

Solid-State Reaction between Sulfacetamide and Phthalic Anhydride by Grinding¹⁾

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Sulfacetamide reacted with phthalic anhydride in the solid state and was gradually converted into phthalylsulfacetamide with mechanical grinding. Formation of phthalylsulfacetamide was confirmed by high pressure liquid chromatography and Fourier transform infrared spectroscopy. The X-ray diffraction pattern of ground powder of sulfacetamide and phthalic anhydride mixture (1:1 by molar ratio) gradually became a halo with the formation of phthalylsulfacetamide, indicating that amorphous phthalylsulfacetamide was obtained by the solid-state reaction with mechanical grinding. The solid-state reaction between sulfacetamide and phthalic anhydride also occurred when a mixture of the two was heated. Crystalline phthalylsulfacetamide was formed by the solid-state reaction with heating.

Keywords solid-state reaction; grinding; amorphous; sulfacetamide; phthalic anhydride

Grinding (comminution) is defined as the process of particle size reduction in pharmaceutical manufacturing.²⁾ It is known that grinding may decrease the crystallinity of crystalline powder and alter the molecular state of pharmaceuticals in solid dosage forms. Therefore, there are many reports about the effect of grinding on the physicochemical and pharmaceutical properties of solid dosage forms.³⁾ Nakai *et al.*, stated that when solid pharmaceuticals were ground with microcrystalline cellulose or cyclodextrins, ground powders became amorphous and showed anomalous pharmaceutical properties.⁴⁾ The effect of grinding on chemical stability of *p*-aminosalicylic acid crystals was also examined.⁵⁾

In the field of pharmaceutical sciences, the solid-state reactions of thermal decomposition and photochemical dimerization have been investigated,⁶⁾ and more recently, there has been progress in detailed studies on topochemical and topotactic reactions in organic crystals and several reviews have been published.⁷⁾ There are, however, few reports about the solid-state reaction of pharmaceuticals by mechanical grinding.

Sulfacetamide (SA) reportedly reacted with phthalic anhydride (PHAN) and was partly converted into phthalylsulfacetamide (PHSA) by heating (Chart 1).⁸⁾ In the present report, we confirmed the formation of PHSA by mechanical grinding of SA and PHAN powders and investigated the physicochemical properties of PHSA obtained.

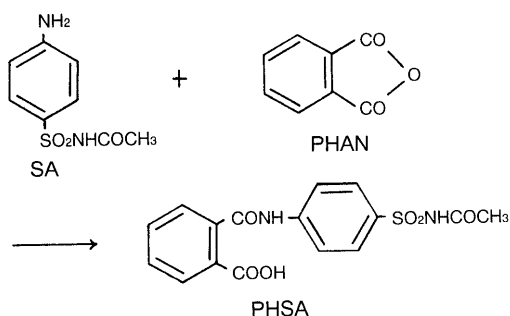


Chart 1. Reaction between SA and PHAN

Experimental

Materials SA (Sigma Co., Ltd.), PHSA (Sigma Co., Ltd.) and PHAN (Koso Chemical Co., Ltd.) were used after being passed through a 250 mesh (63 μ m) sieve. Specific surface areas of SA and PHAN powders were measured to be 1.0 and 0.6 m²/g, respectively, by N₂ gas adsorption method. Other materials used were of reagent grade.

Reaction of SA and PHAN Various molar ratios of crystalline SA and PHAN powders were ground by a ball mill made of tungsten carbide using a grinding apparatus (P-6, Fritsch Co.). Aliquots were taken from the mill at appropriate time intervals, and the remaining (unreacted) amount of SA was determined as described later. In the reaction by heating, the mixture of SA and PHAN powders was compressed under 700 kg/cm² using flat faced punches 6 mm in diameter, and the tablets were heated at various temperatures in an oven. The reaction did not occur only by the compression of mixture of SA and PHAN powders.

Quantitative Analysis of SA The remaining (unreacted) amount of SA was calorimetrically analyzed by diazotization and a coupling with *N*-(2-diethylaminoethyl)-1-naphthylamine oxalate.

High Pressure Liquid Chromatography (HPLC) A Shimadzu LC-6 chromatograph fitted with a C-R6A chromatopack and an octadecyl silica (ODS) column (4.6 i.d. \times 150 mm) was used. The mobile phase consisted of acetonitrile–water (4:1). The flow rate was 0.7 ml/min and ultraviolet (UV) absorption was monitored at 270 nm.

X-Ray Diffraction A RAD type diffractometer (Rigaku Co., Ltd.) was used. The X-ray source was Cu-K α , and the diffracted beam was monochromated by a bent graphite monochromator. Sample powder (150 mg) was packed in a glass plate.

Fourier Transform Infrared Spectroscopy (FTIR) An FTIR-7300 (Nihon Bunko Co., Ltd.) with a powder reflection attachment was used. Sample powder was lightly mixed with micronized KBr powder by spatulation. Spectra were obtained by averaging 200 scans with the resolution at 4 cm⁻¹.

Results

Solid-State Reaction between SA and PHAN by Mechanical Grinding Figure 1 shows the amount of SA remaining after grinding with PHAN at various molar ratios; the amounts were decreased by the grinding. Figure 2 shows changes in the HPLC chromatogram of the mixture of SA and PHAN with the grinding. Peaks for SA, PHAN, and PHSA were observed at retention times of 3.2, 4.1 and 2.1 min, respectively. The peak intensities for SA and PHAN decreased gradually, while that for PHSA increased with longer grinding time. No peak was observed for the decomposition and other reaction products in the HPLC chromatogram of the ground samples. Figure 3 shows the FTIR spectra for SA, PHAN,

PHSA, and ground powders. The intensities of two ν_{NH} observed around 3500 cm^{-1} and δ_{NH} at 1640 cm^{-1} for the SA molecule decreased, and the intensity of a new band at 1550 cm^{-1} , which may be attributable to the formation of PHSA, increased gradually with the progress of mechanical grinding. These results indicate that SA was converted into PHSA by mechanical grinding with PHAN.

Figure 4 shows the changes of X-ray powder diffraction pattern of the mixture of SA and PHAN powders with mechanical grinding. Peaks attributable to SA crystals decreased gradually, and the diffraction pattern became a halo. This result indicates that an amorphous PHSA was formed by mechanical grinding of SA and PHAN powders.

Solid-State Reaction between SA and PHAN by Heating Figure 5 shows changes in the amount of SA remaining after heating of compressed SA and PHAN

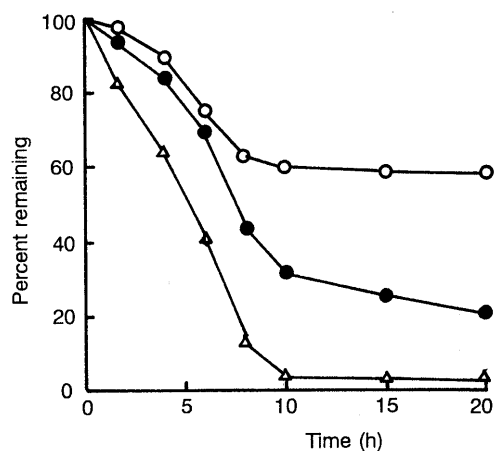


Fig. 1. Change in the Amount of Remaining SA with Mechanical Grinding with PHAN

Molar ratio of SA and PHAN: \circ , 2:1; \bullet , 1:1; \triangle , 1:3. Each point represents the mean value for three measurements.

powders (1:1 by molar ratio) at various temperatures. Changes in the HPLC chromatogram and FTIR spectra of the heating samples indicated that heating caused the formation of PHSA. A portion of SA was converted into PHSA, and the reaction did not progress further. This may be the result of the propagation of reaction being controlled by the reaction temperature.

Figure 6 shows the changes in X-ray diffraction patterns of heating samples of SA and PHAN (1:1 by molar ratio). The intensities of diffraction peaks of SA and PHAN crystals decreased and several new peaks appeared with heating. Among the newly observed peaks, there were some which were not present in the pattern of PHSA crystals purchased from a commercial source. Since HPLC chromatograms did not show the presence of any other

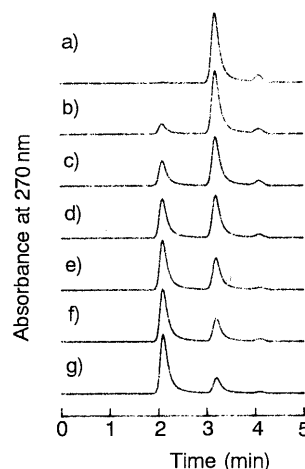


Fig. 2. Change in the HPLC Chromatogram of SA and PHAN Mixture (1:1 by Molar Ratio) with Mechanical Grinding

a) before grinding, b) ground for 2 h, c) ground for 4 h, d) ground for 6 h, e) ground for 8 h, f) ground for 10 h, g) ground for 20 h.

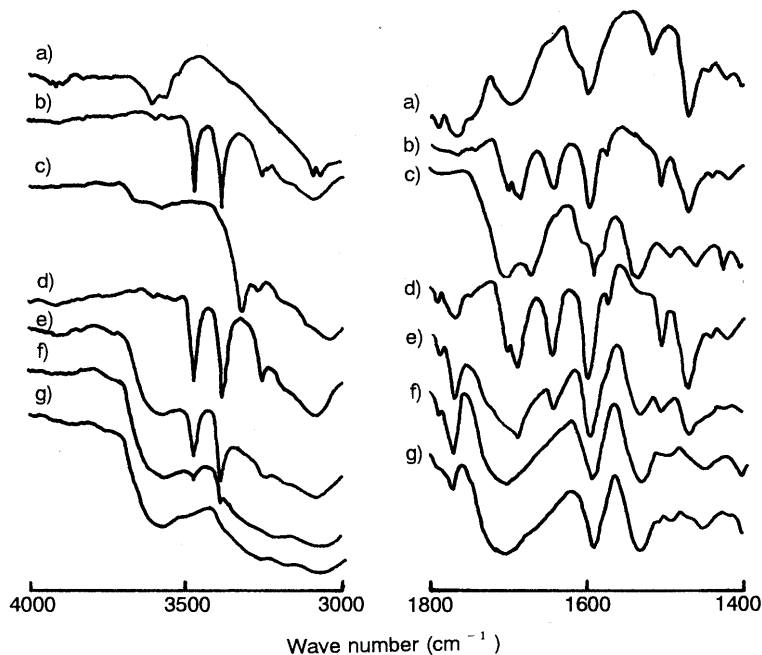


Fig. 3. Change of FTIR Spectra of SA and PHAN Mixture (1:1 by Molar Ratio) with Mechanical Grinding

a) PHAN, b) SA, c) PHSA, d) before grinding, e) ground for 4 h, f) ground for 8 h, g) ground for 20 h.

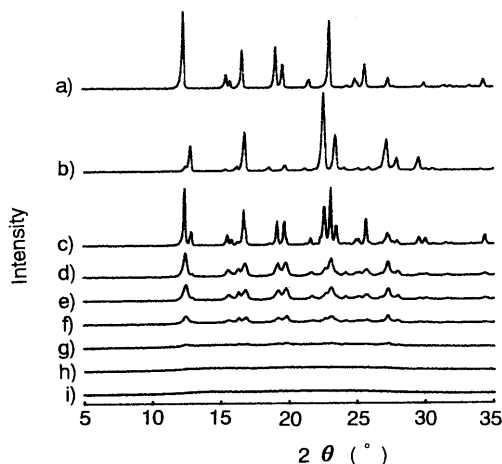


Fig. 4. Change of X-Ray Powder Diffraction Pattern of SA and PHAN Mixture (1:1 by Molar Ratio) with Mechanical Grinding

a) PHAN, b) SA, c) before grinding, d) ground for 2 h, e) ground for 4 h, f) ground for 6 h, g) ground for 8 h, h) ground for 10 h, i) ground for 20 h.

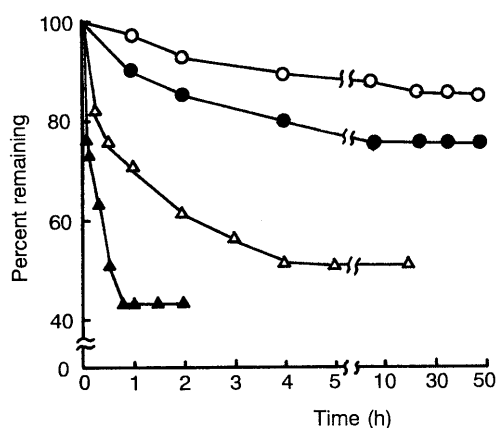


Fig. 5. Change in the Amount of Remaining SA in Tablet of SA and PHAN Mixture (1:1 by Molar Ratio) with Heating at Various Temperatures

Temperature: \circ , 90°C; \bullet , 100°C; \triangle , 110°C; \blacktriangle , 120°C. Each point represents the mean value for three measurements.

products than PHSA, this result may indicate that some polymorphic forms of PHSA were obtained by the solid-state reaction with heating.

Discussion

The solid-state reaction between SA and PHAN proceeded not only by heating but also by mechanical grinding. PHSA obtained by the solid-state reaction with mechanical grinding was an amorphous form. When SA, PHAN and PHSA were ground alone under the same conditions, they did not become amorphous; PHSA was therefore considered to become amorphous when accompanied by the solid-state reaction by mechanical grinding. Since amorphous solids usually have a higher dissolution rate than crystalline solids, they are considered preferential for poorly soluble drugs. There are several methods for preparing an amorphous powder, such as

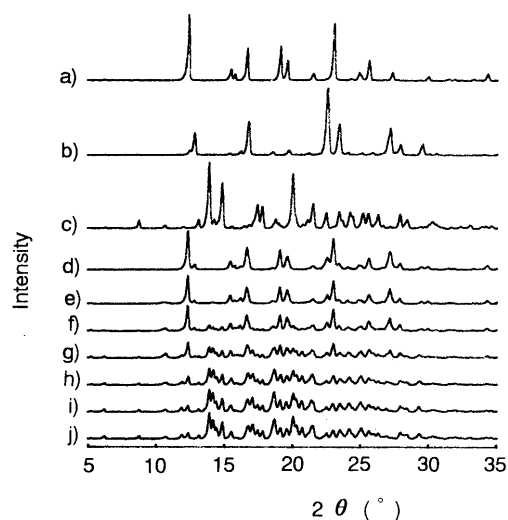


Fig. 6. Change of X-Ray Powder Diffraction Pattern of SA and PHAN Mixture (1:1 by Molar Ratio) with Heating at 120°C

a) SA, b) PHAN, c) PHSA, d) before heating, e) heating for 5 min, f) heating for 10 min, g) heating for 20 min, h) heating for 30 min, i) heating for 45 min, j) heating for 60 min.

cooling the melts, freeze-drying, spray-drying, and so on.⁹⁾ The present report has described a new method for the preparation of amorphous powder using the solid-state reaction by mechanical grinding.

PHSA obtained by the heating of SA and PHAN powders was in a crystalline form. The findings suggest the difference in the mechanism of the solid-state reaction when obtained by mechanical grinding and by heating. The mechanism of solid-state reactions by mechanical grinding will be discussed in a following paper.

References and Notes

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