

[Chem. Pharm. Bull.]
30(2) 734-738 (1982)

Effects of Grinding with or without Microcrystalline Cellulose on the Decomposition of *p*-Aminosalicylic Acid

YOSHINOBU NAKAI,* SHIN-ICHIRO NAKAJIMA,¹⁾ KEIJI YAMAMOTO,
KATSUhide TERADA, MASAFUMI SUENAGA, TAKAKO KUDOH

Faculty of Pharmaceutical Sciences, Chiba University, 1-33
Yayoicho Chiba 260, Japan

(Received July 23, 1981)

The decomposition rates of *p*-aminosalicylic acid were measured in four samples, recrystallized crystals, ground crystals, physical mixture with microcrystalline cellulose and ground mixture with microcrystalline cellulose. The drug in the ground mixture is markedly unstable at 40°C as compared with the physical mixture and the recrystallized crystals. This instability could be attributed to the molecular-scale drug dispersion in the ground mixture together with the presence of sorbed water in the cellulose.

At 80°C the ground crystals decomposed at a constant rate while the decomposition-time curves of the recrystallized crystals exhibited sigmoid characteristics. It is concluded that in the ground crystals, *m*-aminophenol formed does not act as autocatalytic nuclei.

Keywords—decomposition; grinding; stability; dispersion; *p*-aminosalicylic acid; X-ray

A number of papers have been published recently about the effects of grinding on the chemical and physical properties of organic compounds.²⁻⁵⁾ When organic compounds were ground with microcrystalline cellulose or cyclodextrins, both components became amorphous and the ground mixtures showed some peculiar physical properties, that is, loss of the heat of fusion in differential thermal analysis (DTA), the repression of sublimation, faster dissolution and improved bioavailability.⁶⁻⁸⁾ However, little is known about the effect of grinding on the chemical stability of organic compounds in the ground mixture. A study on the reaction rate in the ground mixture seemed desirable.

p-Aminosalicylic acid, an antitubercular agent, decomposes into *m*-aminophenol and carbon dioxide both in the solid state and in solution. The kinetics and mechanisms of the *p*-aminosalicylic acid decomposition have been investigated by many researchers.⁹⁻¹¹⁾ Lin *et al.* reported that the solid-state decarboxylation probably occurs by the same mechanism as the solution reaction (proton electrophilic substitution).^{12,13)}

This report deals with the decarboxylation rates of *p*-aminosalicylic acid in ground mixtures with microcrystalline cellulose, in which *p*-aminosalicylic acid molecules are dispersed monomolecularly. Furthermore, we also investigated the mechanochemical effect on *p*-aminosalicylic acid crystals.

Experimental

Materials—*p*-Aminosalicylic acid of guaranteed reagent grade was obtained from Nakarai Chemicals Ltd. and was used after recrystallization from ethanol. Microcrystalline cellulose (Avicel PH-101, Asahi Chemical Industrial Co.) was used after being dried at 110°C for 3 h. Other chemicals were of analytical reagent grade and were used without further purification.

Grinding of *p*-Aminosalicylic Acid with Microcrystalline Cellulose—A physical mixture of *p*-aminosalicylic acid and microcrystalline cellulose was prepared in a weight ratio of 1:9. The ground mixture was obtained by grinding the above physical mixture for definite times in a vibrational mill made of tungsten carbide, as described previously.¹⁴⁾

Grinding of *p*-Aminosalicylic Acid Crystal—A 2 g sample of recrystallized *p*-aminosalicylic acid (size between 20 and 50 mesh) was ground for 10 or 30 min as described above.

The Measurement of Decarboxylation Rate—To determine the percentage of *p*-aminosalicylic acid

remaining in the stored samples, *m*-aminophenol, the decomposition product, was analyzed by the spectrophotometric method reported by Watanabe and Kamata.¹⁵⁾ For the absorbance measurement, a Hitachi 124 spectrophotometer was used.

One procedure we used to investigate the effect of grinding on the decomposition of *p*-aminosalicylic acid was as follows. The samples employed were recrystallized crystals, the physical mixture with microcrystalline cellulose, and the ground mixture with microcrystalline cellulose. A series of vials, each containing 20 mg of *p*-aminosalicylic acid (net weight), were kept in desiccators in which the relative humidities were maintained at 0, 32, 71, and 100%. Saturated salt solution systems were used to achieve constant humidities. The desiccators were kept in an air thermostat at 40°C. At intervals, samples were removed for analysis.

Another procedure was used for the recrystallized crystals, the 10-min-ground crystals, and the 30-min-ground crystals. Samples (50 mg) were stored at 75°C, 80°C, and 85°C under dry conditions. The amounts decomposed were determined after various times.

Powder X-ray Diffraction Measurement—A Rigaku Denki 2204 diffractometer was used. The measurement conditions were the same as those reported in the previous paper.¹⁶⁾

Specific Surface Area Measurement—A nitrogen gas adsorption apparatus was used as reported previously.¹⁶⁾

Thermal Analysis—A Shimadzu DT-20B unit was used for the measurements of thermogravimetry (TG) and DTA curves. The scanning speed was 5°/min.

Results and Discussion

Grinding of *p*-Aminosalicylic Acid with Microcrystalline Cellulose

Some typical powder X-ray diffraction patterns are shown in Fig. 1. The prolonged grinding of *p*-aminosalicylic acid crystals caused little change in the diffractogram, indicating that the crystalline state is fairly stable to grinding, while the pattern of the ground mixture with microcrystalline cellulose became halo. In the previous papers, the authors reported that the disappearance of the X-ray diffractive peaks in the ground mixtures was due to molecular-scale drug dispersion in the matrix.^{5,6)} The *p*-aminosalicylic acid molecules seem to exist in such a dispersed state here.

The decomposition of *p*-aminosalicylic acid after constant vibrational grinding for 1h was 0.57%.

Figure 2 illustrates the time course of decomposition of *p*-aminosalicylic acid at 40°C and relative humidity (RH) 0%. In the ground mixture, *p*-aminosalicylic acid decomposition occurred to a great extent. However, storage with microcrystalline cellulose resulted in

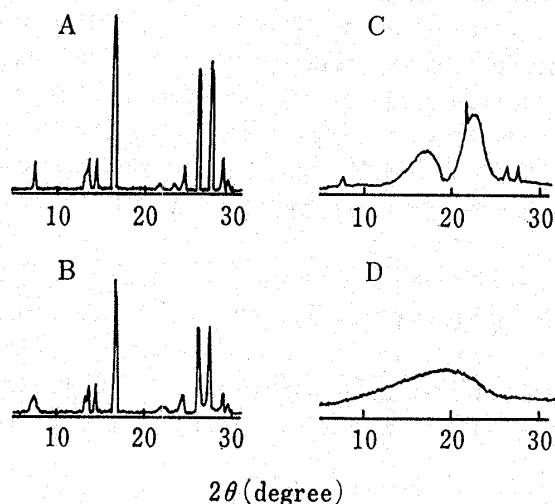


Fig. 1. Powder X-ray Diffractograms of *p*-Aminosalicylic Acid

- A: recrystallized crystals
- B: 10-min-ground crystals.
- C: physical mixture with microcrystalline cellulose.
- D: ground mixture with microcrystalline cellulose.

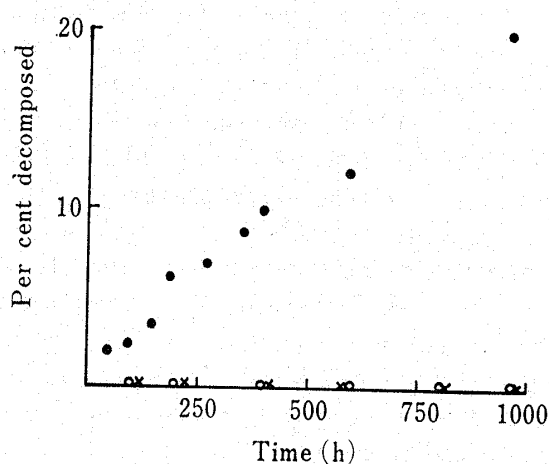


Fig. 2. Plots of the *p*-Aminosalicylic Acid Decomposed against Time at 40°C and Relative Humidity 0%

- ×: recrystallized crystals.
- : physical mixture with microcrystalline cellulose.
- : ground mixture with microcrystalline cellulose.

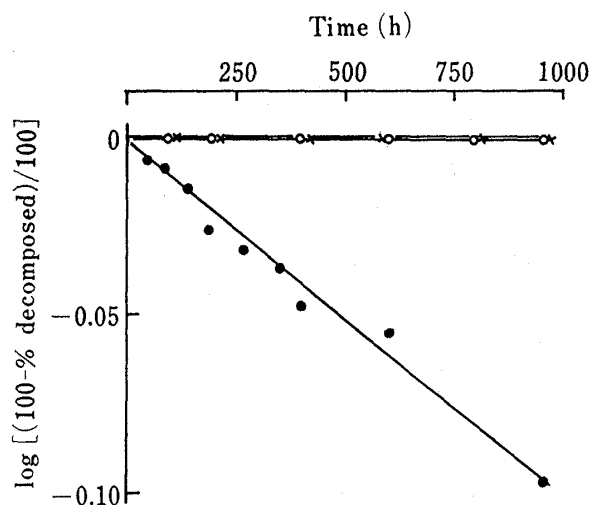


Fig. 3. First-Order Plots of *p*-Aminosalicylic Acid Decomposition at 40°C and Relative Humidity 0%

×: recrystallized crystals.
○: physical mixture with microcrystalline cellulose.
●: ground mixture with microcrystalline cellulose.

TABLE I. First Order Decomposition Rate Constants of *p*-Aminosalicylic Acid under Various Relative Humidities at 40°C

Relative humidity (%)	—Rate constant $\times 10^5$ (h ⁻¹)—		
	Recrystallized crystals	Physical mixture with MCC ^{a)}	Ground mixture with MCC
0	n.d. ^{b)}	0.0761	20.4
32	n.d.	5.16	67.9
71	0.430	24.0	103
100	22.4	69.0	155

a) MCC indicates microcrystalline cellulose.

b) Not detectable.

negligible decomposition. When the logarithms of remaining percentage of *p*-aminosalicylic acid were plotted *versus* time, linear relationships were found, as shown in Fig. 3. As similar relationships were also obtained in other experiments, the apparent first-order rate constants were calculated. The results are summarized in Table I. At low RHs, the stability of *p*-aminosalicylic acid in the ground mixture was markedly reduced as compared with that in the physical mixture and the intact crystals. At 71% RH, however, the decomposition rates became greater. At all four RHs, the decomposition rates observed in the ground mixture were highest.

In the ground mixture, the *p*-aminosalicylic acid molecules are dispersed monomolecularly, which results in an increase in the number of reaction sites, and leads to enhanced decomposition of *p*-aminosalicylic acid.

As shown in Table I, all samples showed increasing decomposition rates with increasing RH. Carstensen and his coworkers studied the effects of sorbed water on the stability of *p*-aminosalicylic acid.¹⁷⁾ They reported that the presence of water increased the decomposition rate of *p*-aminosalicylic acid. In this study, the samples were stored at the same RHs, but their water contents were not identical. Microcrystalline cellulose contains 4.8% water at RH 0%, 6.0% at RH 32%, 6.7% at RH 71% and 9.9% at RH 100%. Ground microcrystalline cellulose samples showed about 1.8 times higher water contents as compared to intact microcrystalline cellulose.¹⁶⁾ Therefore, it is likely that the effect of water will vary significantly among the ground mixture, the physical mixture and the intact crystals.

In the ground mixture, the fast decomposition of *p*-aminosalicylic acid could be attributed to the molecular-scale drug dispersion together with the presence of sorbed water on the ground microcrystalline cellulose. The greater decomposition rates in the physical mixtures as compared with the intact crystals can also be explained in terms of the sorbed water on the microcrystalline cellulose.

Single Grinding of *p*-Aminosalicylic Acid

Figure 4 illustrates the per cent decomposition-time curves of *p*-aminosalicylic acid in a dry state at 75°C, 80°C and 85°C. The curves for the intact crystals exhibited the usual sigmoid characteristics which are frequently observed for solid-state decomposition.¹⁸⁾ With the ground crystals, however, the decomposition occurred at a constant rate without an

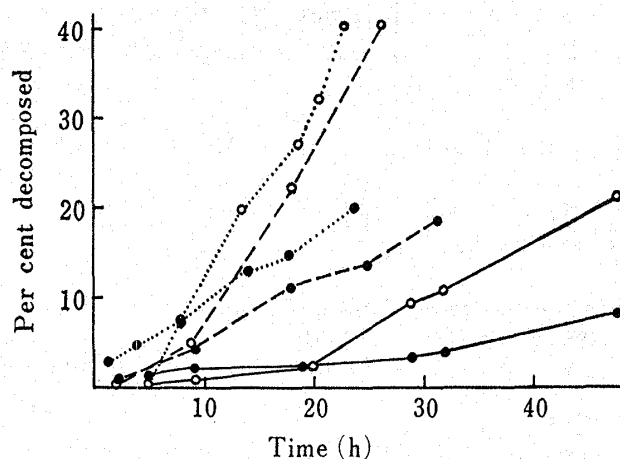


Fig. 4. The Effects of Grinding on the Rate of *p*-Aminosalicylic Acid Decomposition at 75°C, 80°C, and 85°C in the Dry State

○: recrystallized crystals.
●: 10-min-ground crystals.
Solid lines, broken lines, and dotted lines show the results at 75°C, 80°C, and 85°C, respectively.

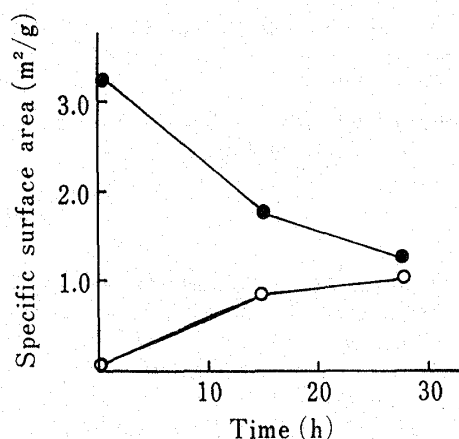


Fig. 5. The Relationship between the Specific Surface Area and the Reaction Time

○: recrystallized crystals.
●: 30-min-ground crystals.

appreciable induction period, in a manner similar to that reported by Kornblum *et al.*¹⁹⁾ From the figure, it is clear that the ground crystals are more stable than the intact ones after 20 h at 75°C, after 10 h at 80°C and after 8 h at 85°C respectively.

We investigated the effect of the intensity of the mechanical grinding on the decomposition patterns of *p*-aminosalicylic acid, using two specimens, one that had been ground for 1 min with a mortar and a pestle, and one that had been ground for 30 min with the tungsten carbide vibrational mill. In the cases of the slightly ground samples, the decomposition-time curves coincided with those of the intact crystals at all temperatures examined. The decrease of the particle size obtained by the grinding with a mortar and a pestle did not affect the solid state decomposition patterns. On the other hand, the decomposition-time curves of the 30-min-ground sample showed good agreement with the curves of the 10-min-ground sample illustrated in Fig. 4.

Figure 5 shows the variations in the specific surface area of *p*-aminosalicylic acid crystals at 80°C. For the intact crystals, the specific surface area could not be detected at $t=0$, but the value increased with increasing reaction time. This result can be attributed to the micronization of the crystal arising from the production of carbon dioxide. After 30-min grinding, the specific surface area had reached 3.5 m²/g and the mean particle size was calculated to be 1.1 μ m (diameter). In contrast to the intact crystals, the value of the 30-min-ground sample decreased due to sintering as the reaction time increased.

The single grinding of *p*-aminosalicylic acid crystals did not lead to marked variations in the TG and DTA curves, as was the case with the X-ray diffraction patterns (Fig. 1).

These results show that fundamental changes of the crystal structure, such as the disruption of dimer structure and the formation of the amorphous state, did not occur during the grinding. The solid state decomposition of *p*-aminosalicylic acid proceeds by the mechanism of proton electrophilic substitution, that is, the addition of a carboxylate proton to the C-1 atom. Lin *et al.* calculated a contact distance of 5 Å between the acid proton and the carbon atom, and they suggested that the reaction can proceed in several directions.^{11,12)}

The decarboxylation process contains two steps; the first is evolution of *m*-aminophenol at a slow rate, and the second is the autocatalytic progress of the reaction from *m*-aminophenol (nuclei) to the surroundings. In the intact crystals, the reaction propagates successively from the nuclei in such a manner. However, successive reaction may be difficult in the ground crystals, due to the small particle size and the presence of crystal boundaries within

particles. That is, when the reaction progresses to a crystal boundary its progress may be inhibited by the lattice defect. Consequently, the plot of per cent decomposition *versus* time is linear.

Acknowledgement This work was supported in part by a grant from the Ministry of Education, Science and Culture of Japan.

References and Notes

- 1) Present address; *Yamanashi Medical University, Tamahomura Yamanashi, Japan.*
- 2) N. Kaneniwa, A. Ikekawa, and M. Sumi, *Chem. Pharm. Bull.*, **26**, 2734 (1978).
- 3) K. Sekiguchi, K. Shirotani, H. Yuasa, E. Suzuki, and F. Nakagawa, *Chem. Pharm. Bull.*, **28**, 3203 (1980).
- 4) Y. Nakai, *Funtai Kogakukaishi*, **16**, 473 (1979).
- 5) I. Krycer and J.A. Hersey, *Powder Tech.*, **28**, 91 (1981).
- 6) Y. Nakai, E. Fukuoka, S. Nakajima, and K. Yamamoto, *Chem. Pharm. Bull.*, **25**, 3340 (1977).
- 7) Y. Nakai, E. Fukuoka, S. Nakajima, and Y. Iida, *Chem. Pharm. Bull.*, **26**, 2983 (1978).
- 8) K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai, *J. Pharm. Sci.*, **65**, 1484 (1976).
- 9) N. Tanaka and M. Nakagaki, *Yakugaku Zasshi*, **81**, 597 (1961).
- 10) G.E. Dunn, E.G. Janzen, and W. Rodewald, *Can. J. Chem.*, **46**, 2905 (1968).
- 11) G.E. Dunn and H.F. Thimm, *Can. J. Chem.*, **55**, 1342 (1977).
- 12) C.T. Lin, P.Y. Siew, and S.R. Byrn, *J. Chem. Soc. Perkin II*, **1978**, 957.
- 13) C.T. Lin, P.Y. Siew, and S.R. Byrn, *J. Chem. Soc. Perkin II*, **1978**, 963.
- 14) Y. Nakai, S. Nakajima, K. Yamamoto, K. Terada, and T. Konno, *Chem. Pharm. Bull.*, **26**, 3419 (1978).
- 15) A. Watanabe and M. Kamata, *Yakugaku Zasshi*, **72**, 972 (1952).
- 16) Y. Nakai, E. Fukuoka, S. Nakajima, and J. Hasegawa, *Chem. Pharm. Bull.*, **25**, 96 (1977).
- 17) J.T. Carstensen and P. Pothisiri, *J. Pharm. Sci.*, **64**, 37 (1975).
- 18) D. Dollimore and D. Tinsley, *J. Chem. Soc. A*, **1971** 3043.
- 19) S.S. Kornblum and B.J. Sciarrone, *J. Pharm. Sci.*, **53**, 935 (1964).