at lower temperature. Slightly higher milling intensity is correlated to the appearance of phase α which also recrystallizes at higher temperature in the nonmilled glass. Milling the amorphous state at high intensity has no apparent effect on the nature of the physical state which remains amorphous. This is coherent with other observations resulting from milling crystalline indomethacine at nitrogen temperature[23] or high intensity which also induce amorphization. This latter situation agrees with the driven material description of a material pushed to an effective temperature higher than melting, and this independently of the initial physical state of the compound.

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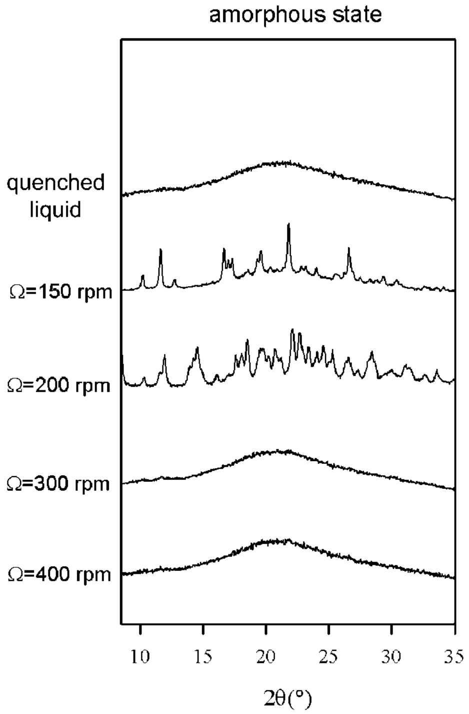

Figure 15. X-ray diffraction patterns of glassy indomethacin milled at room temperature with different milling intensities.

As for the case of the crystal−crystal transformations described above, it is impossible to directly interpret the milled enhanced crystallizations using the same effective temperature concept by which the system would be displaced with regard to an equilibrium phase transition temperature. The correlations existing between the milling intensities and recrystallization temperatures strongly suggest the possibility of considering an effective temperature upon milling which is that time related to the characteristics of the structural relaxation of the amorphous state itself. The latter is enhanced by milling and can promote nucleation, even when the real temperature is lower than T_g. The mechanical activation provides additional noise to the normal thermal one and increases the nucleation probability. The crystallization of a given phase thus occurs when the effective temperature reaches the temperature domain of most rapid recrystallization. If we adopt an Eyring activation process description, this is equivalent to a rescaling of the activation energy ΔE in an Arrhenius contribution:

$$\tau(T) \propto \exp\left(\frac{-\Delta E}{k_B T}\right) \tag{7}$$

It is to be noticed that such an enhancement of the dynamics under external driving was also implicitly considered in the D' term of the Martin equation (eq 2).

Activated dynamics in a glassy system undergoing shear deformation was recently studied numerically by Ilg and Barrat.[74] They have shown that the introduction of an effective temperature in an Arrhenius representation of the slow relaxation processes is close to the effective temperature that can be determined from the fluctuation−dissipation relation.

Very high intensity milling of the glass does not induce a recrystallization because the effective temperature is higher than the melting temperature. The nature of the milled glass however appears to be modified since the nature of the recrystallized form upon heating depends on the milling conditions. After a long enough high energy milling indomethacin recrystallizes toward the metastable α phase upon heating while crystallization toward the γ phase is only observed upon reheating the briefly milled amorphous. The situation is similar to that observed for the recrystallization of amorphous indomethacin initially obtained by cooling the liquid at different cooling rates.[76] Higher cooling rate eventually promotes a recrystallization toward form α, as does a sample milled during a long time. Long high intensity milling is thus able to push the glass to configurations of high energy—i.e. high fictive temperature—where the liquid is also trapped upon fast cooling.

It has been shown recently that spray-drying[77] and lyophilization[78] are also able to produce glasses which are trapped in very specific zones of the energy landscape. Aging these glasses gives rise upon heating to calorimetric signatures which are those of hyperquenched glasses. Recovery is observed below T_g where it gives rises to a sub-T_g endotherm. The specific preparation and history applied to the glass are in these cases able to provide some restoration of mobility below T_g which has nothing to do with secondary relaxations. We have observed somewhat similar characteristics for glasses prepared by milling.

7. Conclusions

Remarks about the Manipulation of the Amorphous State Thanks to External Driving. We have shown that mechanical milling can induce various changes of the physical state of molecular materials. These changes may even appear antagonistic. We can summarize the overall range of behavior which may be observed as follows: (1) amorphization (only for high energy milling performed below T_g); (2) crystal to crystal transformation (for milling performed at higher temperature) (if grinding is performed near T_g a transient amorphous state can be observed); (3) milling the glass can either induce a recrystallization (for low grinding intensity) or drive the amorphous to states of high fictive temperature using higher energy milling (or/and milling at lower temperature).

It is thus possible either to stabilize the glass or to make it more reactive using adequately determined external driving.

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These different behaviors can be made reasonably rational by appealing to an increase of the effective temperature under milling. We have however shown that operationally it is possible to refer to two different types of effective temperatures in order to describe the physical state produced by milling. These two effective temperatures are respectively related to a rescaling of the interaction energy J which drives the phase transition ("Martin effective temperature") and a rescaling of the activation energy ΔE ("Barrat effective temperature").

The consequences of the rescaling of these two energies or equivalently of the temperatures are apparently different. They correspond either to a change of the phase transition temperature ($J \rightarrow J'$) or to a modification of the structural relaxation times ($\Delta E \rightarrow \Delta E'$). This latter change by itself may have consequences on a nucleation rate and may thus give rise in turn to the appearance of a new phase but only for kinetic reasons. Such a modification of the relaxation times has been effectively observed by measuring in situ the volume relaxation of an irradiated selenium glass at a temperature slightly below T_g.[79] In this latter case an acceleration of the aging was observed.

Creation of defects and increase of disorder is often advocated to "explain" the physical changes induced by milling.[71] In the case of glasses the characteristic structural relaxation time was correlated with the configurational entropy (S_c) according to the expression proposed by Adam and Gibbs:[80]

$$\tau = \tau_0 \exp\left(\frac{C}{TS_c}\right) \qquad (8)$$

in which C is a constant proportional to the free energy of activation for local rearrangements. An amorphous solid which has higher S_C has shorter τ. This equation may provide a heuristic model for the enhanced relaxation in a milled glass. If we express that S_C is an increasing function of the number of defects, n, we may write the effective relaxation time under milling:

$$\tau_{eff} = \tau(T) \exp(-C'\Delta n) \qquad (9)$$

where Δn is the excess of defects created by milling and $C' = C(\partial S_c/\partial n)/TS_c^{2}$.[81] Such an approach is sufficient to account for changes of the relaxations in glass resulting from milling at not too high intensity and not too low temperature: the shortening of the structural relaxation time is able either to accelerate aging or to promote nucleation of crystalline phases. The situation is opposite in the case of high milling intensity below T_g for which a glass with a high fictive temperature is obtained. In the case of irradiation at temperatures much lower than T_g, a rejuvenation of the glass has also been observed, i.e., an effect contrary to that resulting from irradiation near T_g which hyperstabilizes the glass.[81]

All these observations suggest that some competition occurs between (1) a thermally activated ordering—even enhanced by the driving mechanism—which is predominant at high temperature and low milling intensity and (2) a ballistic disordering in the glass without enough thermal compensation at low temperature and high milling intensity.

There is no hope that a single order parameter may describe a glass, and it is certainly difficult to adapt directly the driven material concept in the form of a simple equation like eq 2. However a combination of the two effective temperature concepts could certainly help providing a unified description of driven glasses. The need for such a theoretical development in this area where industrial formulation problems catch up with nonequilibrium physics is acute.

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