Contributions of mechanical stress on the "frustrated" thermal response of griseofulvin

During milling, changes in material properties are mainly induced by the degree and extent of exposure to mechanical stress, which affects thermal response and stability of materials

Takanori Ito and M. Teresa Carvajal
Department of Industrial and Physical Pharmacy and Department of Agricultural and Biological Engineering, Purdue University

Introduction

Milling is a common process for particle size reduction of pharmaceutical powders. The overall purpose of this unit operation is to improve dissolution rate[1] or formulate dry powder inhalers (DPI).[2] The milling performance can vary according to the operating conditions[3] of the equipment or the physico-chemical properties[4] of the material. The dynamics of the milling equipment is complicated,[5] it is actually difficult to control the real energy or mechanical stress imposed on the samples during comminution.

The milling process and exposure time may give unfavorable effects to the physico-chemical properties of the active pharmaceutical ingredient (API), such as creation of defects,[6] amorphization,[7] polymorph transformation[8] or chemical stability reduction.[9] In particular, amorphization by milling has been a problem for drug development.[10-13] The generation of amorphous regions changes the physico-chemical properties and stability of APIs. Therefore, it is important to find suitable milling operation conditions for each compound.

For laboratory research purposes, cryogenic milling (cryomilling) has been widely used as a practical and common sample preparation technique in pharmaceutical research, as well as in polymer studies, food analysis and material sciences. Cryogenic conditions involve placing the samples in liquid nitrogen. This has two important effects on sample preparation: 1) it embrittles materials such that they can be pulverized by impact milling and, 2) it prevents temperature increases that may lead to chemical degradation and polymorphic transformation or production of amorphous materials, which often occurs during grinding at room temperature.[12,14]

The objective of this study was to probe various cryomilling conditions that may affect the thermal properties (shape of the exothermal peaks) of the milled powder. For this purpose, in an attempt to assess cryomilling efficiency in a qualitative manner, analysis of exothermal peaks was carried out at different operating variables, such as the sample load (volume), milling time, impact stress, rate and extent (number).

Materials and methods

Crystalline griseofulvin (GSV) was purchased from Hawkins (Minneapolis, MN) stored at 25 °C over desiccant prior to use.

Cryogenic milling of griseofulvin

The milled material was obtained by a cryogenic impact grinder (SPEX CertiPrep 6750, SamplePrep LLC, Metuchen, NJ) using a method previously reported.[13] The impactor mill was composed of a magnetic coil, sample tube and steel impactor rod. The mill process sequence alternated milling and post-cooling intervals. The operation variables were the sample load, milling time, impact rate, momentum and number; these are described in the next section. Milled samples were collected in a glove box under dry nitrogen atmosphere and stored over phosphorus pentoxide (P_2O_5) at -20 °C.

Differential scanning calorimetry (DSC)

Thermal analysis was done with a Q10 differential scanning calorimeter (DSC) (TA Instruments, New Castle, DE) using sealed aluminum pans. About 5 mg of sam-

ple was scanned from -20 °C to 240 °C with a heating rate of 10 °C/min for a single scan experiment.

Results

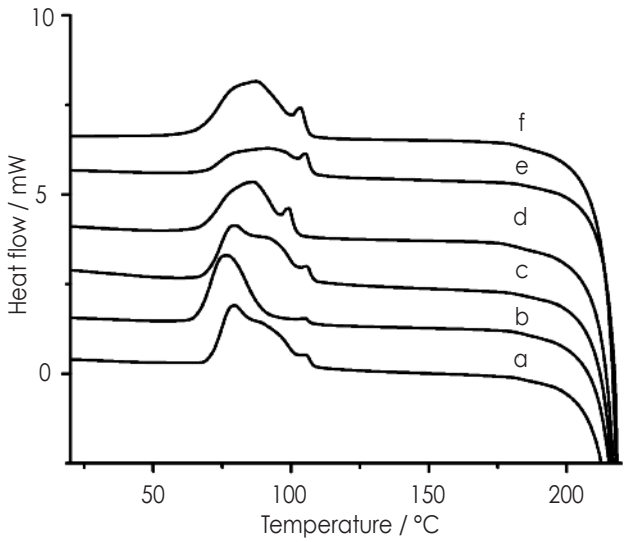
Griseofulvin (GSV) was chosen as a model drug because it is a stable compound that does not have polymorphs, or undergo amorphization, and is chemically stable upon the process of milling at the working conditions of temperature and pressure.

The effect of sample volume and powder position

It was observed that during or after cryomilling, some powder samples agglomerated in the sample tubes. This could be attributed to the heterogeneity of milling. Therefore, after milling, the samples (0.5 g or 1 g) were collected according to the position in which they ended up in the tube and they were separated into three parts: middle, right or left side of the tube, followed by DSC analysis. Figure 1 shows the thermograms for the two sample loads (0.5 and 1.0 g) with the corresponding position (right, middle and left). Overall, sample size seems to have some effect on the outcome of the thermogram peaks and slight effect on the position.

Figure 1

DSC thermograms for cryomilled crystalline griseofulvin samples: impact rate of 10, total milling time 10 min, sample volume either 0.5 or 1 g and sample position in the milling tube (right, left or middle). For 1 g sample: (a) right side, (b) middle, (c) left side; for sample volume: 0.5 g, (d) right side, (e) middle, (f) left side.

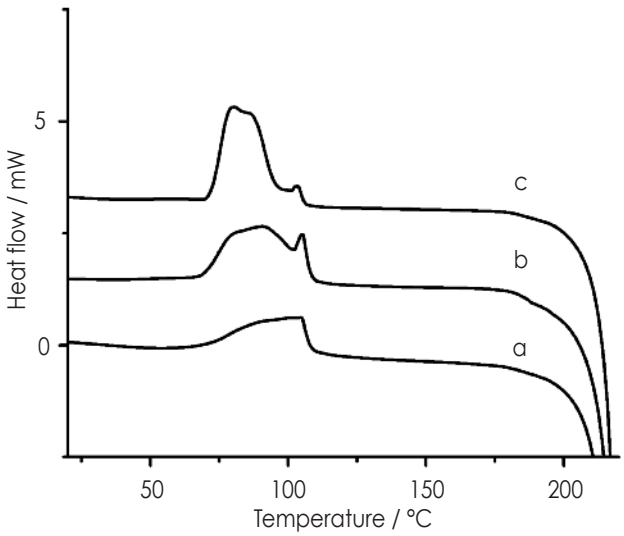


The effect of total milling time

About 0.5 g of crystalline GSV was milled at different times with a milling rate of 10 (i.e., an impact rate or IR of 10). This was calculated to correspond to 20 impacts per second. Figure 2 shows that exothermal peaks appeared between 80-100 °C and the peak shape and height changed with milling time. Therefore, Figure 2a shows a broad peak after milling for 4 minutes. After milling for 10 minutes, a split occurs having a sharp peak at a higher temperature (Figure 2b). For the 30 minute milling time, the peaks seemed to be better resolved (Figure 2c). It can be observed that the peaks gradually shifted from high temperature to lower temperature along the lines of expansion of milling time.

Figure 2

DSC thermograms for cryomilled crystalline griseofulvin samples: sample volume 0.5 g, impact rate: 10 and various milling times: (a) 4 min, (b) 10 min, (c) 30 min.



The effect of impact energy (mechanical stress)

The effect of mechanical stress was assessed and the following parameters were considered. The 'impact rate (R)' is defined as the half number of impaction per second. Therefore, the total number of impacts (N) during the total milling operation time (T) can be described as follows:

$$N = 2RT \qquad \text{(Equation 1)}$$

Assuming that the impactor continuously moves at the same speed (without a break or lag time) and according to the impact rate in a sample tube during milling, the impactor speed (V) can be written as follows:

$$V = 2LR \qquad \text{(Equation 2)}$$

where L corresponds to the total length the impactor can move per collision. Thus, the total energy (E) given to the sample by the impactor during the milling operation can be calculated by considering equations (1) and (2) and the impactor weight (M) as follows:

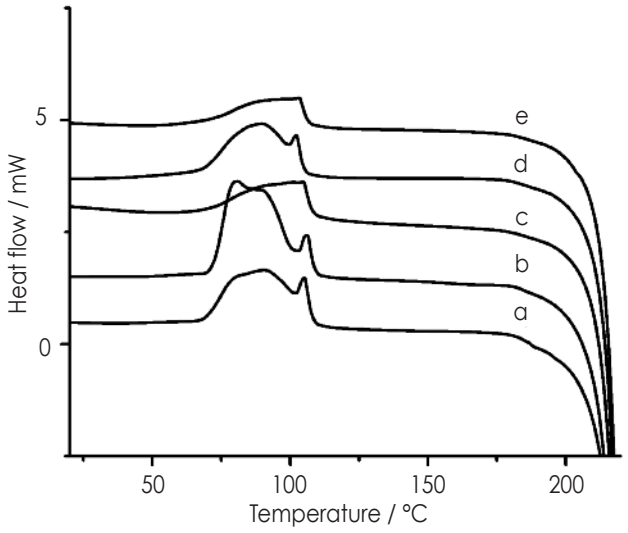
(Equation 3)

$$E = \frac{MV^2}{2} \times N = \frac{M(2LR)^2}{2} \times 2RT = 4L^2MR^3T$$

Because M and L are constants, the total impaction energy can be determined by R^3T. Figure 3 shows the DSC thermograms of cryomilled crystalline griseofulvin corresponding to a 0.5 g sample (volume) with varying impact rate and milling time. Thereby, different average energies could be calculated from equation 3. The relative total energy (RTE) of impaction is based on the energy added to the sample. The different peak scenarios in Figure 3 and RTE values could be interpreted and categorized in three groups: i) sample a with RTE = 1; ii) sample b and c in which the RTE is ~ 0.5 and 0.4, respectively; and iii) samples d and e which have an RTE of 0.7 and 0.74, respectively. Clearly, the RTE impaction energies gained during milling are not homogeneous. The result suggests that the total impaction energy (mechanical stress) may not be the main or only factor that determines the shape of exothermal peaks for this compound. The time of exposure also may be a factor.

Figure 3

DSC thermograms for cryomilled crystalline griseofulvin material for a sample volume of 0.5 g at various impact rate (IR), milling time and with respective relative total energy (RTE) of impaction. Figure: (a) IR = 10, total milling time: 10 min, RTE = 1; (b) IR = 5, total milling time: 40 min, RTE = 0.5; (c) IR = 10, total milling time: 4 min, RTE = 0.4; (d) IR = 10, total milling time: 7 min, RTE = 0.7; (e) IR = 15, total milling time: 2.2 min, RTE = 0.74.



The effect of impact momentum

Newtonian mechanics is an approach that could be used to inspect the relationship between impaction momentum and peak shape on DSC thermograms for griseofulvin.

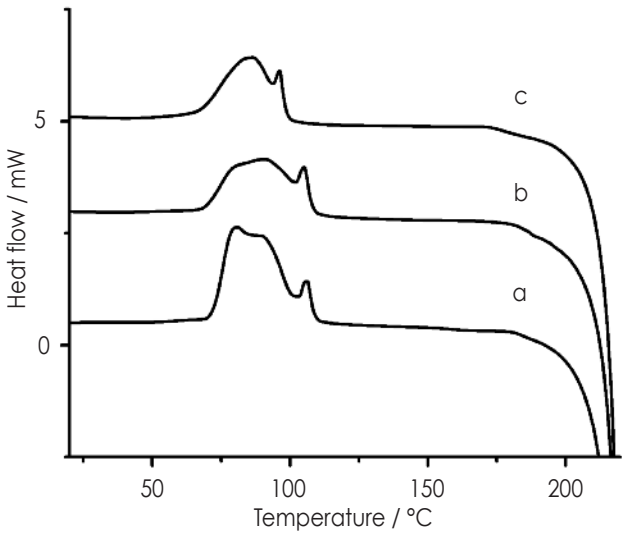
Total momentum (P) given by the impaction is described by equations (1) and (2) above, therefore P is given by:

$$P = MVN = 4LMR^2 \quad \text{(Equation 4)}$$

Figure 4 displays the milled samples of a, b and c. These have the same value for total momentum calculated by equation 4, in spite of the different impact rates and milling times. It is clear that all three thermograms (a, b and c) show bimodal exothermal events on DSC with peak shapes differing slightly. Therefore, the total momentum does not appear to be the solely determinative factor for the peak shape on the DSC thermogram for griseofulvin.

Figure 4

DSC thermograms of cryomilled crystalline griseofulvin material where the same total momentum was imposed on the samples (a, b and c) under each milling condition presented for a sample volume of 0.5 g. Line (a) IR = 5, total milling time: 40 min, (b) IR =10, total milling time: 10 min, (c) IR = 15, total milling time: 4.4 min.



The effect of total impact extent (number)

The DSC thermograms are similarly-shaped peaks for milled GSV with different impact rate and milling time, with similar number of impactions (IN), i.e. 12,000. These results suggest that the impaction number defines the shape of the peak of the milled material. In other words, this indicates that the impaction energy provided by the cryomill relies mainly on the impaction number or impaction extent, rather than the impact rate in a case when constant sample volume (size) is used.

Discussion

Figure 1 shows that the sample volume had an effect on both product nature and powder position. It has been

reported that sample load affects particle size reduction upon milling.[15] Although information about particle size distribution corresponding to the sampling point in the sample tube is not available, mechanical stress seems to be not homogeneous in the mill since the nature of milled griseofulvin depends on mechanical energy given during milling. The homogeneity of product may also depend on the powder movement in the mill, which is influenced by the sample volume. Tao et al. reported that cryomilling technique improved uniformity for the preparation of API-polymer mixtures.[16] However, experimenters should still consider suitable sample volume and milling time when using cryomilling and dealing with uniformity. Moreover, impaction and friction usually contribute to the reduction of particle size. In this study, it is suggested that the grinding mode of this particular mill influences the particle properties of milled griseofulvin. Although the impaction seems to do the job of reducing particle size, it does it in a non-homogeneous manner. When Krycer and Hersey compared the comminution efficiency of rotary and vibratory ball mills, it was found that agglomeration occurred in the rotary ball mill due to consolidation and high stress relaxation induced by its tumbling motion.[17]

Figure 2 shows the maximum peak height gradually shifted from high temperature to lower temperature and the entire peak shape varied along the lines of milling time. During the operation that generated the data in Figure 2, all conditions were consistent except for the milling time, indicating that GSV is a good qualitative indicator of milling efficacy because of its sensitivity to mechanical stress.

In Figures 3 and 4, the shape of the exothermal peaks on DSC thermograms showed no tendencies corresponding to the total impact energy[18] and momentum[19] imparted to the powder sample during milling. Consequently, no relationship between shape and energy/momentum could be recognized. It has been reported that is not possible to correlate milling operation conditions and physico-chemical properties of the ground product,[20-23] because temperature may increase in ground samples and only a fraction of the mechanical stress can be consumed by powder samples to achieve physico-chemical transformation during milling.[18] Yet notoriously, material physical changes occur after mechanical stress and are a function of the starting materials' properties and type of mill used. In the experimental design used here, it appears that only the total impact number is related to the DSC peak shape of the milled product. This may suggest that the impactor constantly hits the powder samples at the same velocity regardless of the impaction frequency numbers (impact rate). Although the movement mechanism of impaction is not known, it can be assumed that the impact energy and movement per single impaction are always the same, in spite of operation conditions, if the sample volume is constant. Thus, the total mechanical stress during milling might be proportional to the total number of impactions.

Conclusions

Cryomilling output was studied by relating operating conditions to exothermal peak shapes of milled GSV on DSC thermograms. Both the estimated impact energy and momentum did not show a relationship with the peak shapes. Only the total impaction numbers had a direct correlation with the thermal properties of the ground product. This suggests that the impactor always hits the powder samples at the same speed, such that the total mechanical stress given to samples during milling might be influenced only by total number of impactions. These findings are relevant and significant enough to bring to the attention of the milling community. This means that, even if the milling conditions seem to be constant, changes in the sample may occur. Additional studies should be conducted with more compounds having different physico-chemical properties to relate them to their thermal properties and/or phase transformations. Also, perhaps in the future, milling equipment should be designed with optional parameters such that the operator/formulator controls in a stricter manner the extent, rate and force of material fracturing and exposure to stress. If milling equipment does not change configuration, detrimental issues will persist for active drugs and, if not detected in time, issues of stability and unpleasant surprises will continue.

Acknowledgements

The authors are grateful for the support of Mitsubishi Tanabe Pharma Co. in Japan and the National Science Foundation 0003064-EEC, Dane O. Kildsig Center for Pharmaceutical Processing Research (CPPR). The authors also express their thanks to Ms. Xin Chen.

References

1. Florence AT, Salole EG, Stenlake JB. (1974). The effect of particle size reduction on digoxin crystal properties. J Pharm Pharmacol 26:479-480.

2. Saleem I, Smyth H. (2008). Prediction of dry powder inhaler formulation performance from surface energetics and blending dynamics. Drug Dev Ind Pharm 34(9):1002-1010.

3. Midoux N, Hošek P, Pailleres L, Authelin JR. (1999). Micronization of pharmaceutical substances in a spiral jet mill. Powder Technol 104(2):113-120.

4. Zügner S, Marquardt K, Zimmermann I. (2006). Influence of nanomechanical crystal properties on the comminution process of particulate solids in spiral jet mills. Eur J Pharm Biopharm 62(2):194-201.

5. McMillan J, Briens C, Berruti F, Chan E. (2007). Particle attrition mechanism with a sonic gas jet injected into a fluidized bed. Chem Eng Sci 62(14):3809-3820.

6. Feng T, Pinal R, Carvajal MT. (2008). Process induced disorder in crystalline materials: Differentiating defective crystals from the amorphous form of griseofulvin. J Pharm Sci 97(8):3207-3221.

7. Otsuka M, Kaneniwa N. (1990). Effect of grinding on the crystallinity and chemical stability in the solid state of cephalothin sodium. Int J Pharm 62(1):65-73.

8. Desprez S, Descamps M. (2006). Transformations of glassy indomethacin induced by ball-milling. J Non-Cryst Solids 352(42-49):4480-4485.

9. Graeser KA, Strachan C, Patterson JE, Gordon KC, Rades T. (2008). Physicochemical properties and stability of two differently prepared amorphous forms of simvastatin. Cryst Growth Des 8(1):128-135.

10. Suryanarayanan R, Mitchell AG. (1985). Evaluation of two concepts of crystallinity using calcium gluceptate as a model compound. Int J Pharm 24(1):1-17.

11. Crowley KJ, Zografi G. (2002). Cryogenic grinding of indomethacin polymorphs and solvates: Assessment of amorphous phase formation and amorphous phase physical stability. J Pharm Sci 9(2):492-507.

12. Descamps M, Willart JF, Dudognon E, Caron V. (2007). Transformation of pharmaceutical compounds upon milling and comilling: The role of Tg. J Pharm Sci, 96(5):1398-1407.

13. Otte, A. and Carvajal, M.T. (2011). Assessment of milling-induced disorder of two pharmaceutical compounds. J Pharm Sci 100: 1793-1804.

14. Zhou D, Zhang GGZ, Law D, Grant DJW, Schmitt EA. (2008). Thermodynamics, molecular mobility and crystallization kinetics of amorphous griseofulvin. Mol Pharm 5(6):927-936.

15. Shoji K, Austin LG, Smaila F, Brame K, Luckie PT. (1982). Further studies of ball and powder filling effects in ball milling. Powder Technol 31(1):121-126.

16. Tao J, Sun Y, Zhang GGZ, Yu L. (2009). Solubility of small-molecule crystals in polymers: D-mannitol in PVP, indomethacin in PVP/VA, and nifedipine in PVP/VA. Pharm Res 26(4):855-864.

17. Krycer I, Hersey JA. (1980). A comparative study of comminution in rotary and vibratory ball mills. Powder Technol 27(2):137-141.

18. Abdellaoui M, Gaffet E. (1996). The physics of mechanical alloying in a modified horizontal rod mill: Mathematical treatment. Acta Mater 44(2):725-734.

19. Huang J, Pan J, McCormick PG. (1997). On the dynamics of mechanical milling in a vibratory mill. Mater Sci Eng A232(1-2):55-62.

20. Buckton G, Choularton A, Beezer AE, Chatham SM. (1988). The effect of the comminution technique on the surface energy of a powder. Int J Pharm 47(1-3):121-128.

21. Hajaratwala, BR. (1982). Particle size reduction by a hammer mill I: Effect of output screen size, feed particle size and mill speed. J Pharm Sci 71(2):188-190.

22. Meier M, John E, Wiechhusen D, Wirth W, Peukert W. (2008). Characterization of the grinding behaviour in a single particle impact device: Studies on pharmaceutical powders. Eur J Pharm Sci 34(1):45-55.

23. Midoux N, Hošek P, Pailleres L, Authelin JR. (1999). Micronization of pharmaceutical substances in a spiral jet mill. Powder Technol 104(2):113-120.

Takanori Ito is with the Department of Industrial and Physical Pharmacy (IPPH) and M. Teresa Carvajal is in the Department of Agricultural and Biological Engineering and has a courtesy appointment in IPPH, Purdue University, West Lafayette, Indiana, 47907, US. Corresponding author: M. Teresa Carvajal, Tel: +1 765 496-6438, tcarvaja@purdue.edu.