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Effect of Milling on Solid State Transformation of Sulfamethoxazole

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Abstract: The purpose of this research was to investigate the influence of milling process on solid state transformation of sulfamethoxazole. Raw material Sulfamethoxazole was obtained from Virchow Lab. India. Milling was carried out by using Retsch Mühle with definite rate and pressure, for 10, 20 and 30 min. The milled samples were characterized by scanning electron microscope, powder X-ray diffraction, Fourier transform Infra Red Spectroscopy and thermal analysis DSC. Raw material sulfamethoxazole was found to be a form 1. According to SEM analysis, powder X-ray diffraction pattern, FT-IR analysis and thermal analysis, Milling process of form 1 sulfamethoxazole with various milling time didn't caused polymorphic transformation and amorphisation. But the milling can created defect on crystal lattice of sulfamethoxazole form 1. Milling process also reduced the particle size of sulfamethoxazole form 1, but not its crystallinity. The result of this research demonstrates that milling process can produced defect on crystalline solid of sulfamethoxazole form 1.

Key words: Sulfamethoxazole, milling, crystal defect

INTRODUCTION

The effects of pharmaceutical processing on the crystalline state of drug polymorphs and solvates have been discussed recently by Brittain and Fiese (1999). The stresses applied to crystals during pharmaceutical processing can cause defects in their crystal lattices and contribute to lattice disorder, thus affecting the physical properties of the resulting powder (Morris *et al*., 2001).

Milling is a key process in the preparation of many solid dosage forms, particularly in the last processing step in the production of bulk drug substance to reduce particle size, is often accompanied by a decrease in crystallinity due to the creation of lattice defects, beginning at the surface. The defects created by mechanical activation of the solid on the surface can migrate, transform and change their number and nature. If the defects in the mechanically activated crystal heal to produce a crystal lattice different from the initial lattice, then a polymorphic transformation has taken place (Vippagunta *et al*., 2001; Brittain, 2002). Milling induced polymorphic changes have been observed for many small drug molecules, such as ranitidine hydrochloride, famotidine and indomethacin (Chieng *et al*., 2006; Lin *et al*., 2006; Crowley and Zografi, 2002).

Sulfamethoxazole (SMZ), one of the sulfonamides is a class of drugs whose molecular structures contain the sulfanilamide moiety or a sulfanilamide analog. The structural resemblance between the sulfanilamide grouping and p-aminobenzoic acid enables the sulfanilamides to block folic acid synthesis in bacteria, which accounts for the antibacterial (bacteriostatic) action of these drugs. Sulfonamides exhibit interesting solid-state properties, among which is the ability for many of these drugs to exist in two or more polymorphic forms (Adsmond and Grant, 2001).

Pharmaceutical solid polymorphism is defined as the ability of a drug compound to crystallize into more than one different crystalline forms, which the molecule have different packing arrangement and/or conformations within the crystal lattice (Byrn *et al*., 1995). Different crystalline polymorph can significantly influence the physicochemical properties, formulation development and manufacturing production of drug, resulting in the problems of compatibility, dissolution, bioavailibility, bioactivity and shelf-life of drug substance (Newmann and Byrn, 2003).

The solid-state properties of sulfonamides have been studied by Yang and Guillory (1972), who postulated that the propensity for hydrogen bonding in the solid state, due to the presence of various hydrogen-bond donors and acceptors, can give rise to polymorphism. Crystal forms of Sulfamethoxazole are known to exist in three polymorphic form 1, 2 and 3 (hemihydrate) (Takasuka and Nakai, 2001).

The aim of this research was to study the effect of milling process on solid state transformation sulfamethoxazole using Retsch Mühle as a function of

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milling time. Scanning electron microscopy, powder X-ray diffraction, differential scanning calorimetry and Fourier transform infrared (FT-IR) spectroscopy were used to characterize the milled samples at milling times between 10 and 30 min.

MATERIALS AND METHODS

This study was performed in September-November 2007. Preparation of milled samples, FT-IR spectroscopic analysis and powder X-ray analysis was conducted in ITB Bandung Indonesia. Scanning electron microscope analysis was done in the centre research of geology Bandung Indonesia. While Thermal analysis DSC was conducted in the centre research of physics LIPI Bandung Indonesia.

Sulfamethoxazole was kindly obtained from P.T Pyridam (Imported from Virchow Lab. India, batch No. 09150307), the KBr crystal for the pellets.

Preparation of milled samples: A certain amount of sulfamethoxazole was respectively milled for different times 10, 20 and 30 min by Retsch Mühle apparatus. It was adjusted with definite rate and pressure.

Scanning electron microscopy: Electron-micrographs of crystal habit of unmilled and milled particles was examined using SEM (JEOL model JSM-6360LA, Tokyo, Japan). The specimen were mounted on a metal stub with double sided adhesive tape and coated under vacuum with gold-paladium (Au 80% and Pd 20%) prior to observation. The particles size of crystals was estimated from electron micrographs.

Powder X-ray diffraction: The XRD patterns of solid-state forms of sulfamethoxazole and the milled samples were measured using Philips PW 1710 diffractometer (Philips, Holland). Radiation generated from CuKα source. Current of 30 mA and generator voltage of 40 kV were used for the study. The instrument was operated over the 2θ range 5-40° with a step size of 0.01, time per step of 0.5 sec and receiving slit of 0.2 mm.

Differential scanning calorimetry: DSC analysis of approximately 6.5 mg samples in pin-holed aluminium crimped pans was performed using Seiko Instrument Inc. DSC (Japan), at heating rate of 10°C per min over a temperature range 30-200°C. Samples were purged with nitrogen gas at 60 mL min^{-1} throughout the analysis.

Fourier transform infrared (FT-IR) spectroscopy: The infrared spectra of the samples were obtained using KBr pellet using a FT-IR spectrophotometer (Jasco model FT-IR-4200 type A), over a range of 400-4000 cm^{-1}.

RESULTS AND DISCUSSION

Before milling process was performed on powder sample of sulfamethoxazole, it was characterized the crystal form by spectroscopy IR, thermal and powder X-ray diffraction analysis. It has been reported that crystal form of Sulfamethoxazole had three polymorphic form 1, 2 and 3 (hemihydrate), in which form 1 was the most stable form (Takasuka and Nakai, 2001; Yang and Guillory, 1972). Figure 1a shows DSC thermogram of raw material SMZ, it was observed single sharp endothermic peak at 172.7°C (melting point of SMZ). This endothermic peak was specific for polymorf 1 of SMZ. FT-IR Spectra of

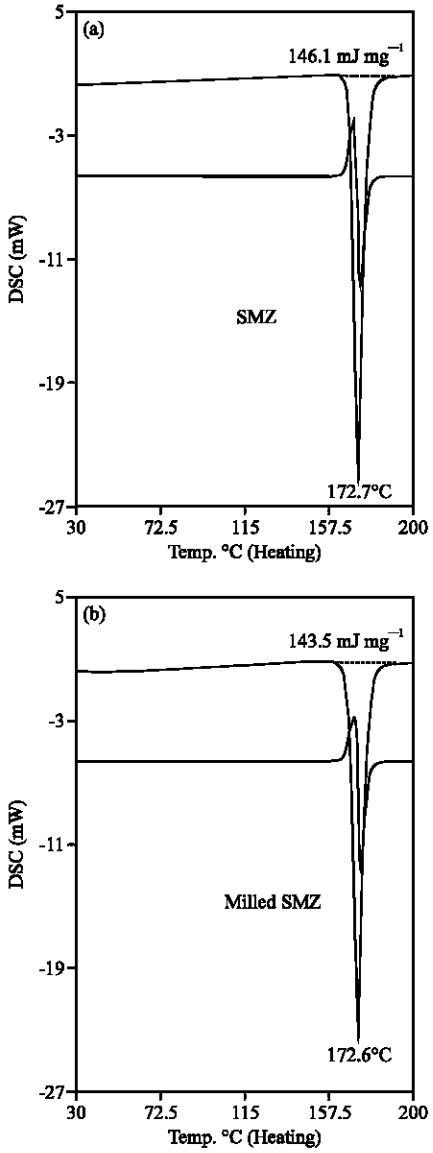

Fig. 1: DSC thermogram of (a) Unmilled SMZ and (b) milled SMZ after 30 min

SMZ also supported thermal analysis (Fig. 2), several characteristic absorption bands at 3300 dan 3150 cm^{-1} were observed that attributed to the amide N-H stretching vibration for form 1. Both data of this study were consistent with the report of previous studies. The raw material of sulfamethoxazole used in this study was proved to be a form 1.

In preparing pharmaceutical solid dosage form, milling process is generally used for reducing the particle size of a solid drug to increase its dissolution rate, particularly for water insoluble drug. Many papers have reported about the effect of milling on the physical and chemical properties of drugs (Lin *et al*., 2006; Heng *et al*., 2006). In the present study, the sulfamethoxazole form 1 was milled for variously of time. The changes in habit crystal, DSC thermogram, X-ray diffraction pattern and FT-IR spectra of sulfamethoxazole form 1 were determined.

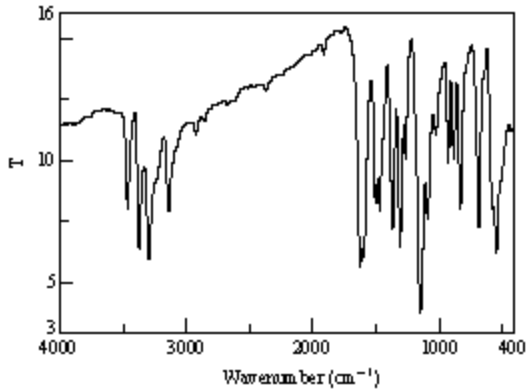

Fig. 2: FT-IR spectra of raw material of sulfamethoxazole

Upon milling, sulfamethoxazole form 1 showed a single endothermic event of melting (Fig. 1) with no significant difference in melting point between the milled and unmilled powder of SMZ. The milling process only changes in enthalpy values in milled (143.5 mJ mg^{-1}) and unmilled SMZ (146.1 mJ mg^{-1}) indicated occurrence of crystal defects during milling (Chikhalia *et al*., 2006).

The effect of milling on electron-micrographs of crystal habit of sulfamethoxazole is shown in Fig. 3. It showed plate like habit crystal of sulfamethoxazole form 1 was obtained from supplier. From the SEM images for the milled sample, Fig. 3b and d, it could be seen that particle size reduction was taken place and defect on surface of crystal was observed. However if SEM images was magnified until 10.000x (Fig. 3d), it can still found the habit crystal of microcrystalline of sulfamethoxazole form 1.

The mechanical processing can produce defect in crystalline solids has been known for sometime and it is equally established that defects can influence powder

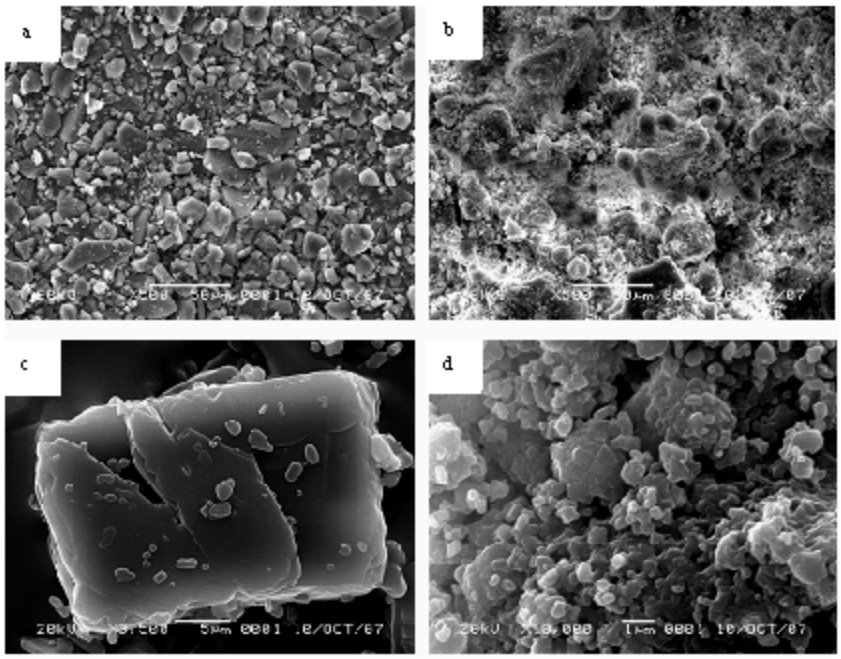

Fig. 3: Scanning electron micrographs of sulfamethoxazole powder (a) unmilled sample magnifications 500x, (b) milled 30 min magnifications 500x, (c) unmilled sample magnifications 3.500x and (d) milled sample 30 min magnifications 10.000x

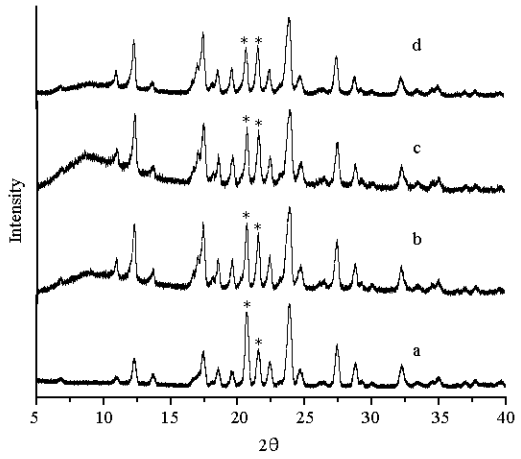

Fig. 4: The powder X-ray diffraction pattern of sulfamethoxazole (a) unmilled sample, (B) milled 10 min, (c) milled 20 min and (d) milled 30 min

properties. Point defects can be classified as vacancies (lattice sites from which units are missing), interstitials (molecules that have slipped into voids between lattice sites), or substitutionals (a foreign molecule occupying a lattice site). Additional defects that are encountered in crystals are line defects (i.e., edge and screw dislocations), or surface defects (i.e., tilt or twist boundaries). The mechanical activation actions of either grinding or compression serve to cause a variety of deformations and fractures in a solid, which is of sufficient magnitude, will serve to destroy the long-range order characteristic of a crystal and leave only the short-range order of an amorphous material (Brittain, 2002).

Introduction of a polymorphic species during milling is not an uncommon event and is well documented in the literature. Some phase transformation can take several hours to occur (Zhang *et al*., 2002), while others can occur in minutes (Lin *et al*., 2006). It is thought that phase changes in the solid state require three steps (Byrn *et al*., 1999); molecular loosening, solid solution formation and crystalisation of new phase.

The powder X-ray diffraction pattern of milled samples from different time of milling are shown in Fig. 4. powder X-ray diffraction is a useful method for determining the presence of amorf and polymorphic or crystal habit modifications in drug crystal. In general, for two form of crystal, when the pattern (i.e., peak position) are identical, they have the same internal structures. Whereas if the patterns are different, then the crystal have different internal structures and are polymorphic (Byrn *et al*., 1999). Here, all the sample exhibited interference with similar peak positions (2 theta values). Therefore, the presence of different phase in milled SMZ was ruled out. However the relative intensities of their

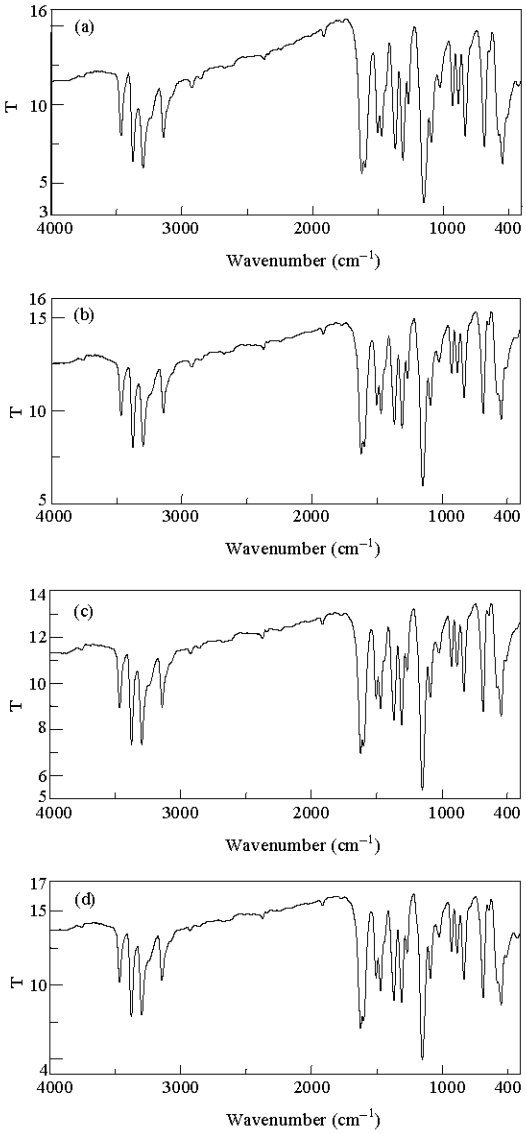

Fig. 5: FT-IR spectra of sulfamethoxazole (a) unmilled sample, (b) milled 10 min, (c) milled 20 min and (d) milled 30 min

interference peak XRD were modified. Peak intensities at 2 theta 20.6° and 21.5° as shown on Fig. 4 changed during milling. This was attributed to the markedly different crystal habit and crystal defect of the samples. Therefore, the relative abundance of the planes exposed to the X-ray would have been altered, producing the variations in the relative intensities of the interference peaks or this may be due to differences in the crystal sizes.

As presented in Fig. 5, the principal absorption bands in the infrared spectra of unmilled and milled of sulfamethoxazole form 1 were similar, suggesting there

were no differences between the internal structure and conformation of these samples. The infrared spectrum is extremely sensitive to structure and conformation of a compound and thus can be used to compare the structure of a compound in different solid states (Brittain, 1997).

CONCLUSION

Mechanical energy by milling process during 30 min were not able to transform solid state phase of sulfamethoxazole form 1. The milling only caused crystal defect on lattice and changes on particle size and crystal habit.

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