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Thermal insight of mechanically activated bile acid powders

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ABSTRACT

Mechanical activation of pharmaceutical materials presents an important but poorly understood phenomenon of milled molecular crystals. In this work, a strategy was followed in an effort to understand this phenomenon, cryo-milled of both crystalline and amorphous counterpart of bile acids materials were characterized by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). The XRPD results for the 30-min milled crystalline powders displayed a characteristic amorphous halo patterns for all compounds tested. The DSC thermograms exhibited the typical glass transition temperatures (T_g) associated with amorphous but only for two materials. For the remaining four milled compounds, a rather interesting behavior was manifested through a characteristic exothermal bimodal peak. The findings seemed to suggest that the occurrence of this event was not related to the (T_g), but likely to the melting temperature (T_m). The DSC results for the melt-quenched (amorphous) ursodeoxycholic acid after cryo-milling revealed that the material crystallized after the influence of the mechanical stress, and a bimodal peak was also observed similar to that of the cryo-milled crystalline material. It is contemplated that the response of the physical instability of the disordered phase could be explained either by the result of surface crystallization kinetics which is different from that of the bulk crystallization, or by the creation of supersaturated dislocated crystal prior to amorphization.

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1. Introduction

Mechanical milling is a common process in the pharmaceutical industry to reduce particle size of crystalline active pharmaceutical ingredients (APIs), to improve handling (Vendola and Hancock, 2008), to enhance dissolution rate (Florence et al., 1974) or for dry powder inhaler (DPI) formulations (Saleem and Smyth, 2008). This pharmaceutical manufacturing unit operation process not only reduces the size of drug particles, but also causes a partial or complete physical transformation to a new solid form (polymorph or amorphous form) (Crowley and Zografi, 2002; Gusseme et al., 2008). Many compounds are reported to become amorphous upon milling (Bates et al., 2006; Han et al., 1998; Mosharraf and Nyström, 2003; Otsuka and Kaneniwa, 1990; Price and Young, 2005; York et al., 1998), with solid-state properties different from those of the melt-quenched (Graeser et al., 2008) or spray-dried (Yonemochi et al., 1999b) samples. The physical transformation of API may result in drastic changes in dissolution rate (Terada et al., 2000) or chemical stability (De Villiers et al., 1992). In addition, mechanical stress during the milling process may produce mechanically activated powders. The mechanical activation of powders, where the milled material stores some of the energy imparted to it during milling, is an intrinsic aspect of milling pharmaceutical materials and presents an important but poorly understood phenomenon. Of particular interest is the understanding of the microstructure of mechanically activated materials. Mechanical activation is associated with decreased crystallinity of the material. It can take the form of crystal dislocations (Feng et al., 2008) or of full fledged (cooperative) amorphous regions (Johnson, 1986; Savolainen et al., 2007). Mechanical activation also affects the physical stability of powders, leading to physical transformations, such as polymorphic transformations and dehydration hydrated molecular crystals (Chieng et al., 2006; Shakhtshneider and Boldyrev, 1993; Wang et al., 2002; Willart et al., 2001; Yajima et al., 1997).

Therefore, milled materials should be carefully monitored and characterized during and after milling. To-date, several milling mechanisms have been proposed (Fecht, 1992; Wildfong et al., 2006), but up till now, a fundamental insight to explain the milling behavior of organic compounds is still needed. Pharmaceutical organic compounds are usually very anisotropic, have a wide variety of orientations and conformations that makes the task challenging.

The behavior of crystalline compounds during milling is governed by crystal stability, i.e. fragility or hardness in the initial step of pulverization, and then by physical stability of phase transformations, especially amorphization, have long been observed in

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mechanically milled pharmaceutical molecular crystals (Willart and Descamps, 2008; Bates et al., 2006). The crystal stability of organic compounds toward mechanical stress has been studied with respect to brittleness (Meier et al., 2009), slip planes (Sun and Kiang, 2008), dislocation density (Wildfong et al., 2006), heat capacity (Chamarthy and Pinal, 2008) and surface energetics (Chamarthy and Pinal, 2008; Otte and Carvajal, 2011).

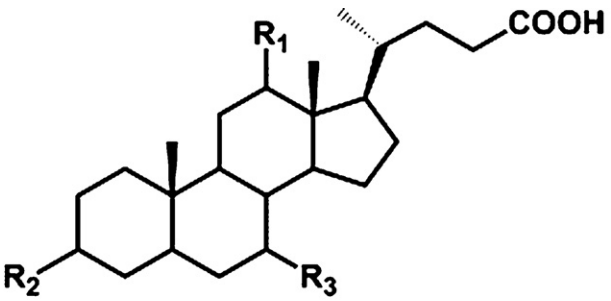
The benefit of the particle size reduction on dissolution is of interest but this is accompanied by detrimental effects on the physico-chemical properties and stability of the milled materials. Hence, it is important to assess the fundamentals, effects and consequences of milling, to interrogate materials subjected to milling in an effort to better understand the crystal integrity during drug development. The work of Feng et al. (2008) started to study in more detail the consequences of milling, the strategy was to compare thermal analyses of cryomilled vs. quench-melt griseofulvin, both samples gave XRPD pattern typical of amorphous. However, DSC thermograms of the milled crystalline sample, exhibited unusual bimodal exothermal peaks without a glass transition, whereas the T_g was obvious for the quench-melt sample. Yonemochi et al. (1999a) reported that milled ursodeoxycholic acid crystallized faster than the melt-quenched material over ethanol–water vapor environment where the milled sample might retain the local structure similar to the crystalline form whereas the molecular structures in quenched sample were distributed more randomly than that in the milled form. Descamps et al. (2007) stated that physical transformation or crystallization often occur at room temperature during grinding.

The rational, for choosing the compounds and experimental conditions in the study presented herein, was based on previous literature reports. Thus, the objective of this study was to investigate the effect of cryomilling on the thermal behavior using ursodeoxycholic acid and various similar bile acids derivatives. Cryomilling was chosen to avoid reaching high temperatures, thus it is reasonable to assume that any changes in the sample are attributed only to mechanical activation. It was hypothesized that after milling all compounds become mechanically activated but some store the energy prior to trigger amorphization. Hence, in this study, 'disorder' will be used for any state showing a halo pattern on its X-ray diffractogram, while amorphous will refer to a specific state exhibiting an XRPD halo pattern with the presence of glass transition on the DSC.

2. Materials and methods

2.1. Materials

The bile acids used in this study are displayed in Fig. 1. These compounds have in the chemical structure the same framework with changing functional groups. These are crystalline materials and used as received: dehydrocholic acid ("DEH" β-form, TCI America, Portland, OR, USA), lithocholic acid ("LIT", TCI America, Portland, OR, USA), cholic acid ("CHO", Sigma, St. Louis, MO, USA) and deoxycholic acid ("DEO", Spectrum, Gardena, CA, USA), ursodeoxycholic acid ("URS", generously supplied by Mitsubishi Tanabe Pharma Co., Osaka, Japan). The crystalline form of chenodeoxycholic acid ("CHE", Sigma, St. Louis, MO, USA) was metastable form (III) (Oguchi et al., 2003), the sample was heated at 140 °C for 1 h under dry nitrogen atmosphere, to obtain the most stable form (I). All samples were stored at 25 °C over desiccant prior to use. Glassy materials only for two compounds out of the six were chosen, these were prepared by quench melt procedure followed by cryomilling and were analyzed under similar conditions as the cryomilled crystalline counterparts.



	abbreviation	R_1	R_2	R_3
dehydrocholic acid	DEH	= O	= O	= O
ursodeoxycholic acid	URS	— H	··· OH	— OH
cholic acid	CHO	··· OH	··· OH	··· OH
lithocholic acid	LIT	— H	··· OH	— H
deoxycholic acid	DEO	··· OH	··· OH	— H
chenodeoxycholic acid	CHE	— H	··· OH	··· OH

Fig. 1. Structures and abbreviations of bile acids used in this study. All compounds have the same cholesterol scaffolds, but the functional groups in R_{1-3} positions are different.

2.2. Methods

2.2.1. Cryomilling procedure

Cryomilling was performed by using the reported method (Feng et al., 2008) with a cryogenic impact grinder (SPEX CertiPrep 6750, Metuchen, NJ, USA). Briefly, for the preparation of the processed materials, 1 g of crystalline cholic acids were ground with milling rate 10 (corresponding to 20 impacts/s) under liquid nitrogen temperature for 30 min. The samples were ground at different lengths of time, and immediately analyzed by XRPD and DSC.

For the assessment of the effect of milling time on recrystallization upon DSC analysis, 1 g of URS and DEO were cryomilled with milling rate 10 for 10, 30, 60 and 120 min for URS and 10, 30 and 60 min for DEO. A half gram of glassy URS and DEO was also milled with milling rate of 10; URS milling times were 10, 30 and 60 min and whereas for DEO were 10 and 30 min. Milled samples were collected in a glove box at room temperature under dry nitrogen atmosphere and stored over P_2O_5 at −20 °C. Samples were allowed to reach room temperature prior analysis.

2.2.2. Preparation of melt-quenched bile acids

Glassy bile acids were prepared by the melt-quench method reported by Feng et al. (2008). The crystalline sample was melted on a hot plate at a temperature about 10 °C higher than melting temperature and immediately submerged in liquid nitrogen. The resulting sample was collected and gently pulverized with a spatula to avoid excess mechanical stress and then stored over P_2O_5 at −20 °C. Samples were allowed to reach room temperature prior analysis.

2.2.3. X-ray powder diffraction (XRPD)

XRPD was measured by using Shimadzu XRD-6000 (Kyoto, Japan) X-ray powder diffractometer with Cu Kα radiation at 40 kV and 30 mA. The sample was scanned in steps of 0.04° (2θ/s) from 4 to 40° (2θ) with a silicon holder. A silicon standard was used to check the alignment of the instrument before carrying out all measurements of the milled substrate.

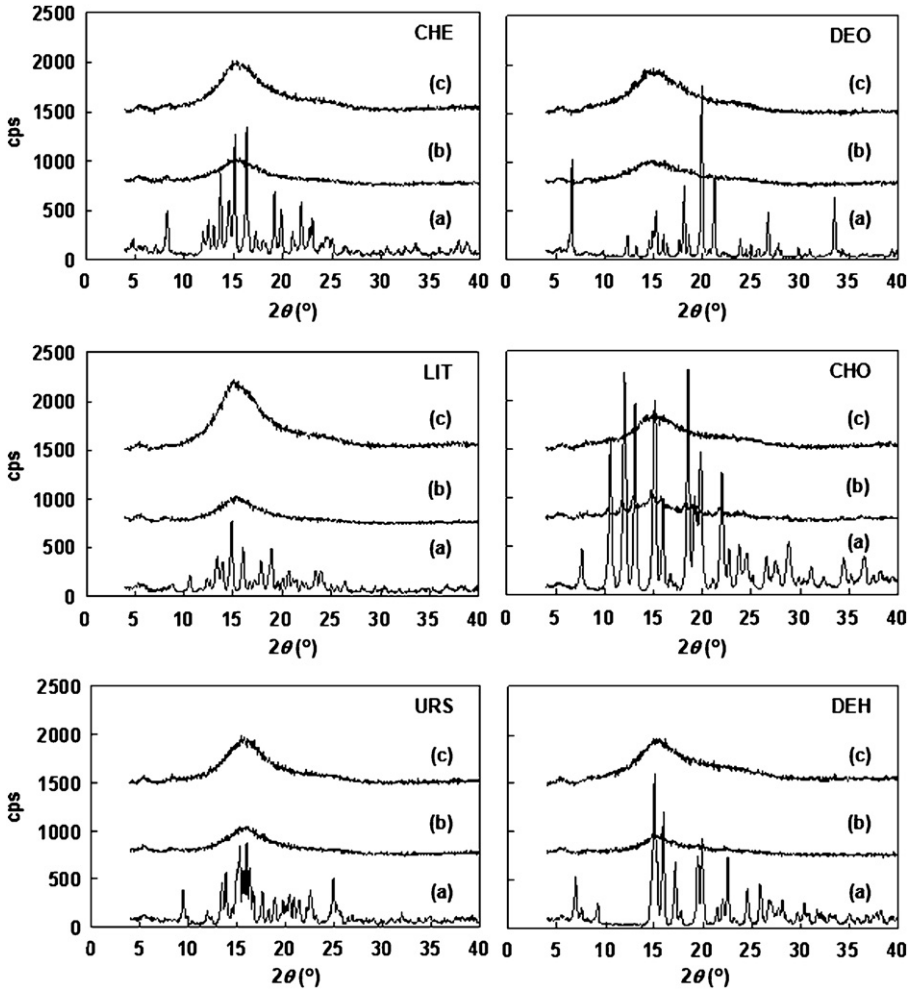


Fig. 2. XRPD patterns of bile acid samples: (a) crystalline, (b) cryomilled, and (c) melt-quenched, respectively.

2.2.4. Differential scanning calorimetry (DSC)

Thermal analysis was done with a Q10 DSC (TA Instruments, New Castle, DE, USA) in sealed aluminum pans. Dry nitrogen gas was used to purge the system at a constant flow rate of 50 mL/min. About 5 mg sample was scanned with a heating rate of 10 °C/min for a single scan experiment. Temperature ranges for each sample were DEH: 0–260 °C, URS: 0–220 °C, CHO: 0–220 °C, LIT: 0–210 °C, DEO: 0–200 °C and CHE: 0–190 °C, respectively. The crystallinity of the milled samples was calculated using the heat of crystallization and heat of fusion. The thermal properties and degree of crystallinity were reported as mean values with their respective standard deviation. All measurements were performed in triplicate.

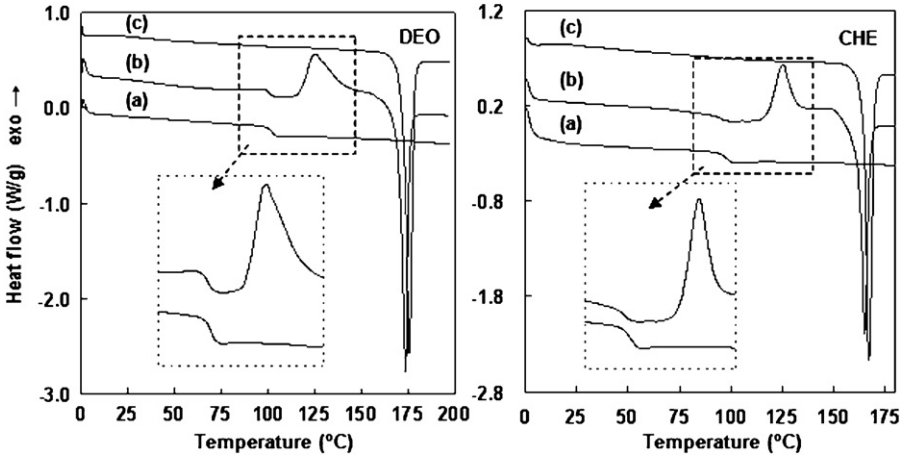


Fig. 3. DSC thermograms of cryomilled crystalline bile acids, milled samples of DEO and CHE. These compounds showed unimodal (crystallization) peaks with glass transitions. Compound abbreviations are on the right upper corner of each thermograms: (a) melt-quenched, (b) cryomilled, and (c) crystalline, respectively.

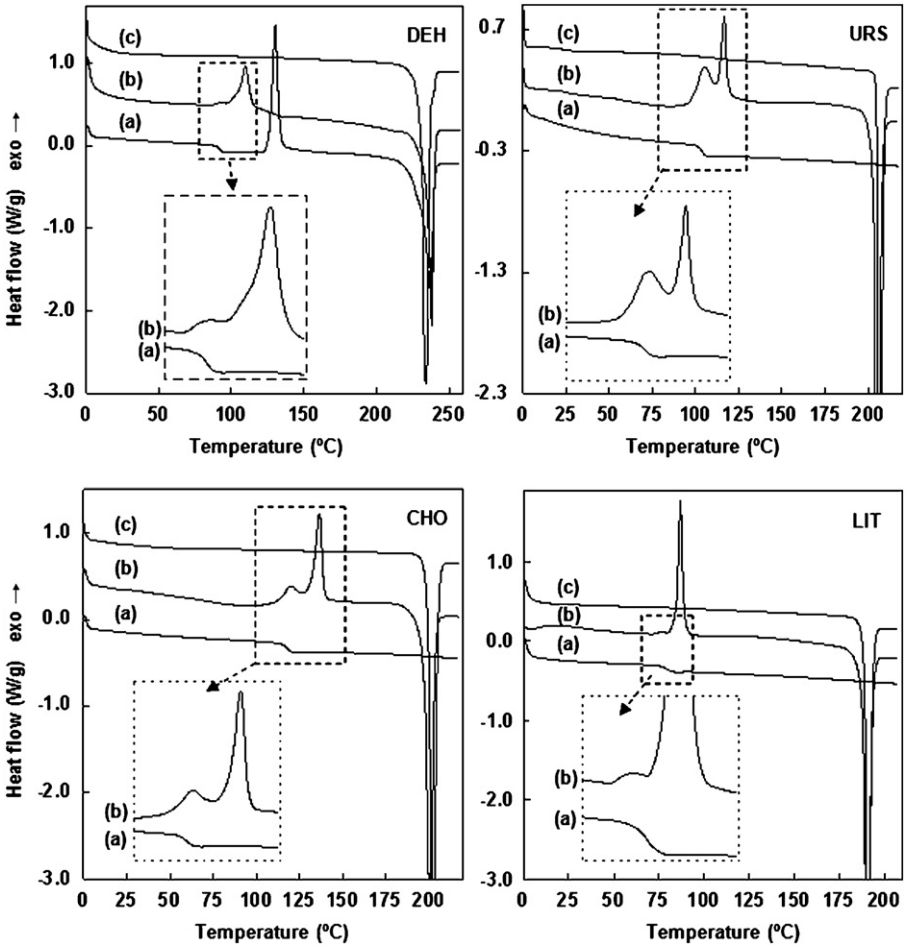


Fig. 4. DSC thermograms of cryomilled crystalline bile acids, milled samples of DEH, URS, CHO and LIT samples. Compound abbreviations are on the right upper corner of each thermograms: (a) melt-quenched, (b) cryomilled, and (c) crystalline, respectively. These compounds showed bimodal peaks around the glass transition temperatures of the melt-quenched counterparts.

3. Results

3.1. Cryomilled crystalline bile acids

All crystalline samples prior milling displayed sharp X-ray diffraction peaks, whereas all compounds after cryomilling gave the typical XRPD halo patterns associated with amorphous samples (Fig. 2).

The DSC thermograms of the crystalline, 30-min cryomilled and melt-quenched bile acid are displayed in Figs. 3 and 4. Two of the milled crystalline compounds (CHE and DEO) exhibited glass transition followed by unimodal exothermal peak attributed to crystallization (Fig. 3); while four of the milled crystalline compounds (LIT, CHO, URS and DEH) exhibited bimodal exothermal peaks without apparent glass transition (Fig. 4). The thermal properties of the melt-quenched, cryomilled and crystalline samples were compiled and listed in Table 1. The results in Table 1 showed that the exothermal events (unimodal or bimodal) were related to the melting temperature (T_m) or the heat of fusion (ΔH_f) but not to the glass transition temperature (T_g). The relationship observed was that the unimodal exothermal peak was accompanied with low T_m and the bimodal exothermal peaks with high melting compounds. Additionally, glass transition is apparent in the unimodal but not on the bimodal under the experimental conditions used in this study. It is interesting to note that although each crystalline compound was subjected to the same mechanical stress during milling, the resulting substrate acquired different loss of crystallinity.

For more detailed characterization, URS was chosen as a model compound for those compounds who display exothermal bimodal peak on the DSC after milling. Similarly DEO was selected for those compounds that show unimodal DSC peak followed by the glass transition. The results for both compounds are discussed in the following sections.

3.2. Effect of milling time on the thermal behavior of milled crystalline URS and DEO

Fig. 5 shows the resulting thermal behavior of URS after 10, 30, 60 and 120 min of milling time. As the milling time progressed, unusual peaks were observed on the DSC thermograms for 10, 30 and 60 min (b)–(d), whereas after milling for 120 min only one peak appeared preceded by glass transition at around 100 °C (e).

Milled crystalline DEO showed glass transition followed by the crystallization peak, typical of an amorphous material (Fig. 6). The milled samples showed glass transition temperature followed by exothermal peaks due to crystallization after milling for 10, 30 and 60 min. However, the calculated crystallinity seems to indicate that about 40% is still present even after milling for 60 min. Due to the presence of T_g at 10 min after milling, it was decided to check a shorter milling time to assess at what point in time of milling the T_g starts appearing. Thus, crystalline DEO was milled for 4 min and analyzed by DSC. The thermogram did not shows neither T_g nor

Table 1
Thermal properties of melt-quench, cryo-milled and crystalline cholic acids.

	Melt-quenched	Cryomilled					Intact (crystalline)	
	T_g (°C)	Exothermal peak				Crystallinity (%)	T_m (°C)	ΔH_f (J/g)
		On-set (°C)	Top (°C)	ΔH_c (J/g)	Peak shape			
DEH	90.60 ± 0.79	85.08 ± 1.37	107.59 ± 1.80	27.29 ± 2.44	Bimodal	36	231.31 ± 0.22	115.5 ± 3.59
URS	104.02 ± 0.29	93.46 ± 2.11	117.25 ± 0.46	40.77 ± 1.54	Bimodal	51	204.11 ± 0.97	95.40 ± 1.54
CHO	118.55 ± 0.44	110.10 ± 0.93	136.55 ± 0.08	42.15 ± 0.74	Bimodal	53	200.17 ± 0.13	1145 ± 3.52
LIT	78.92 ± 26.1	71.51 ± 1.16	87.90 ± 1.20	34.85 ± 0.55	Bimodal	69	189.52 ± 0.04	110.0 ± 2.91
DEO	102.24 ± 0.85	109.65 ± 2.09	125.54 ± 1.75	32.59 ± 1.74	Unimodal	46	172.73 ± 0.44	81.71 ± 2.19
CHE	98.65 ± 1.51	110.75 ± 2.74	124.55 ± 0.52	26.40 ± 0.11	Unimodal	49	165.22 ± 0.38	65.53 ± 1.40

exothermal peak. Hence, a 10-min milling time was necessary to start affecting the crystal.

3.3. Effect of milling time on the thermal behavior of milled melt-quenched URS and DEO

The glassy DEO was cryomilled for 10 and 30 min and examined under the DSC. The thermal differences among the three different melt-quenched samples are displayed in Fig. 6. All three thermograms indicated that milling the molten sample (amorphous) were practically the same and independent of the milling time in which they were subjected.

The effect of mechanical stress on the melt-quenched sample was assessed by subjecting the glassy URS to cryomilling and analyzed by DSC (Fig. 7). The vitrified URS showed the glass transition at around 115 °C (a). After the glassy URS was milled for 10 min, a small hump appeared around 100 °C just around the same range of temperature as the glass transition (b), but neither the hump nor the glass transition was clearly observed after milling for 30 min (c). Interestingly, after milling for 60 min, the hump and the glass transition emerged again with a slight temperature shift (d).

4. Discussion

A trend was observed when milling the series of compounds with common framework and changing functional groups in the structure. A classification was assigned for the bile acids compounds based on the crystallization behavior observed on the DSC after milling. The data showed that T_m or ΔH_f are likely to correlate with the findings and the T_g is the consequence rather than the factor. Thermodynamic parameters, T_m or ΔH_f, are dominated by the

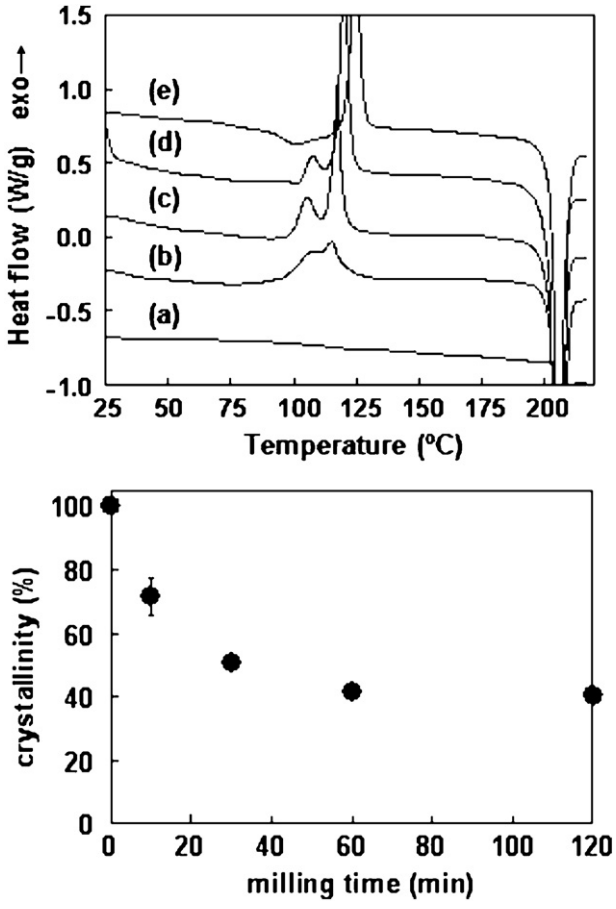


Fig. 5. (Top) DSC thermograms of cryomilled crystalline URSs. Crystalline material was milled for 0 min (a), 10 min (b), 30 min (c), 60 min (d) and 120 min (e), respectively. Curves (b)–(d) showed bimodal peaks without glass transitions, whereas curve (e) exhibited unimodal peak accompanied by glass transition. (Bottom) Milling time vs. crystallinity.

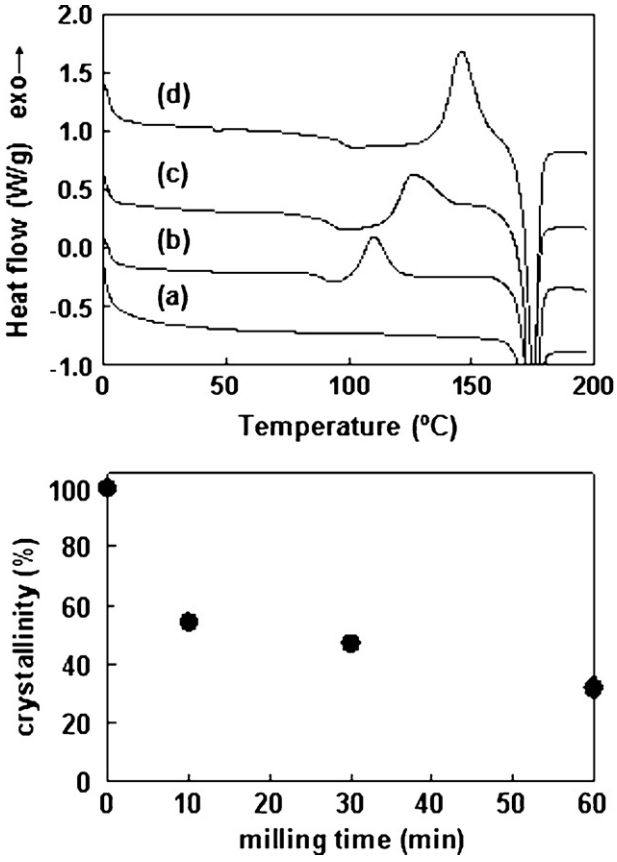


Fig. 6. (Top) DSC thermograms of cryomilled crystalline DEOs. Crystalline material was milled for 0 min (a), 10 min (b), 30 min (c) and 60 min (d), respectively. Curves (b)–(d) showed unimodal peaks with glass transitions. (Bottom) Milling time vs. crystallinity.

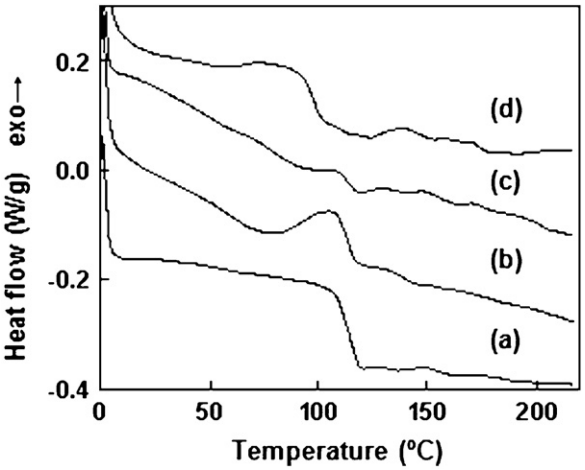


Fig. 7. DSC thermograms of cryomilled glass URSs. Melt-quenched material was milled for 0 min (a), 10 min (b), 30 min (c) and 60 min (d), respectively. Curve features vary according to the milling times.

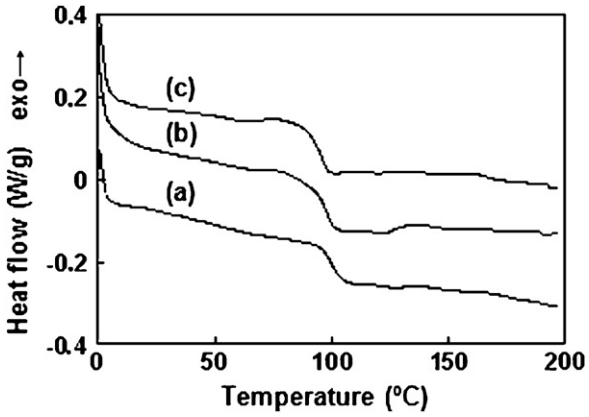


Fig. 8. DSC thermograms of cryomilled glass DEOs. About 0.5 g of melt-quenched material was milled for 0 min (a), 10 min (b) and 30 min (c), respectively.

existing interactions in the molecule. Looking at the interactions of the molecule, the crystal properties of bile acids are dominated mainly by hydrogen bonding network between carboxyl, oxo and hydroxyl groups (Bertolasi et al., 2005). Thus, strong interactions among molecules may affect not only the values, but also thermal behavior of milled samples upon heating since H-bonds are very sensitive to temperature. The findings suggest that in our systems strong interactions between molecules in the crystal resist deformation by mechanical stress. This actually was reported by Finnie et al. (2001) where crystal resists deformation to leave partial structures. As a matter of fact, it has been reported that the molecules with intermolecular hydrogen bonding showed smaller difference in heat capacities (C_p) between the glassy and crystalline states than those without hydrogen bonding (Yamamuro et al., 1997). Further, hyper-quenched amorphous samples released excess energies upon heating so that the C_ps of them are apparently smaller than the C_p of standard amorphous sample (Yue, 2004). Hence, clearly, interactions, once again, affect T_m or ΔH_f. Therefore, from the structural point of view, the ability of intermolecular interaction might contribute to energy state of URS after severe milling. Although the crystal structure of URS is reported (Higuchi et al., 1985), the counterpart of DEO is not available. Therefore, we cannot directly compare the structures between them but still a reasonable conjecture can be made.

The phenomenon of mechanical activation of milled materials is poorly understood and one can offer a hypothesis, or speculate based on experimental limited observations. In the mean time, numerical approaches have started to take place to elucidate the mechanisms that drive phase transitions. Lei and Koslowski (2011) developed a model based on phase field dislocation dynamics (PFDD) to simulate plastic deformation in molecular crystals as they undergo deformation. The PFDD model includes the energy barrier that molecules in the dislocation regions experience as they travel in their slip planes and the effect of an external stress. The strain energy due to the presence of dislocations is calculated and then compared to the energy needed for the nucleation and growth of amorphous material. Experimentally, it is widely acceptable (hypothesized) that physical instability of amorphous phase depends on both mobility and nucleation of residual seed crystals (Yonemochi et al., 1999b; Oguchi et al., 2003). In the current work, we attempt to explain the behavior of URS by previous findings and by our own inference based on the experimental observations. Fig. 5 shows the existence of bimodal peaks, these could be attributed to residual seed crystals that may induce crystallization at low temperatures around the T_g (not observed because overlaps with the bimodal peaks) when the compound is milled for the first 60 min of milling time; when milling longer (~120 min) the crystalline URS gives up leading to amorphization, this is evident with the appearance of the glass transition followed by crystallization. Another explanation for URS characteristic behavior is that, molecular crystals are subjected to mechanical milling, suffering large stresses during this process that after producing fracture, some compounds may develop a supersaturated dislocation (still crystalline) regime (no T_g observed), an extensive plastic deformation and finally amorphization (T_g). For the cryomilled crystalline DEO, the material did not develop dislocation but rather amorphization at milling time as short as 10 min (Fig. 6); DEO has similar almost immediate amorphization as indomethacin (Bhugra et al., 2008; Crowley and Zografi, 2002).

A further insight to account for the mechanism of mechanical stress and how it affects the thermal properties of ground material is related to the dislocation density concentration which is considered to account for the energy stored as dislocations (Tromans and Meech, 2001). It is speculated that URS accumulates energy in the disordered phase, such that the activated domain at the beginning could be supersaturated with dislocations (10, 30 and 60 min) and after further application of stress, the mechanically activated materials reach a critical concentration of dislocations that triggers amorphization (120 min, as explained above). Thus, in the case of URS, potential two mechanisms occurred, one dislocation concentration followed by amorphization. It is not discarded other mechanisms such as dealing with only unstable amorphous form that crystallized by intimate contact with the residual seed crystals at lower temperature than the temperature where a fully amorphous region crystallizes. Bhugra et al. (2008) reported that milling may allow transformations either from the crystalline form to an amorphous counterpart or a totally different crystalline form; additionally, thermal properties of the disordered phase may also be affected by mechanical stress. This mechanical stress generates levels of energy states for instance, adiabatic calorimetric experiments on ground tri-O-methyl-β-cyclodextrin demonstrated that a much larger configurational enthalpy is attained than the molten version (Tsukushi et al., 1994). In addition, the mobility of mechanically activated region is high enough to induce a rapid nucleation below T_g, bimodal crystallization may occur (Qi et al., 2010; Shakhtshneider et al., 2007). Zhu et al. (2008) showed that the crystal growth of amorphous nifedipine at the surface was much faster than the bulk counterpart phase due to the higher mobility. It is assumed that the energy state of the disordered phase may not be homogeneous in the milled samples. The heterogeneity of molecular mobility is widely recognized in polymer science

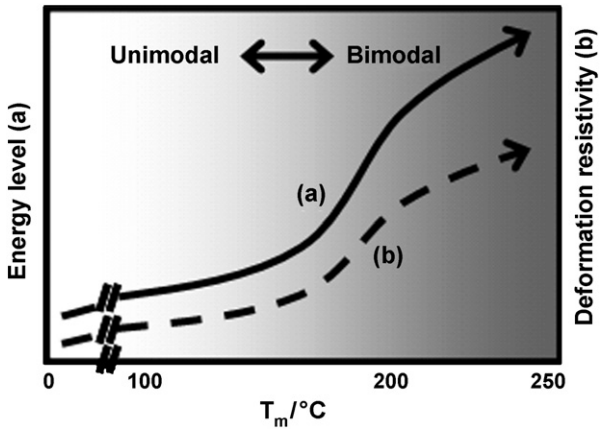


Fig. 9. Competing structure-response regime map of bile acids: (a) mechanochemical activation and (b) resistance against crystal deformation. Both factors rise with increasing T_m to show bimodal DSC peaks for cryomilled bile acids.

(Suzuki et al., 1985). Another explanation to the thermal response is given by the mobility of the disordered phase in the milled URS which can be heterogeneous with regards to the difference in energy state induced by mechanical stress. This mechanical stress has been reported to produce a defective state for cryo-milling crystalline griseofulvin (Feng et al., 2008; Chamarthy and Pinal, 2008), metastable state after cryo-milling crystalline griseofulvin (Otte and Carvajal, 2011) and fast surface crystallization of amorphous griseofulvin (Zhu et al., 2010). In contrast, the behavior of milled crystalline DEO displayed a standard T_g followed by recrystallization as depicted the DSC thermograms (Fig. 6); additionally, the thermal response of glassy DEO was not affected by milling (Fig. 8).

5. Conclusions

Cryomilling produced various extents of disorder in all crystalline bile acids. Two categories were proposed with respect to the presence of the exothermal peak (s) upon analysis by the DSC. The unimodal/bimodal exothermal events in this study were correlated to T_m or ΔH_f, since molecular interactions define these parameters, compounds with similar properties and behavior to URS may have the potential to accumulate and maintain more energy than those compounds similar to DEO.

A schematic representation on the structure-response to milling regime considers the ability of (a) mechanical activation and (b) resistance against plastic deformation by mechanical stress, as shown in Fig. 9, both events increased as the T_m increased. It is considered that specific molecular interactions such as hydrogen bonding or dipole interaction are affected over mechanical shear and in turn, the residual local structures or the energy state of disordered phase. The results seemed to suggest that the level of disorder depended on the initial physico-chemical properties of materials. This work offers an interpretation on the way the disorder was produced, suggesting dislocation density or disorder population in certain regions that eventually arrived to amorphous. The possibility of amorphous (not dislocations) that recrystallizes is presented as well. It is reasonable to recount that various possible rationale may describe the phenomenon, either residual crystal, defects, metastable state and interactions at the surface, followed by bulk activity. All might have a significant influence on the crystallization behavior of milled samples in order to stabilize these highly mechanically generated-energetic materials. It is evident that the phenomenon occurs in many pharmaceutical compounds and the selection of potential mechanism (s) has to be in the context of those factors that trigger the behavior. In this respect, the phenomenon hence the mechanism, especially close to the real or potential detectable or not T_g needs additional study.

Acknowledgements

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