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Effects of Ball-milling and Cryomilling on Sulfamerazine Polymorphs: A Quantitative Study

Pól MacFhionnghaile, Yun Hu, Katarzyna Gniado, Sinead Curran, Patrick McArdle,* Andrea Erxleben*

School of Chemistry, National University of Ireland, Galway, Ireland

ABSTRACT
The effects of ball-milling and cryomilling on sulfamerazine forms I and II (SMZ FI, FII) were investigated using X-ray powder diffraction, IR and NIR spectroscopy. Cryomilling resulted in the complete amorphization of both polymorphs. Milling at room temperature gave mixtures of amorphous SMZ (FA) and FII. Calibration models were developed for the quantitative analysis of binary (FI/FII, FI/FA and FII/FA) and ternary (FI/FII/FA) mixtures using NIR spectroscopy combined with partial least-squares (PLS) regression. The PLS models for binary (0 - 100 %), ternary (0 - 100 %) and low level (0 - 10 %) binary mixtures had root-mean-square errors of prediction of ≤1.8, ≤5.1 and ≤0.80 %, respectively. The calibration models were used to obtain a detailed quantitative picture of solid-state transformations during milling and any subsequent recrystallizations. FA prepared by cryomilling FI for less than 60 min. recrystallized to mixtures of FI and FII, while samples milled for more than 60 min. crystallized to pure FII. The effect of co-milling SMZ with stoichiometric amounts of additives was investigated. SMZ formed amorphous materials with oxalic, DL-tartaric and citric acids that were more stable towards recrystallization than FA. Amorphous SMZ/oxalic acid was found to recrystallize to a 2:1 co-crystal during storage.

Keywords: Amorphous; Near-infrared spectroscopy; X-ray powder diffractometry; Stability; Multivariate analysis
INTRODUCTION

Milling or grinding of active pharmaceutical ingredients (APIs) is an important and frequently used secondary process in the manufacturing of pharmaceuticals.\textsuperscript{1-4} During the milling process mechanical stress is utilized to reduce the particle size of a powder while concurrently creating a uniform particle size distribution. As milling is a high energy process, it can induce solid-state transitions to a different polymorph or to the amorphous phase. The effect of milling on a number of compounds has been reported. D-salicin,\textsuperscript{5} \(\gamma\)-indomethacin,\textsuperscript{5,6} famotidine,\textsuperscript{7} ranitidine hydrochloride,\textsuperscript{8} fananserine,\textsuperscript{9} and sulfathiazole,\textsuperscript{10,11} for example, undergo either polymorphic transformations or amorphization during milling. However, milling is not commonly used by the pharmaceutical industry to produce amorphous pharmaceuticals that have a solubility advantage over their crystalline counterparts.\textsuperscript{12-15} The reason for this may be challenges with scale-up and the possibility of recrystallization during the milling process. Cryomilling (cryogenic milling), the operating of a ball mill at low temperature with the aid of liquid nitrogen, represents a method that reduces the chance of recrystallization of the amorphous materials formed during the milling process. Furthermore, it is often a more efficient way to produce an amorphous API than is milling at ambient or higher temperature.\textsuperscript{6,11,16-19}

Co-processing of APIs with excipients can have significant effects on the physical stability of the crystalline or amorphous forms. API-excipient interactions can stabilize the amorphous state or suppress amorphization during milling. Mixing an API with a high \(T_g\) polymeric excipient to produce an amorphous dispersion is a well-known strategy to increase the stability of the amorphous state.\textsuperscript{20} On the other hand, co-milling of an API with stoichiometric amounts of small-molecule compounds (excipient or other API) can produce composite amorphous systems or co-crystals.\textsuperscript{21-26} The factors that determine whether a co-amorphous system or a co-crystal is formed are poorly understood.

Sulfamerazine (SMZ, Figure 1) is a widely used sulfonamide antibacterial drug. To date there are three known polymorphs.\textsuperscript{27-29} Form I and II (F1, FII) are enantiotropically related such that FII is more stable at room temperature, whereas FI is more stable at higher temperature.\textsuperscript{30,31} FIII was discovered only recently in 2006.\textsuperscript{29} Solvent-mediated transformations of SMZ polymorphs in solution have been extensively studied.\textsuperscript{32-38} The effect of compression and milling on powder samples has also been reported.\textsuperscript{30,39-41} Chattoraj \textit{et al.} observed partial amorphization of FI during cryomilling.\textsuperscript{39} Recently, the preparation of
amorphous dispersions of SMZ and other sulfonamides by co-milling with polymeric excipients has been described.\textsuperscript{40} In the same qualitative study amorphization was observed by X-ray powder diffraction (XRPD), when SMZ was cryomilled in the absence of excipients, while room temperature milling was found to lead to a FI $\rightarrow$ FII transition.

XRPD is the standard technique for the analysis of polymorphic mixtures and for quantifying the degree of crystallinity. However, XRPD suffers from a range of problems such as preferred orientation effects that affect the accuracy of quantitative analysis. Over the years vibrational spectroscopy has attracted growing interest as a method for solid-state analysis and has been successfully applied to the qualitative and quantitative analysis of polymorphic pharmaceuticals. In particular Raman and near-infrared (NIR) spectroscopy in conjunction with multivariate analysis are now routinely used and are often the methods of choice due to their speed, non-destructive nature, suitability for real-time \textit{in situ} analysis and minimal sample preparation and handling requirements.\textsuperscript{42} NIR spectroscopy combined with multivariate analysis has been used by Lee and co-workers for the in-line monitoring of the solvent-mediated transformation of SMZ FI to FII.\textsuperscript{35} Analytical work on SMZ polymorphs has also been reported by Li \textit{et al.} who compared the effectiveness and accuracy of XRPD, Raman microscopy and differential scanning calorimetry (DSC) for the quantitative analysis of binary mixtures of FI and FII.\textsuperscript{43}

Here we report a detailed XRPD and NIR-spectroscopic investigation of the solid-state transformations of SMZ during room temperature and cryomilling in the absence and presence of small-molecule additives and of the recrystallization of amorphous SMZ under different storage conditions. In the first part of the study multivariate NIR-spectroscopic calibration models have been developed to monitor the solid-state transformations of SMZ FI and FII and to evaluate the effect of milling time on the recrystallization kinetics and pathway. In the second part the effect of additives on the milling outcome (co-amorphous material, co-crystal, polymorphic transformation) and on the stability of the amorphous phase was investigated.

\section*{MATERIALS AND METHODS}

\subsection*{Materials}
SMZ FI was purchased from Sigma Aldrich (St. Louis, Missouri) with a purity of ≥ 99.0 % and was used as received. The polymorphic form of the commercial sample was confirmed by comparing the experimental XRPD patterns with the simulated ones using the single crystal structures with refcodes SLFNMA02, SLFNMA01, and SLFNMA03. SMZ FII was prepared according to the literature by crystallization of commercial SMZ from an aqueous acetonitrile solution (800 mL, H2O:acetonitrile 20:80) containing 5 g of SMZ. The solution was heated to 60°C for 2.5 hours to ensure complete dissolution. Then seeds of FII were added and the solution was stirred overnight at 300 rpm using a magnetic stirrer. The solvent was decanted leaving a slurry which was left to dry under vacuum.

**Methods**

**Cryomilling and Room Temperature Milling**

An oscillatory ball mill (Mixer Mill MM400; Retsch GmbH & Company, Germany) was used for all milling experiments. 1 g of SMZ FI or FII was milled at 25 Hz in a 25 mL stainless steel jar containing one 15 mm stainless steel ball. For room temperature milling breaks of 15 minutes were taken every 30 minutes of milling to avoid overheating of the sample. For cryomilling the milling jars were sealed and immersed in liquid nitrogen for 3 min. before milling for up to 180 min. Every 7.5 min. the milling jars were recooled with liquid nitrogen for 2 min. The average sample temperature measured at 7.5 min. intervals was -10±2°C. For the stability studies amorphous SMZ (FA) was prepared by cryomilling FI for 30, 45, 60, 75, and 90 min. to obtain five different samples.

**Stability Study of Amorphous SMZ**

The samples of FA were kept at room temperature (22±2°C) and 4°C. All samples were stored in a desiccator over silica gel under vacuum. NIR spectroscopy was used to monitor the crystallization of the amorphous phase.

**Preparation of Binary and Ternary Mixtures**

Three sets of binary mixtures were prepared, FI/II, FI/FA and FII/FA, using the following mass ratios; (0:1), (1:9), (2:8), (3:7), (4:6), (5:5), (6:4), (7:3), (8:2), (9:1), and (1:0) (w/w). The preparation of the binary and ternary polymorphic mixtures followed a previously described procedure. The compositions of the 16 ternary mixtures consisting of FI, FII
and FA are shown in the diagram in Figure 2. The mass ratios are; (1:0:0), (0:1:0), (0:0:1),
(1/2:1/2:0), (1/2:0:1/2), (0:1/2:1/2) (7/10:0:3/10), (0:7/10:3/10), (7/10:3/10:0), (0:3/10:7/10),
(3/10:0:7/10), (3/10:7/10:0), (1/3:1/3:1/3), (2/3:1/6:1/6), (1/6:2/3:1/6), and (1/6:1/6:2/3)
(w/w/w). FA used in the binary and ternary mixtures was obtained by cryomilling FI for 60
min.

Physical mixtures (300 mg total for each mixture) were prepared and mixed uniformly
for 3 min. using a vortex mixer (Thermolyne Maxi Mix II, Type 37600). NIR spectroscopy
was used to check the stability of the samples to ensure that no solid-state transformations
took place. All samples were stable over the course of the analysis. Mixtures were prepared
and analyzed in triplicate. In order to avoid possible systematic changes caused by
instrumental and/or environmental fluctuations, samples were prepared in a random manner
and immediately analyzed.

Preparation of the Co-crystal of SMZ with Oxalic Acid
100 mg SMZ F1 (0.378 mmol) and 34 mg anhydrous oxalic acid (0.378 mmol) were
dissolved in 10 mL methanol. Slow evaporation at room temperature gave colourless blocks
suitable for single crystal X-ray diffraction.

Co-milling of SMZ with Small-molecule Additives
400 mg (1.51 mmol) SMZ FI and 1.51 mmol of the small-molecule additive were placed in a
25 mL stainless steel jar containing one 15 mm stainless steel ball and cryomilled as
described above. The total milling time ranged from 30 to 180 min. (see below).

Analytical Techniques

X-Ray Powder Diffraction
X-ray powder diffraction patterns were collected on a Siemens D500 powder diffractometer
(Munich, Germany), which was fitted with a diffracted beam monochromator. Diffraction
patterns were recorded between 5° and 40° (2θ) using CuKα radiation with steps of 0.05° and
with a 2 s counting time per step. The Oscaill PC Windows software package was used to
generate the simulated patterns of FI, FII and the SMZ/oxalic acid co-crystal.46,47

Near-Infrared Spectroscopy
Near-infrared spectra were collected in glass vials (15 x 45 mm$^2$) on a PerkinElmer Spectrum One (Waltham, Massachusetts) fitted with an NIR reflectance attachment. Spectra were collected with interleaved scans in the 10,000–4000 cm$^{-1}$ range with a resolution of 8 cm$^{-1}$, using 32 coadded scans. Sample vials were shaken and repositioned between the triplicate measurements of each sample. The mean spectrum for each sample was used in the analysis.

**Attenuated Total Reflectance-Infrared Spectroscopy**

ATR-IR spectra were recorded from 4000 to 650 cm$^{-1}$ using a PerkinElmer Spectrum 400 (FT-IR/FT-NIR Spectrometer) with 32 accumulations at a resolution of 4 cm$^{-1}$. This instrument was equipped with a DATR 1 bounce Diamond/ZnSe Universal ATR sampling accessory. Every sample was measured in triplicate and for each of the three measurements a fresh 5 mg aliquot of sample was used.

**DSC Measurement**

DSC experiments were performed on a STA625 thermal analyzer from Rheometric Scientific. The heating rate was kept constant at 40 °C min$^{-1}$ and all runs were carried out from 25 °C to 250 °C. The measurements were made in open aluminum crucibles, nitrogen was used as the purge gas in ambient mode, and calibration was performed using an indium standard.

**Data Analysis**

Data analysis was carried out using the multivariate data analysis software The Unscrambler v.10.0 (Camo, Trondheim, Norway). Several different preprocessing algorithms were used to remove unimportant baseline (offset) interferences and scattering effects and to accentuate the spectral signals of interest. The methods used for NIR and IR data included multiplicative scatter correction, standard normal variate (SNV) transformation, first-derivative and second-derivative calculations. Savitzky-Golay first and second-derivative calculations and smoothing were performed with a window size of 11 points and a second-order polynomial. A total of 48 samples (3 x 16) were prepared for the ternary analysis (FA/FI/FII), and 33 for each of the binary analyses (FA/FI, FA/FII, and FI/FII). These data sets were divided into calibration sets to build the model and prediction sets to test the model. For the analysis of the binary mixtures 22 samples were chosen for the calibration set and 11 samples were used for the prediction set. In the case of the ternary system, 32 and 16 samples were used as calibration and prediction sets. The spectroscopic data were subjected to mean centering
before partial least squares (PLS) regression analysis was carried out. The optimal number of PLS factors was determined by using a leave-one-out cross-validation procedure. The performances of the models were evaluated by using the limit of detection, root mean square error of calibration (RMSEC), cross-validation (RMSECV), and prediction (RMSEP), defined as:

\[ RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}} \]

where \( y_i \) is the reference value, \( \hat{y}_i \) the calculated value and \( n \) is the number of samples.

**Single Crystal X-ray Diffraction**

Crystal data for the SMZ/oxalic acid co-crystal were collected at room temperature on an Oxford Diffraction Xcalibur CCD diffractometer using graphite-monochromated Mo-K\(\alpha\) radiation (\(\lambda = 0.71069 \text{ Å}\)). The structure was solved by direct methods and subsequent Fourier syntheses and refined by full-matrix least squares on F\(^2\) using SHELXS-97 and SHELXL-97\(^{48}\) within the Oscail PC Windows software package.\(^{46,47}\) Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were found in the difference Fourier maps and refined isotropically. Graphics were produced with ORTEX.\(^{47}\) Crystallographic data and details of refinement are reported in Table S1. CCDC-960773 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, Cambridge, UK.

**RESULTS AND DISCUSSION**

**Effect of Cryomilling on SMZ FI and FII**

SMZ FI and FII are easily accessible in bulk quantities\(^{30}\) and the identity and purity of SMZ FI and FII samples were confirmed by comparing the experimental XRPD patterns with the simulated patterns (Figure S1) and with experimental ones reported in the literature.\(^{28}\) FI gives specific 2\(\theta\) peaks at 16.2, 20.3 and 24.4 °, while peaks at 15.7, 19.2, 21.3 and 26.6 ° are
characteristic for FII. FIII can be prepared in milligram quantities only. Its theoretical pattern (Figure S1) has a specific peak at 14.00°. This peak is absent in all powder patterns throughout this study so that FIII does not appear to form at any stage. Figure 3 shows the XRPD patterns of the cryomilled SMZ polymorphs at selected time intervals. The intensities of the diffraction peaks of FI decrease rapidly within the first 15 min. of cryomilling and after 30 min. the sample is fully amorphous. In the case of the more stable polymorph II amorphization is complete after 120 min.

The IR and NIR spectra of FI and FII samples at various milling times are displayed in Figure 4. A notable feature of the IR spectrum of FI is the split of the νas(NH2) (3497, 3482 cm⁻¹) and the NH2 scissoring (1641, 1628 cm⁻¹) bands. This is due to the lower symmetry of the FI structure that contains pseudo-centrosymmetric NH···N dimers in contrast to the centrosymmetric NH···N dimers in FII. In the IR spectrum of FII single peaks are observed at 1645 and 3458 cm⁻¹. Furthermore, the spectrum of FI shows a peak at 748 cm⁻¹ that is specific to this form, while FII gives a characteristic peak at 762 cm⁻¹. The S=O stretching vibrations of FI and FII appear at 1150 and 1147 cm⁻¹, respectively. The conversion of FI and FII into the amorphous phase results in a general peak broadening and the IR spectra of the milled samples show clear changes in the 750 - 1100 cm⁻¹ and 1300 - 1700 cm⁻¹ regions (Figures 4 and S2). The peaks at 748 cm⁻¹ (FI) and 762 cm⁻¹ (FII) disappear during milling (★ and ◊ in Figure 4a). The NH2 scissoring vibration bands shift to lower wavenumbers and a single peak is observed at 1626 cm⁻¹ for the amorphized samples. By contrast, the S=O stretching vibration of both forms remains essentially unaffected. In the spectrum of FI, peaks at 1372 and 1492 cm⁻¹ (★) decrease in intensity, while the peaks at 1046 and 1445 cm⁻¹ (■) increase and shift to 1038 and 1436 cm⁻¹, respectively. In the spectrum of FII the peak at 1369 cm⁻¹ (◊) decreases in intensity, the absorption at 1038 cm⁻¹ (●) increases and the peak at 1449 cm⁻¹ (■) shifts to 1437 cm⁻¹ and increases.

In the NIR spectrum of FI clear changes are observed in the 5700 - 7000 cm⁻¹ and 4100 - 5200 cm⁻¹ ranges upon milling (Figures 4b and S2). These regions encompass the first overtones of the N-H stretching vibrations and the combination bands of N-H stretching and NH2 bending vibrations, respectively. The split peak with maxima at 6935 and 6907 cm⁻¹ is replaced by a broad band at 6902 cm⁻¹ (▽). The peaks at 4979, 4944, 4714, 4316, 4236, 4205, and 4162 cm⁻¹ (★) disappear. The bands at 4826 (◊) and 4562 (■) cm⁻¹ shift to 4809 and 4540 cm⁻¹, respectively. A broad band at 5078 cm⁻¹ replaces the split peak at 5109/5088 cm⁻¹ (●). Changes in the NIR spectrum of FII are less pronounced and the NIR spectrum of amorphous
SMZ (FA) is most similar to that of FII. Nevertheless, the amorphization of FII can be monitored by the general broadening of peaks and the disappearance of the bands at 4967, 4895, 4674, 4592, 4327, and 4188 (*) cm$^{-1}$. Furthermore, FII gives a characteristic peak at 6857 cm$^{-1}$ (■) that disappears during milling, while a broad band appears at 6902 cm$^{-1}$ (▼).

**Effect of Milling at Room Temperature on SMZ FI and FII**

The effect of room temperature milling on both polymorphs was monitored by XRPD, IR and NIR spectroscopy (Figure 5 and Figure S3). The intensity decrease and broadening of the diffraction peaks in the XRPD pattern of FI indicates a rapid reduction of crystallinity within the first 45 min. of milling. After 45 min. the peaks sharpen again. However, the 2θ peaks at 16.2, 20.3 and 24.4 ° that are characteristic of FI are no longer visible. Instead, peaks specific to FII (15.7, 19.2, 21.3 and 26.6 °) are detected. The changes in the NIR and IR spectra also indicate the solid-state transformation during milling. The decrease of the IR peaks at 748, 1372, and 1492 cm$^{-1}$ and the increase of the absorption at 1436 and 1038 cm$^{-1}$ confirm the transition of FI into the amorphous phase within 45 min. In the NIR spectra, the disappearance of the peaks at 6935, 4979, 4944, 4714, 4316, 4236, 4205, and 4162 cm$^{-1}$ shows the conversion of FI. When samples are milled for more than 45 min., NIR and IR peaks at 6857, 4895, and 762 cm$^{-1}$ that are specific to FII reveal the formation of the more stable polymorph. As described below, this process can be catalysed by a drop of solvent.

By contrast, the XRPD patterns of FII exhibit no significant visible changes upon milling at room temperature except for a small broadening of the diffraction peaks due to the reduction in crystallinity and / or particle size (Figure S3). Likewise, the IR and NIR spectra of FII samples suggest that no polymorphic transition takes place during room temperature milling.

**Quantification of Binary and Ternary Mixtures of FI, FII and FA**

In order to quantify the solid-state transformations during room temperature and cryomilling, multivariate calibration models were developed. As described above it is possible to differentiate FI, FII and FA by spectroscopy, since the three forms show distinct peaks in the
5700 - 7000 and 4000 - 5200 cm\(^{-1}\) regions. Water that is often readily absorbed by amorphous materials causes broad bands at 5200 and 7070 cm\(^{-1}\). Therefore a combination of the 6475 - 6965 and 4000 - 5115 cm\(^{-1}\) ranges was selected for the construction of the calibration models. First, models were built for the quantification of FI, FII and FA in binary mixtures (FI/FA, FII/FA, FI/FII) using NIR spectroscopy and a partial least-squares (PLS) regression. Besides PLS models for the 0 - 100 % range, models were constructed for the detection of low levels of one component (0 - 10 %). Different spectral pre-processing algorithms including multiplicative scatter correction (MSC), standard normal variate (SNV) transformation, 1\(^{st}\) and 2\(^{nd}\) derivative calculations and combinations of MSC or SNV with derivation were applied to the data. The best results were obtained, when SNV or a combination of SNV and 1\(^{st}\) derivative was used. The performance characteristics of the best-performing models are summarized in Table 1. The RMSEP values of the 0 - 100 % models are below 2 %. The lowest RMSEP value (1.04 %) is observed for the FI/FII mixture. The spectra of FI and FII differ most and have several distinct peaks in the selected range (e.g. 6935, 6910, 5109, 4979, 4826, 4562, 4236, 4205, 4162 cm\(^{-1}\) for FI and 6857, 4967, 4895, 4802, 4188 cm\(^{-1}\) for FII). The results of the multivariate spectroscopic method for the 0 - 100 % FI/FII binary mixtures compare favourably with the XRPD method reported in the literature where RMSEC and RMSEP values of 1.28 and 1.65 % have been obtained.\(^{43}\) The speed of analysis represents an additional advantage of NIR spectroscopy over XRPD. NIR spectroscopy clearly outperforms Raman microscopy (RMSEC and RMSEP values of 5.98 and 6.75 % \(^{43}\)). Plots of the predicted vs. actual content for the different binary mixtures which all show excellent linear correlations are displayed in Figure S4. For the low content analysis, RMSEC, RMSECV and RMSEP values are \(\leq 0.80\ \%\). Limits of detection (LOD) and limits of quantification (LOQ) have been determined using blank samples and LOD = 3.3\(\sigma\)/s (\(\sigma\) = standard deviation; s = slope of the calibration plot) and LOQ = 10\(\sigma\)/s Table 2).\(^{50,51}\) LODs and LOQs for the minor component in the 0 - 10 % mixtures are \(< 1\ %\) and \(< 3.2\ \%\), respectively, except for the detection of low levels of the amorphous phase in FI/FA mixtures and of FI in FI/FII mixtures, where the LOD and LOQ are \(< 2\ %\) and \(\leq 6\ \%\). FI in FI/FA has the lowest LOD (0.52 %), while the LOD of FA in the presence of FI is highest (1.79 %). Low levels of FI can be easily detected by the appearance of two specific bands at 6935 and 6764 cm\(^{-1}\). By contrast, no specific new bands emerge in the NIR spectrum, when small amounts of FA are added to FI (Figure S5).
A satisfactory calibration model for the simultaneous determination of the three solid-state forms in ternary mixtures has also been derived (Table 3, Figure S4). RMSEP values for the three components are ≤ 5.1 %. The LODs of forms FA, FI, and FII are 6.2, 5.6, and 0.7 %, respectively. FII has distinct peaks at 4895 and 6857 cm\(^{-1}\) so that small amounts of this form can be easily detected in the presence of FI and FA. The detection of low levels of FI and FA in ternary mixtures is more difficult due to the lack of clearly distinguishable peaks.

The suitability of IR spectroscopy combined with multivariate analysis for the quantification of binary mixtures was explored. However, the calibration models obtained had significantly higher RMSE values than the NIR models (data not shown) which might be due to the small sample size. Typically, 5 mg samples were used for an ATR-IR measurement. The problem of the small sampling size has been discussed in the literature as the major source of quantification error in ATR-IR spectroscopy. IR spectroscopy was discarded as a means of quantitative analysis in our study.

**Quantification of Solid-State Transformations During Milling**

The NIR spectroscopic calibration models were applied to monitor the degree of crystallinity vs. time during cryomilling. Plots for both polymorphs showing the percentage decrease in crystallinity with cryomilling time are displayed in Figure S6. Likewise, the compositions of FI samples were analyzed during room temperature milling (Figure 6). As evident from the time profile, FI rapidly converts into the amorphous form within the first 20 min. of milling. After that time increasing amounts of FII are detected and the percentage of FA decreases. After 60 min. FI has disappeared and the mixture contains 78 % FII and 22 % FA. No more changes occur after longer milling times. The same FII/FA mixture (75 % / 25 %) results, when FII is milled at room temperature (Figure S7). This indicates that the milling-induced FA → FII transformation is reversible.

Zhang et al. used XRPD to qualitatively monitor the solid-state transitions of FI and FII during ball-milling at room temperature. They reported the complete conversion of FI into FII after 120 min. Our multivariate NIR spectroscopic analysis gives further insight into the polymorphic transformation in that the sample composition-time profile for FI clearly demonstrates that the FI→FII conversion is not direct but takes place via the amorphous state.
Milling-induced polymorphic transformations and amorphization have been extensively discussed in the literature. Descamps and co-workers have highlighted the relative position of the glass transition temperature, $T_g$, with respect to the milling temperature as the key factor that determines the end-product of the milling process. Their analysis showed that compounds with a $T_g$ above the milling temperature generally convert to the amorphous state while compounds with a $T_g$ below the milling temperature transform to either a more stable or to a less stable polymorph. Our results are in agreement with this. During cryomilling the average sample temperature was -10 °C, i.e. 72 degrees lower than the reported $T_g$ of melt-quenched amorphous SMZ (62 °C). During room temperature milling a maximum temperature of 37 °C was recorded on the outside of the milling jars. Thus, it is possible that the actual sample temperature reached values close to the glass transition temperature and triggered crystallization of the amorphized fraction to FII.

Although several theories have been put forward, the physical mechanism of milling-induced amorphization is not understood to date. Hypotheses include a local heating and quenching process and an increase in the entropy of the crystal lattice due to the accumulation of crystal lattice defects. Descamps et al. could rule out the former for the amorphization of sugars during milling by using the absence of mutarotation as an indicator that the temperature in the sample did not reach the melting point under the milling conditions. They ascribe the amorphization to a dynamical shearing process below the melting point and discuss the transformation in the context of the concept of driven materials proposed by Martin and Bellon. The driven materials concept suggests a competition between temperature-independent ballistic disordering and temperature-dependent restoration to a lower energy state and defines an “effective” temperature $T_{eff}$ as the temperature at which the non-milled material would have the same level of disorder as the milled one. Amorphization occurs, when $T_{eff}$ is above the melting point. Possible mechanisms for milling-induced transformations to another polymorph include a direct crystal-crystal transformation and the transient amorphization or the transient formation of an unstable crystalline phase followed by a rapid recrystallization process. Descamps et al. discussed the crystal-to-crystal transformation of fananserine, sorbitol and indomethacin as two-step processes involving amorphization according to the driven materials model followed by crystallization of the amorphized part. As pointed out in the literature, the detection of a transient amorphous phase is inherently difficult, as recrystallization is generally faster than amorphization, in particular when a crystalline component is present that can act as a crystallization catalyst. By milling just above the $T_g$ where the recrystallization kinetics are
slow, De Guesseme, Descamps et al. could show that in the case of fananserine grinding-induced polymorphic transitions occur via a transitory amorphous state. It has been hypothesized earlier that the FI→FII transformation of SMZ also occurs via a transitory amorphous phase and our quantitative analysis presented here clearly supports the two-step model.

The amorphized SMZ fraction crystallizes towards FII and not back to the starting form. As this requires the nucleation of the new form, the time-profile of the milling process shows an induction period before the percentage of FII increases rapidly after 40 min, while FA accumulates at the start and reaches a maximum after 20 min. When a drop of ethanol or isopropanol is added to FI before milling, FI is completely converted to FII after 20 (ethanol) and 30 (isopropanol) min. milling time. Thus, these hydroxylic solvents act as solid state transformation catalysts.

FI requires shorter cryomilling times to undergo complete amorphization than does FII. This has been rationalized by the different packing arrangements in the crystal lattices of FI and FII. In both polymorphs, the basic building blocks are z-shaped hydrogen-bonded dimers that form infinite hydrogen-bonded chains. These chains give rise to rigid layers parallel to the ac plane with only weak van der Waals forces existing between layers. In FI the layers are flat and give rise to slip planes, while the layers in FII are zigzag-shaped and interlock. The presence of slip planes in the crystal structure of FI results in high plasticity and facilitates amorphization, while the slip of layers in FII is more difficult.

Stability Study of Amorphous SMZ Samples

The stability of amorphous SMZ obtained by cryomilling FI for 30, 45, 60, 75, and 90 min. was evaluated by NIR spectroscopy (Figure S8). Samples were kept under vacuum over silica gel at 4 °C and 22 °C. Plots of the sample composition vs. storage time are shown in Figure 7. In samples kept at 4 °C, 50 % of the amorphous SMZ recrystallize within 2 to 5 days depending on the milling time. Longer milling times give a less stable amorphous phase, as the reduction in particle size with milling duration which is accompanied by an increase in the surface to volume ratio leads to enhanced nucleation properties due to an enhanced molecular mobility of the molecules on the surface. A similar effect of particle size on the stability has been reported for quench-cooled simvastatin and indomethacin. The milling time also affects the polymorphic forms observed. Samples milled for 30 and 40 min.
recrystallize to mixtures of 79 % FII / 21% FI and 68% FII / 32% FI, respectively, while samples milled for 60 min. or longer recrystallize to FII only. Most likely the presence of FI seeds that remain after shorter milling times induces the crystallization of this polymorph besides FII. A similar behaviour is observed, when samples are stored at room temperature. Samples milled for less than 60 min. crystallize to a mixture of FI and FII and samples milled for more than 60 min. recrystallize to pure FII. It is worthy of note that the amorphous SMZ recrystallizes within hours when kept at room temperature and easily absorbs water in air. The measurement of the composition-time profiles required a fast analytical method with minimal sample handling and thus is a further example of the effectiveness of NIR spectroscopy for solid-state analysis.

According to Ostwald’s Rule of Stages recrystallization of the amorphous samples should occur toward the less stable polymorph FI which should then convert to FII as the most stable form at room temperature. As clearly evident from Figure 7 FA crystallizes directly to the more stable polymorph in the absence of FI seeds. In the presence of FI seeds both polymorphs form concomitantly with the crystallization of FI being driven by the growth (without nucleation) of residual nuclei. There is no indication of polymorphic conversion on the timescale of the stability studies. The extreme slowness of the FI → FII transformation has been pointed out by Zhang et al.\textsuperscript{30} The observation that the recrystallization of the amorphized samples does not follow Ostwald’s Rule when stored under vacuum has also been made by us in the case of sulfathiazole.\textsuperscript{54}

The stability of an amorphous material towards recrystallization is related to its T\textsubscript{g}. A T\textsubscript{g} of 62 °C was reported for melt-quenched SMZ.\textsuperscript{40} We found a similar T\textsubscript{g} for the amorphous SMZ prepared by cryomilling (Figure S9).

**Co-milling of SMZ FI with Small-molecule Additives**

As described in the introduction, co-milling with excipients or additives can promote polymorphic transformations, prevent amorphisation or result in the formation of composite amorphous systems or co-crystals. We have therefore studied the effect of a range of multifunctional carboxylic acids, amides and sugars on the milling behaviour of SMZ. For the sake of a general analysis we have not limited the choice of co-formers to GRAS
(generally recognized as safe) or EAFUS (everything added to food in the US) substances. The details and results of the co-milling experiments are summarized in Table 4.

After cryomilling SMZ FI with L-tartaric acid, adipic acid, succinic acid, terephthalic acid, trehalose, and D-mannitol for 180 min. the XRPD patterns indicated partially amorphous materials. Sorbitol, saccharin, and pimelic acid significantly halted amorphization during cryomilling. Although the XRPD patterns showed some peak broadening, the diffraction peaks of FI were still clearly visible after 120 min. milling time (Figure 8a-c). Glutaric acid suppresses amorphization even more effectively. After 120 min. cryomilling relatively sharp diffraction peaks of FI were observed indicating that glutaric acid stabilizes the crystalline phase (Figure 8d).

The XRPD patterns of the co-milling experiments with maleic acid and malonic acid (Figure S10) show an initial peak broadening. However, cryomilling SMZ/maleic acid and SMZ/malonic acid samples for an extended time period (120 min.) results in the formation of FII.

Cryomilling equimolar mixtures of SMZ FI with oxalic, citric, fumaric, DL-tartaric, and barbituric acids resulted in complete amorphization. The stabilities of the amorphous materials were monitored over 8 weeks. At 4 °C under vacuum, SMZ/citric acid remains fully amorphous for 2 months. When kept at room temperature in a sealed vial, the amorphous mixture is stable for 7 d. After 14 d the XRPD pattern shows sharp diffraction peaks. Attempts were made to determine the Tg of amorphous SMZ/citric acid. However, the glass transition seems to overlap with the broad crystallization exotherm (Figure S11). Amorphous SMZ/DL-tartaric acid can be kept in a sealed vial for one week. After 2 weeks the XRPD pattern displays diffraction peaks with an underlying amorphous halo. SMZ/fumaric acid and SMZ/barbituric acid fully recrystallize within 5 days. Except for SMZ/oxalic acid all mixtures recrystallize to SMZ FII.

In the case of amorphous SMZ/oxalic acid a different recrystallization behaviour was observed. After 7 d at 4 °C under vacuum, a new XRPD pattern emerges (Figure 8) that corresponds to an SMZ/oxalic acid co-crystal as confirmed by crystallization from solution (see below). The DSC plot of amorphous SMZ/oxalic acid which shows a Tg of 65.4 ° is displayed in Figure S12. The co-crystal formation during storage of the binary mixture in the absence of moisture is noteworthy, as co-amorphous systems usually crystallize to the pure components. Mechanically activated carbamazepine/saccharin and carbamazepine/nicotinamide represent rare examples of cocrystallization upon storage under 0 % relative humidity.65,66 In the case of co-ground amorphous carbamazepine/saccharin the
transformation into a 1:1 co-crystal was attributed to the increased molecular mobility in the amorphous phase combined with favourable heteromeric interactions that prevented the crystallization of the pure phases. However, even in unmilled (crystalline) samples slow co-crystal formation was observed. Ibrahim et al. reported the spontaneous formation of urea-2-methoxybenzamide and caffeine-malic acid co-crystals upon low-energy convection mixing of the individually pre-milled components. No extensive amorphous intermediate phase was observed.

Additives can inhibit or decelerate the crystallization by sterically hindering the association of the API molecules, through intermolecular interactions, such as hydrogen bonding, or by acting as an antiplasticizer. In order to further investigate the increased stability of SMZ/citric acid, SMZ/DL-tartaric acid and SMZ/oxalic acid towards recrystallization, we have compared the IR and NIR spectra of the co-milled samples with those of FA. Vibrational spectroscopy probes differences in H bonding and other weak interactions in the solid state and is a useful method for obtaining information on interactions between the API and excipients in mixtures. Small shifts of some SMZ bands were noted in the spectra that indicated intermolecular interactions between SMZ and the carboxylic acids in the amorphous phase. The band at 5078 cm\(^{-1}\) in the NIR spectrum of FA shifts to 5081 and 5086 cm\(^{-1}\) in the co-milled SMZ/oxalic acid and SMZ/DL-tartaric acid sample, respectively. The FA peak at 4539 cm\(^{-1}\) moves to a lower wavenumber in SMZ/oxalic acid (4535 cm\(^{-1}\)) and SMZ/DL-tartaric acid (4532 cm\(^{-1}\)), while the band at 4384 cm\(^{-1}\) experiences an 8 cm\(^{-1}\) (SMZ/DL-tartaric acid) and 9 cm\(^{-1}\) (SMZ/oxalic acid) shift to higher wavenumbers. The band at 4810 cm\(^{-1}\) in the NIR spectrum of FA is observed at 4802 in the SMZ/DL-tartaric acid sample. The band at 6009 cm\(^{-1}\) appears at 6015 cm\(^{-1}\) after co-milling with oxalic acid. The NH\(_2\) scissoring vibration in the IR spectrum of SMZ/oxalic acid appears at 1620 cm\(^{-1}\) compared to 1626 cm\(^{-1}\) in FA. The FA bands at 3473 and 3376 cm\(^{-1}\) move to 3463 and 3372 cm\(^{-1}\) and the peak at 1501 cm\(^{-1}\) is shifted to 1497 cm\(^{-1}\). Co-milling with DL-tartaric acid results in a shift of the 3473 and 3376 cm\(^{-1}\) peaks to 3470 and 3372 cm\(^{-1}\), while the band at 1437 cm\(^{-1}\) in the spectrum of FA shifts to 1442 cm\(^{-1}\). The S=O stretching vibration that appears at 1446 cm\(^{-1}\) in FA is observed at 1150 cm\(^{-1}\) in the co-milled SMZ/DL-tartaric acid and SMZ/oxalic acid samples. The NIR and IR bands of amorphous SMZ are less affected by citric acid, although SMZ/citric acid is the most stable co-amorphous system. The only significant change in the NIR spectrum is a shift of the band at 4809 cm\(^{-1}\) in FA to 4813 cm\(^{-1}\) in SMZ/citric acid. In the IR spectrum of SMZ/citric acid peaks do not differ by more than two wavenumbers from those in FA.
Formation and Structure of the SMZ/Oxalic Acid Co-crystal

To confirm that the recrystallization product of cryomilled amorphous SMZ/oxalic acid is indeed a SMZ/oxalic acid co-crystal and to study the hydrogen bonding network co-crystallization experiments from solution were carried out. Crystals suitable for single-crystal X-ray analysis were obtained from acetone. Co-crystals also formed, when SMZ FI and oxalic acid were milled at room temperature. Figure 9d shows the XRPD patterns of a 1:1 mixture after different milling times. After 7.5 min. broad peaks with an underlying diffuse halo are observed suggesting partial amorphization. A new XRPD pattern emerges after 15 min. and no further changes occur during milling for up to 90 min. The XRPD patterns of the co-milled SMZ/oxalic acid mixture and of the bulk crystalline material isolated from solution are identical and match the theoretical pattern calculated from the single crystal data (Figure 9a-c). The co-crystals are stable towards amorphization, when cryomilled for 60 min.

Figure 10 gives a view of the crystal structure of the SMZ/oxalic acid co-crystal, hydrogen bond interactions are listed in Table 5. The asymmetric unit contains one molecule of SMZ and half a molecule of oxalic acid giving an overall stoichiometric ratio of 2:1. It is generally accepted that salts will be obtained, when the difference between the pK_a values of the base and the acid, ΔpK_a, is > 3, while a ΔpK_a < 0 will lead to a co-crystal. The pK_a values of the pyrimidine group in SMZ and of oxalic acid are 2.375 and 1.276 respectively so that ΔpK_a falls in the overlap range where either a co-crystal or a salt can result. The hydrogen atoms were located in the difference Fourier map and this clearly showed that a co-crystal rather than a salt was present. Furthermore, distinct C-O and C=O bond lengths (1.304(2) and 1.207(2) Å) are observed for the carboxyl groups of oxalic acid which confirms that no proton transfer takes place between the API and the co-former. The hydroxyl groups of oxalic acid form a hydrogen bond with one of the pyrimidine nitrogens of SMZ, while the carbonyl oxygens act as H bond acceptor to the amide NH so that an R_2^2(8) motif results. One of the hydrogen atoms of the amino group of SMZ forms a bifurcated H bond with the carbonyl oxygen of oxalic acid and one of the sulfonyl oxygens of SMZ. The second amino hydrogen is not involved in hydrogen bonding. This is also the case in the structure of SMZ. In all three polymorphs only one of the hydrogen atoms of the amine group forms an intermolecular H bond with a sulfonyl oxygen, while the second hydrogen atom is only
involved in weak N-H⋯O interactions. In addition to N-H⋯O and O-H⋯N hydrogen bonding interactions, bifurcated C-H⋯N and C-H⋯O hydrogen bonding is observed between C(4)-H and N(3) and O(2). Hydrogen bonding connectivities and preferences in sulfonamides have been reviewed in the literature. The analysis of 39 sulfonamide structures has revealed that the amido protons show a greater preference for H bonding to co-crystal guests and amidine nitrogens, whereas the amino protons preferentially hydrogen bond to the sulfonyl oxygens. The most frequently observed motif in sulfonamides is a chain of sulfanilamide molecules linked through H bonds between an amino proton and a sulfonyl oxygen. This C(8)-motif is also present in SMZ/oxalic acid, as are R₂(8) rings that are another important motif in sulfonamides and sulfonamide co-crystals. SMZ contains two different R₂(8) binding sites: the sulfonamide and the amidine site. Oxalic acid interacts via the amidine site of SMZ and this appears to be the preferred binding site. In all carboxylic acid co-crystal structures of the related sulfa drug sulfamethazine reported to date preferential H bonding between the carboxyl group and the amidine group was observed. This has been attributed to the empirical rule “the best donor bonds to the best acceptor”. It should be noted that in contrast to other sulfonamides X-ray structures of co-crystals of sulfamerazine are surprisingly rare.

CONCLUSIONS

NIR spectroscopy combined with multivariate analysis is an effective method to quantitatively monitor solid-state conversions of SMZ polymorphs during storage and milling. The milling-induced transformation of SMZ FI into FII proceeds via the amorphous phase. The recrystallization kinetics and pathway of amorphous SMZ prepared by cryomilling depend on the milling duration. Cryogenic co-milling of SMZ FI with citric acid gives an amorphous material that is stable for at least 8 weeks at 4 °C under vacuum. Amorphous co-milled SMZ/oxalic acid kept under vacuum spontaneously crystallizes to a 2:1 co-crystal.

ACKNOWLEDGMENTS
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Additional Supporting Information may be found in the online version of this article.

FIGURE CAPTIONS

**Figure 1.** Chemical structure of sulfamerazine.

**Figure 2.** Ternary diagram showing the composition of the 16 ternary mixtures consisting of SMZ FI, FII and FA.

**Figure 3.** XRPD patterns of SMZ FI (left) and FII (right) at various cryomilling times.

**Figure 4.** IR (a) and NIR (b) spectra of SMZ FI (left) and FII (right) at various times of cryomilling (cf. text for labels).

**Figure 5.** XRPD patterns (a), IR (b) and NIR (c) spectra of SMZ FI after milling at room temperature for the times indicated. (*) Peaks specific to FI; (●) peaks specific to FII; (○) decrease of the IR bands at 748, 1372, 1492 cm\(^{-1}\) and of the NIR bands at 6935, 4979, 4944, 4714, 4316, 4236, 4205 and 4162 cm\(^{-1}\) within the first 45 min. of milling; (■) increase of the IR bands at 1436 and 1038 cm\(^{-1}\) within the first 45 min. of milling.

**Figure 6.** Time profile of the polymorph composition of FI samples during room temperature milling.

**Figure 7.** Solid-state form composition of amorphous SMZ samples prepared by cryomilling FI for 30, 45, 60, 75, and 90 min. vs. storage time.

**Figure 8.** XRPD patterns of (a) SMZ FI/sorbitol, (b) SMZ FI/saccharin, (c) SMZ FI/pimelic acid, and (d) SMZ FI/glutaric acid (1:1) after 120 min. cryomilling.

**Figure 9.** XRPD patterns of (a) a recrystallized sample of a cryomilled SMZ/oxalic acid mixture and (b) the bulk crystalline material obtained by co-crystallization of SMZ and oxalic acid from solution (acetone). (c) Simulated pattern of the 2:1 co-crystal generated from the single-crystal data. (d) XRPD patterns of an equimolar
mixture of SMZ FI and oxalic acid after milling at room temperature for the times indicated.

**Figure 10.** Hydrogen bonding in the 2:1 co-crystal of SMZ with oxalic acid. Carbon-bound hydrogens are omitted for clarity.
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Table 1. Performance Characteristics of the NIR Spectroscopic PLS Models for Binary Mixtures

<table>
<thead>
<tr>
<th>Mixture</th>
<th>Range</th>
<th>Pre-treatment</th>
<th>PC(^b)</th>
<th>RMSEC (%</th>
<th>RMSECV (%)</th>
<th>RMSEP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI / FA</td>
<td>0 - 10 % FA</td>
<td>SNV &amp; 1(^{st}) deriv.</td>
<td>1</td>
<td>0.444</td>
<td>0.492</td>
<td>0.589</td>
</tr>
<tr>
<td>FI / FA</td>
<td>0 - 100 % FA</td>
<td>SNV &amp; 1(^{st}) deriv.</td>
<td>2</td>
<td>1.799</td>
<td>2.64</td>
<td>1.536</td>
</tr>
<tr>
<td>FI / FA</td>
<td>90 - 100 % FA</td>
<td>SNV &amp; 1(^{st}) deriv.</td>
<td>1</td>
<td>0.563</td>
<td>0.591</td>
<td>0.452</td>
</tr>
<tr>
<td>FII / FA</td>
<td>0 - 10 % FA</td>
<td>SNV</td>
<td>1</td>
<td>0.375</td>
<td>0.525</td>
<td>0.574</td>
</tr>
<tr>
<td>FII / FA</td>
<td>0 - 100 % FA</td>
<td>SNV</td>
<td>1</td>
<td>2.287</td>
<td>2.675</td>
<td>1.812</td>
</tr>
<tr>
<td>FII / FA</td>
<td>90 - 100 % FA</td>
<td>SNV &amp; 1(^{st}) deriv.</td>
<td>1</td>
<td>0.521</td>
<td>0.561</td>
<td>0.802</td>
</tr>
<tr>
<td>FI / FII</td>
<td>0 - 10 % FI</td>
<td>SNV &amp; 1(^{st}) deriv.</td>
<td>1</td>
<td>0.333</td>
<td>0.390</td>
<td>0.339</td>
</tr>
<tr>
<td>FI / FII</td>
<td>0 - 100 % FI</td>
<td>SNV &amp; 1(^{st}) deriv.</td>
<td>1</td>
<td>1.414</td>
<td>1.482</td>
<td>1.038</td>
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<tr>
<td>FI / FII</td>
<td>90 - 100 % FI</td>
<td>SNV &amp; 1(^{st}) deriv.</td>
<td>2</td>
<td>0.480</td>
<td>0.615</td>
<td>0.336</td>
</tr>
</tbody>
</table>

\(^a\) spectral range: 6965 - 6475 and 5115 - 4000 cm\(^{-1}\); \(^b\) number of principal components
Table 2. LOD and LOQ for SMZ FI, FII and FA in Binary Mixtures Containing 0 - 10% of the Minor Component Using NIR Spectroscopy

<table>
<thead>
<tr>
<th>Binary Mixture</th>
<th>Minor Component</th>
<th>LOD (wt%)</th>
<th>LOQ (wt%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA / FI</td>
<td>FA</td>
<td>1.79</td>
<td>5.95</td>
</tr>
<tr>
<td></td>
<td>FI</td>
<td>0.52</td>
<td>1.75</td>
</tr>
<tr>
<td>FA / FII</td>
<td>FA</td>
<td>0.96</td>
<td>3.20</td>
</tr>
<tr>
<td></td>
<td>FII</td>
<td>0.53</td>
<td>1.78</td>
</tr>
<tr>
<td>FI / FII</td>
<td>FI</td>
<td>1.38</td>
<td>4.58</td>
</tr>
<tr>
<td></td>
<td>FII</td>
<td>0.72</td>
<td>2.43</td>
</tr>
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</table>

Table 3. Performance Characteristics of the NIR Spectroscopic PLS Models for Ternary Mixtures

<table>
<thead>
<tr>
<th>Polymorph</th>
<th>PC</th>
<th>RMSEC (%)</th>
<th>RMSECV (%)</th>
<th>RMSEP (%)</th>
<th>LOD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>2</td>
<td>5.514</td>
<td>6.580</td>
<td>5.137</td>
<td>6.152</td>
</tr>
<tr>
<td>FI</td>
<td>2</td>
<td>4.500</td>
<td>5.192</td>
<td>3.997</td>
<td>5.618</td>
</tr>
<tr>
<td>FII</td>
<td>2</td>
<td>3.796</td>
<td>5.093</td>
<td>3.348</td>
<td>0.682</td>
</tr>
</tbody>
</table>

*a spectral range: 6965 - 6475 and 5115 - 4000 cm⁻¹; SNV pre-processing*
Table 4. Solid-state Transformations of SMZ FI upon Cryogenic Co-milling with Small-molecule Co-formers

<table>
<thead>
<tr>
<th>Co-former</th>
<th>Cryomilling time [min.]</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>adipic acid</td>
<td>120</td>
<td>partially amorphous</td>
</tr>
<tr>
<td>barbituric acid</td>
<td>120</td>
<td>X-ray amorphous&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>citric acid</td>
<td>120</td>
<td>X-ray amorphous</td>
</tr>
<tr>
<td>fumaric acid</td>
<td>120</td>
<td>X-ray amorphous</td>
</tr>
<tr>
<td>glutaric acid</td>
<td>120</td>
<td>FI</td>
</tr>
<tr>
<td>maleic acid</td>
<td>120</td>
<td>FII</td>
</tr>
<tr>
<td>malonic acid</td>
<td>120</td>
<td>FII</td>
</tr>
<tr>
<td>D-mannitol</td>
<td>120</td>
<td>partially amorphous</td>
</tr>
<tr>
<td>oxalic acid</td>
<td>30</td>
<td>X-ray amorphous</td>
</tr>
<tr>
<td>pimelic acid</td>
<td>120</td>
<td>peak broadening, FI</td>
</tr>
<tr>
<td>saccharin</td>
<td>120</td>
<td>peak broadening, FI</td>
</tr>
<tr>
<td>sorbitol</td>
<td>120</td>
<td>peak broadening, FI</td>
</tr>
<tr>
<td>succinic acid</td>
<td>120</td>
<td>partially amorphous</td>
</tr>
<tr>
<td>DL-tartaric acid</td>
<td>180</td>
<td>X-ray amorphous</td>
</tr>
<tr>
<td>L-tartaric acid</td>
<td>180</td>
<td>partially amorphous</td>
</tr>
<tr>
<td>terephthalic acid</td>
<td>120</td>
<td>partially amorphous</td>
</tr>
<tr>
<td>trehalose</td>
<td>120</td>
<td>partially amorphous</td>
</tr>
</tbody>
</table>

<sup>a</sup> minor diffraction peaks
Table 5. Hydrogen Bonding in the SMZ/Oxalic acid Co-crystal (Å, °)

<table>
<thead>
<tr>
<th>D-H···A</th>
<th>d(D-H)</th>
<th>d(H···A)</th>
<th>d(D···A)</th>
<th>θ(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-H(1)···O(3)</td>
<td>0.85(2)</td>
<td>1.99(2)</td>
<td>2.830(3)</td>
<td>168(2)</td>
</tr>
<tr>
<td>N(4)-H(4B)···O(1)</td>
<td>0.83(3)</td>
<td>2.30(2)</td>
<td>3.090(3)</td>
<td>161(3)</td>
</tr>
<tr>
<td>N(4)-H(4B)···O(3)</td>
<td>0.83(3)</td>
<td>2.59(3)</td>
<td>2.984(3)</td>
<td>111(2)</td>
</tr>
<tr>
<td>O(4)-H(4O)···N(2)</td>
<td>1.23(3)</td>
<td>1.46(3)</td>
<td>2.680(2)</td>
<td>172(2)</td>
</tr>
<tr>
<td>C(4)-H(4)···N(3)</td>
<td>0.94(2)</td>
<td>2.62(2)</td>
<td>3.358(3)</td>
<td>136(2)</td>
</tr>
<tr>
<td>C(4)-H(4)···O(2)</td>
<td>0.94(2)</td>
<td>2.49(2)</td>
<td>3.356(3)</td>
<td>153(2)</td>
</tr>
</tbody>
</table>

*a symmetry operation: #1: 1/2+x, 1/2-y, 1/2+z; #2: 1-x, -y, 2-z.
REFERENCES


