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Mechanochemical Change in the Solid State and the Solubility of Amobarbital

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Influence of ball-milling on the X-ray diffraction pattern, the thermal properties, the IR spectra, the particle size distribution and the solubility of amobarbital was investigated. The fraction of crystal I decreased, and the fraction of crystal III and the amorphous part increased at the first stage of ball-milling. The heat of fusion decreased slightly by ball-milling, which was considered to be due to the increase in the fraction of the amorphous part. The melting point lowered by 1—3 °C and the NH and CO absorptions in the IR spectra were influenced by ball-milling, which was considered to be due to the transformation of crystal I into crystal III. The particle size decreased at the first stage of ball-milling. It was considered that the transformation of crystal I into crystal III was remarkable when the particles were broken. The solubility of amobarbital in the KH_2PO_4–Na_2HPO_4 buffer solution with pH of 6.0 increased by ball-milling, which was considered to be due to the increase in the fraction of the amorphous part and crystal III.

The solubility of the slightly soluble powders in the amorphous state is higher than the solubility in the crystal state.[1] The solubility of the powders in the metastable crystal form is also higher than the solubility in the stable crystal form.[2] The solubility of fine particles is larger than the solubility of large particles, as the surface energy of fine particles is larger than the energy of the large particles.[3]

As reported previously, the solubility of amobarbital (5-ethyl-5-isopentylbarbituric acid) increased, the X-ray diffraction intensities decreased and the melting point lowered by the mechanical treatment with the diluent, such as methylcellulose.[4,5] In this paper, amobarbital was ball-milled without the diluent and influence of ball-milling on the physical and chemical properties was investigated in order to clarify the mechanism of solubilization by the mechanical treatment.

Experimental

Commercial powders of amobarbital was of guaranteed grade purchased from Nihon Shinyaku Co. Ten g of the commercial powders was ball-milled under the conditions as referred to the previous paper.[5] Powder II was obtained by recrystallization of amobarbital from the 25 v/v % aqueous ethanol solution, and powder I was obtained by heating powder II at 150 °C for 1 h.[6] Powder III was obtained by freeze-drying the aqueous solution of amobarbital.

The X-ray diffraction measurement was carried out by a JEOL X-ray diffractometer (Model 7E). The differential thermal analysis was made by a thermal analyser (Model DT-20B) of Shimazu Seisakusho. The heat of fusion of amobarbital was measured by a differential scanning calorimeter (Model SC-20) of Shimadzu Seisakusho, using indium as a standard substance. Infrared (IR) spectra of the samples were measured by the Nujol method with a JASCO diffraction granting infrared spectrometer (Model A-2).

The sample was added to the 0.1 w/v % sodium dodecyl sulfate solution saturated with amobarbital in each of the samples, as the solubility varied by ball-milling. The suspension was stirred intensely for 2 min, and irradiated with the supersonic waves for a min. Then, the size distribution of the particles was measured with a micron photosizer (Model SKN 500) of Seishin Kigyo Co. Solubility of amobarbital from various samples in the KH_2PO_4–Na_2HPO_4 buffer solution (pH 6.0, ionic strength 0.08) at 30 °C was obtained from the absorbance at 238 nm as described in the previous paper.[4]

Results and Discussion

X-Ray Diffraction. Mesley reported two polymorphs for amobarbital, that is, crystal II obtained by recrystallization from a 25 v/v % aqueous ethanol solution and crystal I obtained by heating crystal II at 150 °C.[6] It is considered that powder I is composed of crystal I by Mesley and the amorphous part, and that powder II is composed of crystal II by Mesley and the amorphous part. As shown in Fig. 1, the X-ray diffraction pattern for the commercial powders before ball-milling was identical with the pattern for powder I, and the pattern for the ball-milled powders was identical with the pattern for powder III. The pattern for powder III was different from the patterns for powder I and II. The similar pattern as for powder III was obtained for the powders obtained by condensing the vapor from the solution of the fused amobarbital on a cold glassy wall. The pattern for powder III was identical with the pattern for amobarbital crystallized from diethyl ether by Williams.[7] In this paper, the polymorph in powder III is called crystal III. Vizzini *et al.* obtained single crystals of two kinds of polymorphs, I and II, from the same aqueous ethanol solution by slow evaporation at room temperature. They confirmed that the crystal morphology of these two forms were in agreement with those previously reported by Williams. They also found that the melting point of crystal I was lower than the point of crystal II by 4—6 °C.[8] As shown later in this paper, the melting point of powder III was lower than the point of powder I by 2—4 °C, though powder II was transformed into powder I at 150 °C. It is considered that crystal I by Vizzini is identical with crystal III in this paper.

The crystallinity of various kinds of amobaribtal, x_{cr}, was obtained by the Ruland's method.[9] The results are shown in Table 1.

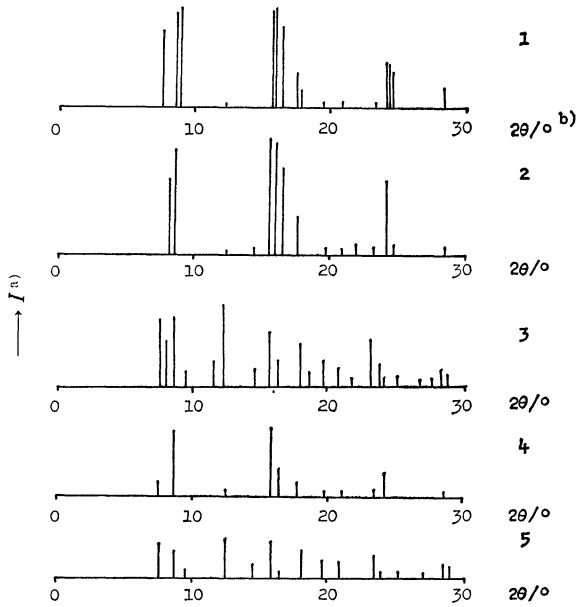

Fig. 1. X-Ray diffraction patterns of various kinds of amobarbital powders.
1: Powder I, 2: powder II, 3: powder III, 4: commercial powders, 5: commercial powders ball-milled for 60 h. a) I is the diffraction intensity. b) 2θ is the angle between the incident X-rays and the scattering X-rays. In this figure, the line broadening is ignored in order to show the difference between the patterns clearly.

TABLE 1. CRYSTALLINITY OF VARIOUS KINDS OF AMOBARBITAL

Sample	bt[a] / h	x_{cr} / %	x_{cr}' / %
Powder I	0	97	—
Powder III	0	77	
Commercial powders	0	87	84
	0.033	85	88
	0.083	84	83
	0.17	84	84
	0.5	84	87
	1	76	74
	3	78	76
	5	76	71
	10	79	78
	20	77	72
	30	76	74
	40	77	75
	60	82	73

a) bt is the ball-milling time.

Hermans *et al.* considered that the coherent scattering was due to the crystal part and that the non-coherent scattering was due to both of the crystal part and the amorphous part. On the basis of this consideration, they obtained the crystallinity of the cellulose fibers.[10] A glassy state was obtained by the rapid cooling of the solution of the fused hexobarbital or phenobarbital, though the state was not obtained for amobarbital. The intensity of the non-coherent scattering for the glassy state of hexobarbital was identical with the intensity for phenobarbital. The mean value of the intensity for these samples was taken as the intensity for the glassy state of amobarbital, assuming that the intensity was independent of the kind of the barbituric acid derivatives. It was confirmed that the kind of the polymorph did not influence the parameters for determining the crystallinity by the Hermans' method, from the results for the glassy state, powder I and III using the values of x_{cr}. The values of the crystallinity by the Hermans' method, x_{cr}', are tabulated in Table 1.

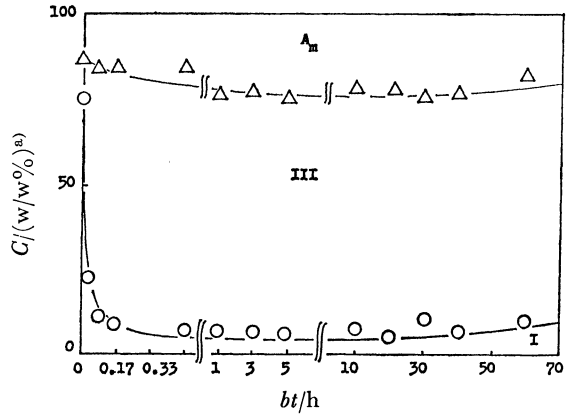

Fig. 2. Influence of ball-milling on the solid state of amobarbital.
○: The content of crystal I, △: the content of the crystal part, I: crystal I, III: crystal III, A_m: amorphous part. a) C is the composition.

The ratio of the intensity of the diffraction lines between 12.4° and 12.7° of 2θ to the intensity between 16.0° and 16.7° of 2θ, R_x, was larger for powder III than for powder I. From the data of R_x and x_{cr} for powder I and III, the fraction of crystal I, III and the amorphous part were obtained for the commercial powders before and after ball-milling. The results are shown in Fig. 2. The fraction of crystal I decreased and that of crystal III increased at the first stage, and the ratio between the fractions was constant after ball-milling for more than 10 min. The fraction of the amorphous part increased at the first stage, but the fraction was approximately constant after ball-milling for more than 1 h.

Thermal Analysis. The melting point of amobarbital lowered by 1—3 °C by ball-milling, as shown in Fig. 3. This phenomenon was already observed after ball-milling for 5 min. The melting point of powder III, 152—154 °C, was 2—4 °C lower than the point of powder I. The lowering of the melting point of amobarbital by ball-milling is considered to be due to the transformation of crystal I into crystal III.

As shown in Table 2, the heat of fusion, ΔH_{obsd}, for powder I and II was larger than the heat for the other samples. It was also shown that ΔH_{obsd} for the commercial powders decreased slightly by ball-milling by the t-test at the probability level of 0.05 and at the freedom of 29. Equation 1 was assumed to be applied, where x_I, x_{III}, and x_a were the fractions of crystal I, III, and the amorphous part and ΔH_I, ΔH_{III}, and ΔH_a were the heat of fusion of crystal

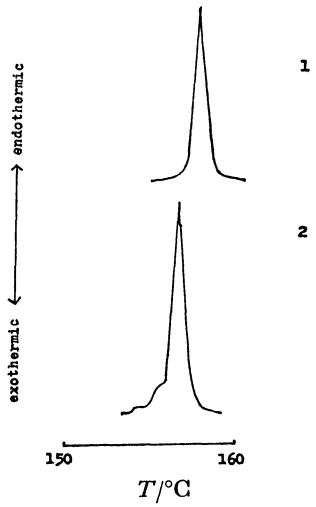

Fig. 3. Influence of ball-milling on DTA thermograms of amobarbital.
The programming speed is 1 °C/min. 1: Commercial powders, 2: commercial powders ball-milled for 60 h.

Table 2. Heat of fusion of various kinds of amobarbital

Sample	$\Delta H_{obsd} \pm \sigma_H$[a] kcal/mol
Powder I	7.0±0.3
Powder II	6.7±0.4
Powder III	6.1±0.5
Commercial powders	6.2±0.5
Commercial powders ball-milled for 60 h	5.7±0.6

a) σ_H is the standard deviation.

I, III, and the amorphous part, respectively.

$$\Delta H_{obsd} = x_I \Delta H_I + x_{III} \Delta H_{III} + x_a \Delta H_a \quad (1)$$

The values of ΔH_I, ΔH_{III}, and ΔH_a, 7.0, 6.9, and 1.2 kcal/mol, respectively were obtained from the data of ΔH_{obsd} and x_{cr} for powder I, the commercial powders before ball-milling and the powders after ball-milling for 60 h. The slight decrease in the heat of fusion of amobarbital by ball-milling is probably due to the decrease in the crystallinity.

IR Spectra. The following facts are confirmed from the study on the IR spectra of various kinds of barbituric acid derivatives by Mesley[6] and the study on the interaction of barbituric acid derivatives with polyethylene glycol by Chang *et al.*[11] The ν-NH absorption band is observed at 3600—3000 cm^{-1} region. The absorption for free NH in the solid state is observed at 3340—3310 cm^{-1} and shifts to the lower frequency by hydrogen bonding. The CO absorption at 1800—1600 cm^{-1} shifts to the lower frequency by hydrogen bonding. The highest frequency band at 1750 cm^{-1} is due to the CO in the 2-position and the other bands are due to the CO in the 4- and 6-position in the spectra of amobarbital. The δ'-NH absorption band at 900—750 cm^{-1} shifts to the higher frequency by hydrogen bonding.

Figure 4 shows the IR spectra of various kinds of amobarbital. In Table 3, $R_{\nu,\nu'}$ is the ratio of the

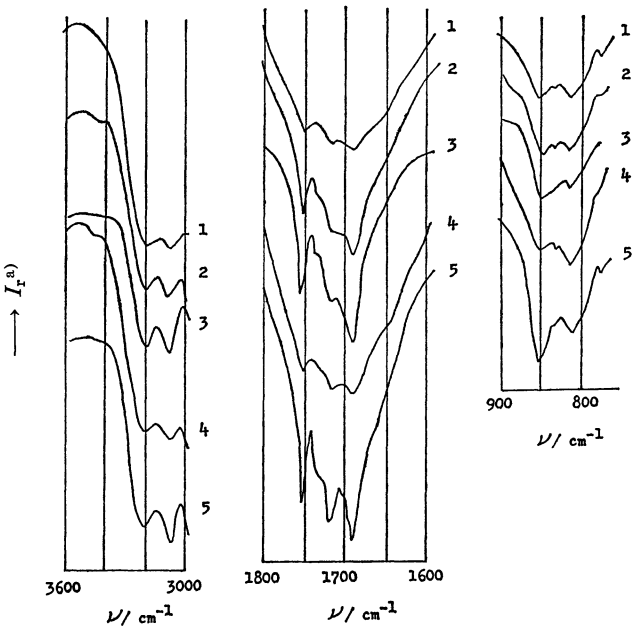

Fig. 4. IR spectra of various kinds of amobarbital powders.
1: Powder I, 2: powder II, 3: powder III, 4: commercial powders, 5: commercial powders ball-milled for 60 h. a) T_r is the transmittance.

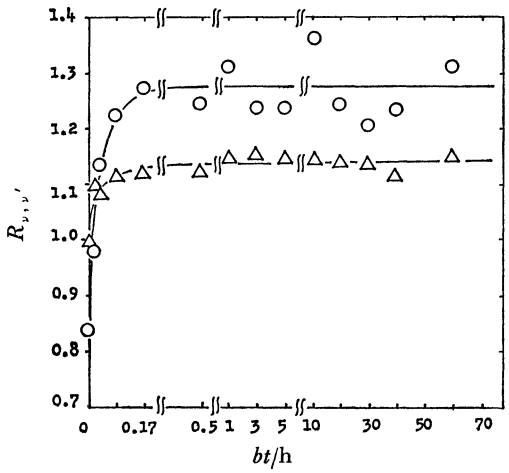

Fig. 5. Influence of ball-milling on IR spectra of amobarbital.
○: ν/cm^{-1}=850; ν'/cm^{-1}=815, △: ν/cm^{-1}=3085; ν'/cm^{-1}=3210.

absorbance at wave number ν to the absorbance at ν' obtained by assuming that the percent transmission at 3450, 2000, 1000, and 700 cm^{-1} are 100. As shown in Fig. 4 and Table 3, the IR spectra of the commercial powders before ball-milling were similar to those of powder I and the spectra of the ball-milled powders were similar to the spectra of powder III. Figure 5 shows the variation in the values of $R_{\nu,\nu'}$ with ball-milling. $R_{\nu,\nu'}$ varied remarkably at the first stage of ball-milling, but the values were nearly constant after ball-milling for more than 10 min. It is considered from the above findings that the variation in the IR spectra of amobarbital with ball-milling is due to the increase in the fraction of the part of

TABLE 3. NUMERICAL VALUES OF $R_{\nu,\nu'} \pm \sigma_R$[a] FOR VARIOUS KINDS OF AMOBARBITAL

ν/cm^{-1} / ν'/cm^{-1}	3085 / 3210	1690 / 1750	850 / 815
Powder I	1.06±0.02	1.17±0.09	0.99±0.04
Powder II	1.06±0.01	1.33±0.07	1.04±0.05
Powder III	1.07±0.03	1.42±0.06	1.25±0.06
Commercial powder	1.06±0.01	1.14±0.04	0.84±0.03
Commercial powders ball-milled for 60 h	1.16±0.02	1.32±0.02	1.32±0.01

a) σ_R is the standard deviation.

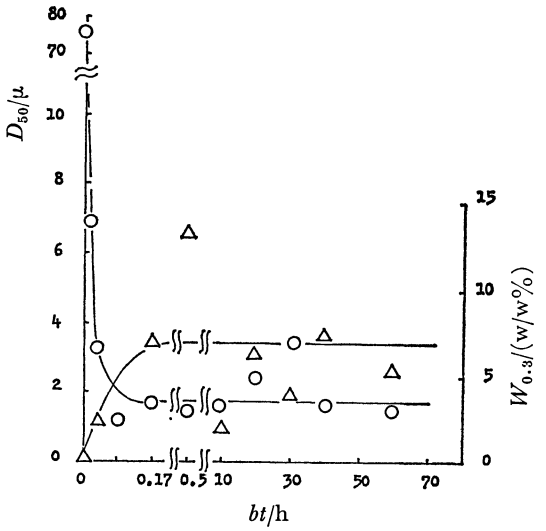

Fig. 6. Decrease in the particle size of amobarbital by ball-milling.
○: D_{50}, △: $W_{0.3}$.

the strong hydrogen bonding between NH and CO, which is probably related to the transformation of crystal I into crystal III.

Particle Size. Figure 6 shows the variation of the particle size of amobarbital with ball-milling. In Fig. 6, D_{50} is the median diameter by weight base and $W_{0.3}$ is the weight fraction of the particles smaller than 0.3 μ in diameter. The value of D_{50} decreased and the value of $W_{0.3}$ increased at the first stage of ball-milling, and these values were nearly constant after ball-milling for more than 10 min. Variation of these values with ball-milling was parallel to the variation of the X-ray diffraction pattern, the IR spectra and the melting point. It is considered that the transformation of crystal I into crystal III is remarkable when the particles are broken.

Solubility. The solubility of amobarbital in the KH_2PO_4–Na_2HPO_4 buffer solution with pH of 6.0 at 30 °C was investigated. The concentration of amobarbital in the filtrate of the suspension in the buffer solution increased at the first stage of dissolution, but the concentration was nearly constant for the dissolution time between 10 min and 2 h. In Fig. 7, c_{2h} is the concentration after shaking for 2 h from the time of the preparation. As shown in Fig. 7 and Table 4, c_{2h} increased by ball-milling.

In the previous paper, the solubility of amobarbital was influenced little by ball-milling with dextran or dextrose, but the solubility increased by 20—30% by ball-milling with methylcellulose only for 10 min.[4] The value of D_{50} for amobarbital ball-milled with methylcellulose for 10 min was larger than the values for amobarbital ball-milled with dextran or dextrose. This finding shows that the decrease in the particle size is not the main factor for the increase in the solubility of amobarbital by ball-milling.

TABLE 4. SOLUBILITY OF AMOBARBITAL IN THE KH_2PO_4–Na_2HPO_4 BUFFER SOLUTION IN pH OF 6.0 AT 30 °C

Sample	$c_{2h} \pm \sigma_c$[a] mg/100 ml
Powder I	58.4±1.9
Powder II	64.6±1.6
Powder III	67.4±0.6
Commercial powders	63.4±0.6
Commercial powders ball-milled for 20 h	67.1±1.1
Commercial powders ball-milled for 60 h	65.7±1.1

a) σ_c is the standard deviation.

The variation in c_{2h} with ball-milling was parallel to the variation in the fraction of the amorphous part. Table 4 shows the numerical values of c_{2h} for various samples. The value for the commercial powders before ball-milling was nearly identical with the value for powder I and the value for the ball-milled powders was similar to the value for powder III. If the solid state is equilibrated with the state of solution and ΔH_{obsd} is constant near the melting point, Eq. 2 is applied, where X_2^s is the mole fraction of the solute, R is the gas constant, T is the absolute temperature at the equilibrated state, T_f is the melting point of the solute by absolute temperature and γ is the activity coefficient of the solute.

$$\ln X_2^s = -\frac{\Delta H_{obsd}}{R}\left(\frac{1}{T}-\frac{1}{T_f}\right) - \ln \gamma \qquad (2)$$

The increase in the solubility of amobarbital in the buffer solution by ball-milling can be calculated from Eq. 2, if γ is influenced little by ball-milling. Using the data of ΔH_{obsd} in Table 2 and setting the lowering of the melting point by ball-milling to be 1 °C, the solubility of the ball-milled powders was calculated to be 1.2 times the solubility of the commercial powders, if the solid state obtained by ball-milling was equilibrated with the state of solution. The ratio of

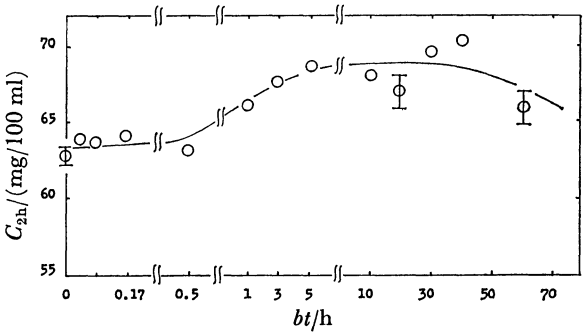

Fig. 7. Influence of ball-milling on solubility of amobarbital in the KH_2PO_4-Na_2HPO_4 buffer solution at 30 °C.

c_{2h} for the ball-milled powders to the value for the commercial powders before ball-milling was approximately 1.1, as shown in Table 4. The above findings show that the increase in the solubility of amobarbital by ball-milling is due to the increase in the fraction of the amorphous part and to the transformation of crystal I into crystal III.

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