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Effects of Grinding on Physical and Chemical Properties of Crystalline Medicinals with Microcrystalline Cellulose. I. Some Physical Properties of Crystalline Medicinals in Ground Mixtures

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Crystalline medicinals were ground with microcrystalline cellulose by a stainless steel shaker mill. The medicinal changed in their physical properties in grinding the mixture of a 10% medicinal. X-ray reflection lines due to the medicinal decreased in their intensities with the increasing time of grinding. The intensity of characteristic lines was not observed after the 2 hr grinding and halo pattern was obtained. The heat of fusion due to the medicinals was not observed for the 2 hr ground mixture. There was the critical content of medicinals in the ground mixture to show the halo pattern on the X-ray diffractogram and no heat of fusion on the thermogram. The medicinals were released rapidly from the ground mixtures in the aqueous solution and the solution reached the saturated concentration in a very short time. These phenomena occurred in all crystalline medicinals independent of the molecular properties, such as structure, size, and polarity. The residual cellulose, the ground mixture of benzoic acid from which the acid had been released, had the large pore volume of capillaries at about 30—40 Å. It was estimated that the medicinal molecules were dispersed within the cellulose as a molecule or a microassembly of the molecules having no preferred orientation. The assembly was probably isolated being enclosed by the cellulose molecules which were bound by hydrogen bond. The ground mixture may be regarded as an "entropy frozen solution," that is, a medicinal dissolves in cellulose without the ability of molecular translation movement.

Keywords——microcrystalline cellulose; crystalline medicinals; mechanochemistry; grinding; crystallinity; X-ray diffraction; heat of fusion; dissolution rate; pore size distribution

In manufacturing powdered preparations, grinding is generally used for reducing the particle size of a solid, since the dissolution rate is strongly affected by the particle size. It has been reported that a strong grinding force gives to a solid an increase in the activation energy on the surface[2] and in the distortion of the crystal lattice[3] together with reducing the size. The field of research including these studies is called mechanochemistry[4] and only inorganic materials have been studied.

Physical properties of microcrystalline cellulose (M.C.C.) were reported in the previous papers[5] where the crystallinities and the fine structures were evaluated for M.C.C. and the ground M.C.C. In this study, organic crystals of medicinals were ground together with M.C.C., and changes in the physical properties of the medicinals were examined.

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3) *a*) G. Yamaguchi and K. Sakamoto, *Bull. Chem. Soc. Jpn.*, **32**, 1364 (1959); *b*) C.E. Pearce and D. Lewis, *J. Catalysis*, **26**, 318 (1972).
4) T. Kubo, "Mechanochemistry Gairon," Tokyo Kagaku Dojin, Tokyo, 1971.
5) *a*) Y. Nakai, E. Fukuoka, S. Nakajima, and J. Hasegawa, *Chem. Pharm. Bull.* (Tokyo), **25**, 96 (1977); *b*) Y. Nakai, E. Fukuoka, S. Nakajima, and K. Yamamoto, *ibid.*, **25**, 2490 (1977).

Experimental

(1) **Materials**——M.C.C.[6] was kept in a desiccator containing P_2O_5 at room temperature for a week. Water content of the dried sample was 4%. Benzoic acid, salicylic acid, and aspirin were of J.P. VIII. Chloramphenicol palmitate (α-form, mp 87°), mefenamic acid, and diazepam were supplied from Sankyo Co. Ltd. Sulfisomezole was supplied from Shionogi and Co. Ltd. All other chemicals were reagent grade.

(2) **Grinding of Mixture of M.C.C. and Medicinals**——A stainless steel shaker mill[7] was used. The volume of the mill was 38 ml, diameter of balls 11 mm, number of balls 17, and weight of sample 1 g. Unless otherwise stated, grinding was carried out for 2 hr.

(3) **X-ray Diffraction (Powder Method)**——Rigakudenki D-3F was used. The measurement conditions were the same as those reported in the previous paper.[5a]

(4) **Measurement of Nitrogen Gas and Water Vapor Adsorption**——The apparatus and the procedures were the same as those reported in the previous paper.[5a]

(5) **Procedures for Dissolution Studies**——250 ml of test solution previously kept at a definite temperature (25° or 30°) was added into 300 ml flask, which was immersed in a constant temperature bath and contained an excess amount of medicinal beyond its equilibrium solubility. Then the solution was stirred with the two-wings glass stirrer at 200 rpm. About 5 ml of the solution was pipetted at definite time intervals, and filtered by a Millipore filter (0.2 μ). The concentration of the filtrate was measured by Hitachi 124 spectrophotometer. The test solution was a 0.1 N HCl solution for benzoic acid, and a distilled water for chloramphenicol palmitate. Fine crystal powder smaller than 200 mesh size was used as the reference test. For the dissolution test of benzoic acid, dioctyl sodium sulfosuccinate was added 0.01% to the test solution in order to disperse the particles.

Dissolution behavior of benzoic acid was also studied using C_2H_5OH and CCl_4 as dissolution media. Each 30 ml of the organic solvent or 0.1 N HCl solution was added into individual flasks which contained 500 mg of the ground mixture. The solutions were kept at $30\pm0.1°$ during the test and were shaken horizontally at the rate of 50 strokes/min. An aliquot of the solution was withdrawn at definite time intervals using a Millipore filter (0.2 μ).

(6) **Thermometric Measurements**——Differential thermal analyser[8] (DTA) and differential scanning calorimeter[9] (DSC) were used for the measurements of melting point and heat of fusion. Scanning speed ranged from 1 to 5°/min. Sample weight was about 3 mg.

Results and Discussion

(1) Changes in the X-ray Diffraction Patterns

X-ray diffraction patterns of the mixture of 10% benzoic acid and 90% M.C.C. are shown in Fig. 1. Fig. 1(A) shows the diffraction pattern of the physical mixture. It consisted of the superposition of the patterns of the benzoic acid and M.C.C.—the radiation diffracted by benzoic acid crystals (the benzoic acid peaks), crystalline portion of M.C.C. (the M.C.C. crystalline peaks), and the diffuse background due to amorphous portion of M.C.C. Indices of the reflections from planes of the benzoic acid crystals are indicated in this figure. Each component contributed its own pattern with an intensity proportional to the amount present in the mixture. Fig. 1(B) shows the pattern of the mixture after the 1/2 hr grinding. The M.C.C. crystalline peaks and the benzoic acid peaks decreased in their intensities. The peak intensity of each characteristic line decreased with the increasing grinding time and halo pattern was observed after the 2 hr grinding as shown in Fig. 1(C). It was reported in the previous paper[5a] that the M.C.C. crystalline peaks decreased with the increasing grinding time and halo pattern was observed after the long time grinding.

In the case of grinding the mixture of M.C.C. and benzoic acid, the benzoic acid peaks together with the M.C.C. crystalline peaks were not observed after the 2 hr grinding. By the X-ray transmission technique, the benzoic acid peaks were not also observed.

The effect of grinding with M.C.C. on diffraction patterns was examined for other crystalline medicinals. The results are shown in Table I where the symbols A and C indicate amor-

6) Avicel PH-101 (Asahi Chemical Industrial Co. Ltd.).
7) Yanagimoto Seisakusho Co. Ltd.
8) Shimazu DT-10.
9) Perkin-Elmer DSC-1B.

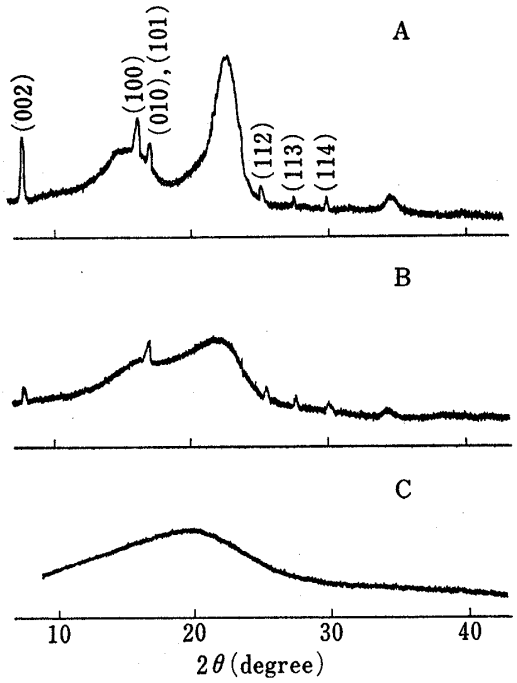

Fig. 1. X-ray Diffraction Patterns of the Mixture of 10% Benzoic Acid and 90% M.C.C.

A: physical mixture.
B: ground for 1/2 hr.
C: ground for 2 hr.

Table I. Grinding Effect of Various Mixtures of Medicinals and M.C.C. on Medicinal Crystallinity after 2 hr Grinding

Medicinals	Mixing concentration (%)	
Benzoic acid	10	A [a]
	20	C [b]
Aspirin	10	A
	20	C
Salicylic acid	10	A
	20	C
Chloramphenicol palmitate	10	A
	20	C
Diazepam	10	A
	20	C
Mefenamic acid	10	A
	20	C
Sulfisomezole	10	A
	20	A
	30	C

a) Amorphous (Peak intensities were not observed on X-ray diffractogram).
b) Crystalline portion remained.

phous and crystalline for the medicinals, respectively. Every ground mixture of 10% medicinal showed no medicinal peak in the diffraction pattern (symbol A), while the ground mixture of 20% showed diffraction peaks due to crystalline medicinal (symbol C) except for sulfisomezole. There exists a critical amount over which a crystalline portion remained in the ground mixture, and the critical amount seems to vary with the kind of medicinal molecules. In the case of the 2 hr ground mixture of aspirin, aspirin underwent hydrolysis of about 4%. However, the decomposition does not appear to be a major factor for the decrease in the peak intensity.

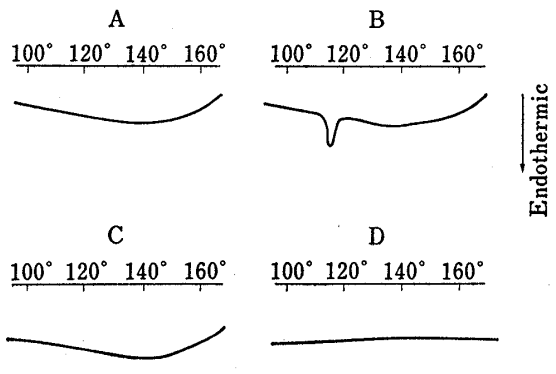

Fig. 2. Effect of Grinding on Thermal Behavior of Benzoic Acid–M.C.C. Mixtures by DTA

A: amorphous cellulose.
B: physical mixture (10% benzoic acid).
C: ground mixture (10% benzoic acid).
D: ground mixture (10% benzoic acid; with amorphous cellulose as the reference).

(2) Changes in the Thermograms

Thermal characteristics of the ground mixtures were measured by DTA and DSC. Fig. 2(A) shows the DTA thermogram of ground M.C.C. (amorphous) in which a small amount of endothermic heat was recorded due to the evaporation of the adsorbed water molecules. Fig. 2(B) shows the thermogram of the physical mixture of 10% benzoic acid and 90% M.C.C. The endothermic heat due to the fusion of benzoic acid was observed in addition to the heat of water evaporation. Figs. 2(c) and (d) are the thermograms of the 2 hr ground mixture. The ground M.C.C. was used as the reference material in the measurement of (d). No heat of fusion due to benzoic acid was observed. Furthermore, when such a sample was cooled down

and a second DTA measurement was carried out, the heat of fusion was not still recorded on the thermogram. The same results with DTA measurements were obtained from the DSC measurements.

It was unusual that the heat of fusion was not recorded on the thermograms of the ground mixture, since the thermal characteristics of benzoic acid are so definite as to be used for the standard material in thermometric measurements.[10] The ground mixtures of other crystalline medicinals and M.C.C. showed the same results as those of benzoic acid. The ground mixture containing 20% medicinal, however, showed the heat of fusion due to the medicinal except for sulfisomezole. The effect of grinding on the peak intensity of X-ray diffraction and the effect on the heat of fusion closely correlated to each other for the ground mixture, that is, the ground mixture showing no reflection produced no heat of fusion and *vice versa*.

The disappearance of the medicinal peaks from the X-ray diffraction pattern may be due to the extreme line broadening; the peaks were included in the diffuse background of amorphous cellulose. In grinding a solid, line broadening originates in the dimension of crystallite and the imperfections such as strains. Effects of grinding on the line broadening were examined by Pearse and Lewis[3b] for the copper and nickel powder. They reported that microstrains and stacking faults contributed the very broadening lines and annealing of the ground powders made the reflection lines sharp again. In the present experiment, the reflections and also the heat of fusion were not observed after repeating the temperature increasing and decreasing. The medicinals, especially benzoic acid, are well crystallized from the liquid state. The reflections and the heat should be observed after the heating even if high degree of the imperfections existed in the crystals. Therefore, it cannot be said that the imperfections mainly contributed the extreme line broadening and the disappearing of the heat of fusion.

It is well known that a small crystallite size leads to line broadening. For the crystallites, melting point and heat of fusion decrease with the size due to the excess free energy on the surface.[11] When crystallites decrease extremely in size, any imperfections will exist in the crystallites. And this will contribute further line broadening and the decreasing in the heat of fusion. The crystallite of extremely small size will not clearly show the heat of fusion on the thermogram and the reflection lines on the X-ray diffractogram. In this circumstance, however, the "crystallite" may not be defined as a phase of crystal, since the phase should be recognized by the most fundamental methods such as X-ray diffraction and thermometrics. Furthermore, the "crystallites" or the micro-assemblies of the molecules are probably isolated being surrounded by cellulose molecules, since they did not gather in heating and not recrystallized.

(3) Specific Surface Areas and Pore Size Distribution of Ground Mixtures

The specific surface areas were measured by nitrogen gas adsorption method for 2 hr ground mixtures. The results are shown in Table II. The specific surface areas ranged 2 to 5 m^2/g and were nearly the same with the value of the ground M.C.C. reported in the previous paper.[5a] Hydrogen bonding between OH radicals of cellulose was investigated by infrared measurement.[12] In the ground mixture, there will be a range of hydrogen bonds of varying strength, similarly to M.C.C. and ground M.C.C. The small surface area of the ground mixture are probably due to the hydrogen bonding as discussed with M.C.C. and ground M.C.C. in the previous paper.[5b] The specific surface area was also measured by water vapor adsorption method. The value was 235 m^2/g for the ground mixture of benzoic acid

10) J.P. McCullough and P.W. Scott, "Experimental Thermodynamics," Vol. 1, Butterworth Scientific Publications, London, 1968.
11) P.J. Flory, "Principles of Polymer Chemistry," Cornell University Press, Ithaca, 1953.
12) H.J. Marrinan and J. Mann, *J. Appl. Chem.*, **4**, 204 (1954).

Table II. Specific Surface Areas of the 2 hr Ground Mixtures calculated from Nitrogen Gas Adsorption Isotherms

Medicinals	Mixing concentration (%)	Specific surface area (m^2/g)
Benzoic acid	10	2.2
Aspirin	10	2.2
	20	2.9
Salicylic acid	10	2.9
Chloramphenicol palmitate	10	5.6
Mefenamic acid	10	1.9
Sulfisomezole	20	2.2
	30	4.0

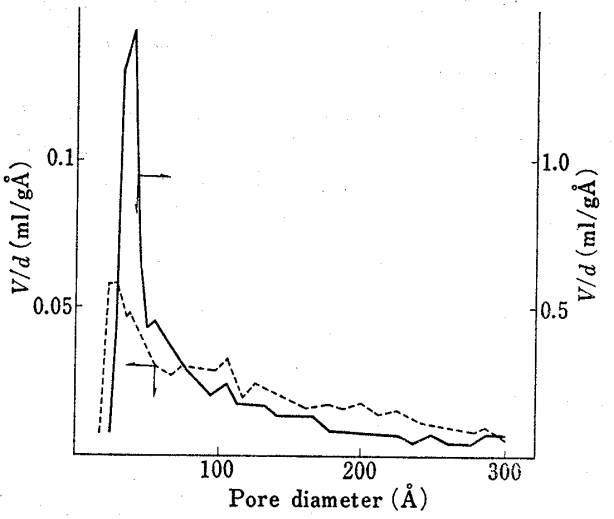

Fig. 3. Pore Size Distribution of Ground Mixture (10% Benzoic Acid) calculated from Cranston-Inkley's Method

------: ground mixture.
——: residual cellulose.

and was of the same order of magnitude as the ground M.C.C. The large value of 235 m^2/g means that water molecules probably adsorbed on the amorphous cellulose in the ground mixture. Therefore, the cellulose seems to take the similar structure in the ground mixture to the ground M.C.C.

Pore size distribution was determined for the residual cellulose—the ground mixture from which benzoic acid had been released. After releasing benzoic acid from the ground mixture, the residual cellulose was removed from the solution and dried by the following procedures; the residual was washed by enough amount of ethanol and *n*-pentane successively and the cellulose in *n*-pentane was dried *in vacuo* at room temperature. The detailed procedures were reported in the previous paper.[5b] Pore size distributions of the dried samples were determined from nitrogen gas adsorption isotherms using Cranston-Inkley's method.[13] Fig. 3 shows the pore size distributions of the residual cellulose and the ground mixture before the drug release. The residual cellulose showed the development of capillaries at about 30—40 Å in comparison with the ground mixture. The increase in the pore volume at 30—40 Å is probably due to the release of benzoic acid molecules from the ground mixture. A single crystal of benzoic acid was monoclinic and the cell constants were a=5.52 Å, b=5.14 Å, c=21.90 Å, and β=97°.[14] The capillary diameter of 30—40 Å is in the same order of magnitude with the size of the unit cell at c-axis. Geometrically considered, number of the unit cells must be smaller than eight in the directions of a- and b- axes to enter the pore. The small number of the repeating units may not be enough to make up a crystallite without strains.

(4) Release of Benzoic Acid and Chloramphenicol Palmitate from the Ground Mixtures

The 2 hr ground mixtures containing 10% medicinals were used for the dissolution experiments. The release profiles for benzoic acid and chloramphenicol palmitate are shown in Figs. 4(A) and (B), respectively. The releasing rates of the medicinals from the ground mixtures were very high and the saturated solutions were obtained in a short time. The rapid dissolution of the medicinals may be attributed to the extremely small size of crystallite

13) R.W. Cranston and F.A. Inkley, *Adv. in Catalysis*, **9**, 143 (1957).
14) G. Sim, J.M. Robertson, and T.H. Goodwin, *Acta Cryst.*, **8**, 157 (1955).

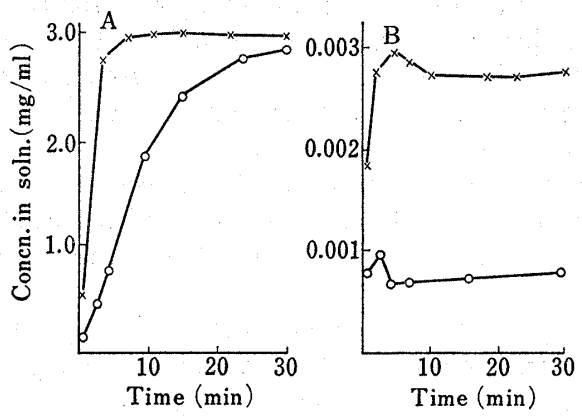

Fig. 4. Dissolution Curves of Benzoic Acid and Chloramphenicol Palmitate

—×—: ground mixture, —○—: fine crystal.
A: dissolution of benzoic acid in 0.1 N HCl aqueous solution at 25° and 200 rpm.
B: dissolution of chloramphenicol palmitate in distilled water at 30° and 200 rpm.

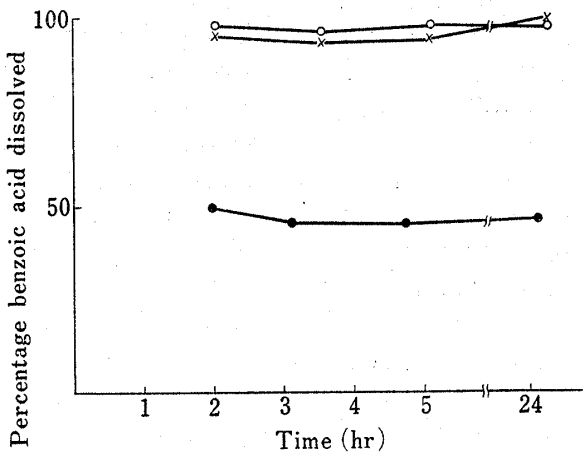

Fig. 5. Dissolution Curves of Benzoic Acid from Ground Mixture in Various Test Solutions at 30°

—○—: 0.1 N HCl aqueous solution.
—×—: ethanol.
—●—: CCl_4.

and/or the high energy of molecules in the distorted crystallites as discussed above. Further the hydrogen bonding between cellulose molecules would be destroyed by water molecules, so the release of the medicinals from the matrixes may be enhanced.

Fig. 5 illustrates the dissolution curves of benzoic acid from the ground mixture in various test solutions. The amount of benzoic acid in the ground mixture released was only 50% when CCl_4, nonpolar solvent, was used as the test solution instead of water. This result showed the important role of water molecules in destructing hydrogen bonding and in enhancing dissolution. It seemed likely that the remaining medicinal was in the network structure of the hydrogen bonding of cellulose molecules. Owing to the varied strength of the hydrogen bonding, however, it was also understandable that the medicinal in the ground mixture did not exist in homogeneous state. Namely, it would be appropriate to consider the structure of the ground mixture was irregularly ordered.

The improvement of dissolution properties influences the absorption characteristics of medicinals when they are orally administered. Such studies were reported previously.[15]

The results and the derived considerations are summarized as follows;

(1) Peak intensity of characteristic lines due to the crystalline medicinal could not be observed on the X-ray diffractogram after the grinding with M.C.C.…This leads to the consideration that the medicinal exists in the ground mixture in the state of the fine crystallite probably having distortions.

(2) Heat of fusion due to the crystalline medicinal could not be observed on the thermogram even if the ground mixture was heated over the melting point and cooled.…The crystallite are very fine and probably isolated being enclosed by the cellulose molecules.

(3) There was a critical content of the medicinal to show the phenomena of (1) and (2).… A certain amount of cellulose molecules need to enclose the medicinal molecules.

(4) The phenomena of (1) and (2) occurred for all medicinals independent of the molecular properties, such as structure, size, and polarity.…Hydrogen bond between the cellulose molecules probably plays a main role in the phenomena although interaction forces between the medicinal molecules and the cellulose molecules may take place in the ground mixture. The interaction forces may result in various critical concentrations over which the crystalline portion of the medicinals remains in the ground mixture.

15) K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai, *J. Pharm. Sci.*, **65**, 1484 (1976).

(5) Medicinals were released very rapidly from the ground mixtures in aqueous solution, and the releasing rate was far higher than the dissolution rate from a solid surface of the fine particles. In CCl_4, however, only 50% of benzoic acid was released from the ground mixture.···The hydrogen bonds between the cellulose molecules were destroyed by water molecules, and the medicinal molecules are released from the cellulose matrix.

(6) The residual cellulose, the ground mixture from which benzoic acid had been released, had a large pore volume of the capillaries of about 30—40 Å diameter.···A crystallite having several number of unit cells can exist in the pore and the number may not be enough to make up a crystallite without disorder.

It may be said that the medicinal molecules dispersed in the cellulose matrix of the ground mixture and that the molecules existed in the matrix as a molecule or a micro-assembly of molecules being isolated by the cellulose molecules which were bound by hydrogen bond. The ground mixture may be regarded as an "entropy frozen solution," that is, a medicinal dissolves into cellulose without the ability of molecules to move throughout the whole system.

The detailed properties of the ground mixture will be reported in the successive papers.