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The Effect of Diluents on the Mechanochemical Change in the Solid State of Amobarbital

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The effect of ball-milling with dextran 2000, microcrystalline cellulose, or methylcellulose (MC) on the solid state of amobarbital was investigated. There are three kinds of polymorphs for amobarbital; Crystals I, II, and III. Crystal I is obtained by heating Crystal II recrystallized from a 25 v/v % aqueous ethanol solution at 150 °C. The part of Crystal I decreased remarkably at the first stage of ball-milling, while the amorphous part increased gradually. The heat of fusion decreased remarkably; this was considered to be due to the increase in the amorphous part. The peak of fusion in the DTA thermogram was broadened, and the temperature at which amobarbital began to fuse was lowered. This phenomenon was considered to be due to the increase in the lattice imperfection. The solubility in the KH_2PO_4–Na_2HPO_4 buffer solution with a pH of 6.0 increased; the increase in the amorphous part was considered to contribute to this increase. This phenomenon was the most remarkable in the case of the mixture with MC. The interaction of amobarbital with MC was suggested by the heat of fusion and the DTA thermograms. It was also suggested that the interaction of amobarbital with the diluent was one of the most important reasons for the increase in the solubility upon ball-milling.

It was reported previously that the solubility of amobarbital in the KH_2PO_4–Na_2HPO_4 buffer solution with a pH of 6.0 increased upon ball-milling with such diluents as methylcellulose,[1)] though the solubility also increased slightly upon ball-milling in the absence of any diluents at all.[2)] In a previous paper, the effect of ball-milling in the absence of diluents on the solid state of amobarbital was investigated.[2)] In this paper, the effect of ball-milling with diluents on the solid state of amobarbital was investigated in order to clarify the mechanism of solubilization.

Experimental

The amobarbital (5-ethyl-5-isopentylbarbituric acid), dextran 2000, microcrystalline cellulose (MCC), and methylcellulose (MC) used were described in a previous paper.[1)]

A 10-g portion of amobarbital, a mixture of 2 g of amobarbital and 3 g of MC, a mixture of 1 g of amobarbital and 9 g of MCC, a mixture of 3 g of amobarbital and 7 g of MCC, and a mixture of 3 g of amobarbital and 7 g of dextran were ball-milled in the way reported in the previous paper.[1)] The following measurements were carried out in the way reported in the previous papers;[1,2)] X-ray diffraction diagrams, DTA and DSC thermograms, and the particle-size distribution of amobarbital in the mixture with dextran or MC (dextran and MC are soluble in distilled water). The dissolution of amobarbital from the mixture into a KH_2PO_4–Na_2HPO_4 buffer solution (pH; 6.0, ionic strength; 0.08) at 30 °C was measured by shaking the suspension as has been reported in a previous paper. The concentration of amobarbital in the filtrate of the suspension was obtained from the absorbance at 238 nm.[1)]

Results and Discussion

X-Ray Diffraction. Three kinds of polymorphs of amobarbital were obtained in a previous paper. Crystal I was obtained by heating Crystal II (at 150 °C), which had been recrystallized from a 25 v/v % aqueous ethanol solution. Crystal III was obtained by freeze-drying an aqueous solution of amobarbital. The X-ray diffraction intensities at 9.0° and 24.7° of 2θ for Crystal I were higher than those for Crystal III, where 2θ is the angle between the incident X-ray and the scattering X-ray. The intensity at 12.6° of 2θ was lower than the intensity at 16.0° of 2θ, and no line was observed at 14.9° of 2θ in the diagram of Crystal I, while the intensity at 12.6° of 2θ was a little higher than the intensity at 16.0° of 2θ and a line was observed at 14.9° of 2θ in the diagram of Crystal III.[2)]

Figure 1 shows the X-ray diffraction patterns of a mixture of amobarbital and MC. No diffraction line was observed in the diagram of MC. The diffraction intensities for amobarbital at 9.0°, 16.0°, and 24.7° of 2θ decreased, while the intensities at 12.6° and 14.9° of 2θ increased, upon ball-milling with diluents; these increases were considered to be due to the transformation of Crystal I into Crystal III. The percentage of Crystal

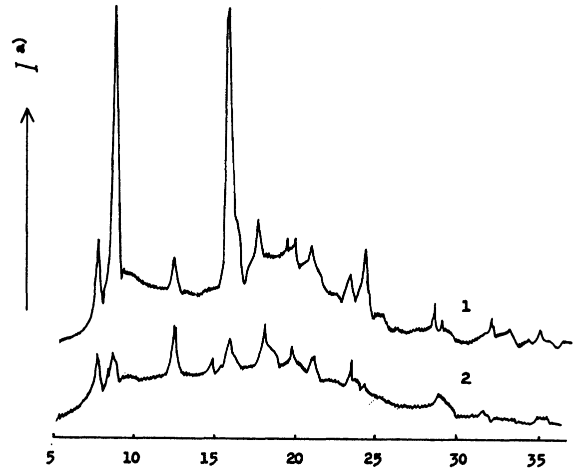

Fig. 1. Variation in the X-ray diffraction pattern of amobarbital with ball-milling in the presence of MC. 1: The physical mixture of MC containing 40 w/w % of amobarbital, 2: the powders obtained by ball-milling "1" for 101 h.
a) I is the diffraction intensity.

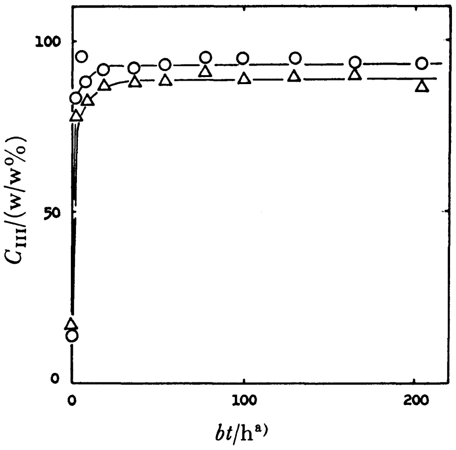

Fig. 2. Increase in C_{III} upon ball-milling with diluents. The content of amobarbital; 30 w/w%, diluent: △; dextran, ○; MCC.
a) *bt* is the ball-milling time.

III in the crystal part, C_{III}, was obtained from the ratio of the diffraction intensity at 12.7° of 2θ to the intensity at 16.0° of 2θ. As is shown in Fig. 2, C_{III} increased remarkably at the first stage of ball-milling, while C_{III} was nearly constant after ball-milling with MC for 10 min.

Ruland reported that the crystallinity, x_{cr}, could be obtained by means of Eq. 1, where λ is the wave length of the X-ray, $I_{cr}(s)$ is the intensity of the diffraction line at s, $I(s)$ is the total intensity of the scattering X-ray at s and K is a constant:[3]

$$x_{cr} = KF_{cr}/\int_{s_0}^{s_p} s^2 I(s)\mathrm{d}s, \qquad (1)$$

$$F_{cr} = \int_{s_0}^{s_p} s^2 I_{cr}(s)\mathrm{d}s, \qquad s = 2\sin\theta/\lambda.$$

The value of $\int_{s_0}^{s_p} s^2\ I(s)\ \mathrm{d}s$ was assumed to be constant in the case of ball-milling with diluents, though the value could not be obtained experimentally. F_{cr} was obtained for the range between 5° and 30° of 2θ, and x_{cr} was obtained from the ratio of F_{cr} for the ball-milled

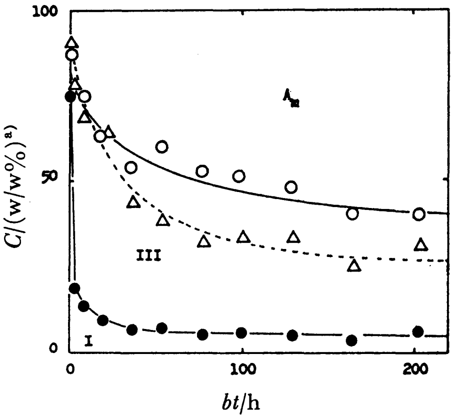

Fig. 3. Effect of ball-milling with dextran on the solid state of amobarbital.
●: The content of crystal I, ○: x_{cr}, △: $x_{cr\ heat}$, I: crystal I, III: crystal III, A_m: amorphous part.
a) *C* is the composition.

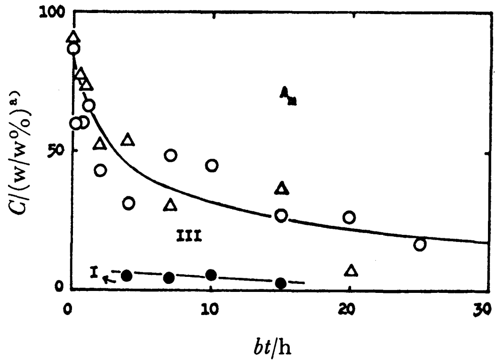

Fig. 4. Effect of ball-milling with MCC on the solid state of amobarbital.
The content of amobarbital: 10 w/w%. ●: the content of crystal I, ○: x_{cr}, △: $x_{cr\ heat}$, I: crystal I, III: crystal III, A_m: amorphous part.
a) *C* is the composition.

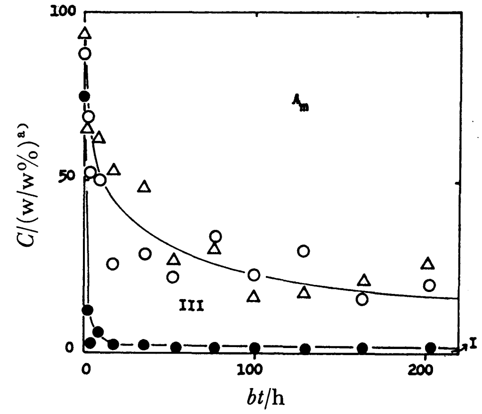

Fig. 5. Influence of ball-milling with MCC on the solid state of amobarbital.
The content of amobarbital: 30 w/w%, ●: the content of crystal I, ○: x_{cr}, △: $x_{cr\ heat}$, I: crystal I, III: crystal III, A_m: amorphous part.
a) *C* is the composition.

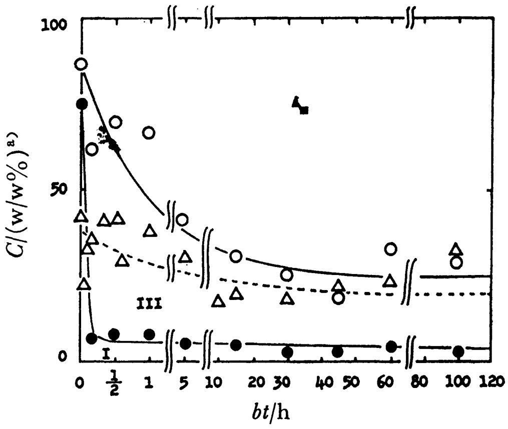

Fig. 6. Effect of ball-milling with MC on the solid state of amobarbital.
●: The content of crystal I, ○: x_{cr}, △: $x_{cr\ heat}$, I: crystal I, III: crystal III, A_m: amorphous part.
a) *C* is the composition.

Table 1. Influence of ball-milling with diluents on the width of the X-ray-diffraction lines of amobarbital

Diluent	—[a)]	—[a)]	Dextran	Dextran	MCC[b)]	MCC[b)]	MC	MC
$bt^{c)}$/h	0	60	0	2—203[d)]	0	100—200[d)]	0	0.17—61[d)]
2θ/°				$\Delta H_{1/2}$/° [e)]				
7.8	0.38	0.40	0.34	0.43	0.32	0.44	0.34	0.42
8.9	0.42	0.38	0.40	0.43	0.34	0.50	0.38	0.45
12.7	0.38	0.40	0.36	0.45	0.36	0.49	0.38	0.45
16.1	0.44	0.43	0.42	0.47	0.34	0.48	0.42	0.47
23.6	0.36	0.40	0.32	0.48			0.28	0.44

a) The content of amobarbital is 100%. b) The content of amobarbital is 30 w/w%. c) bt is the ball-milling time. d) The mean values for the data between the times are tabulated. e) $\Delta H_{1/2}$ is the separation of 2θ where the diffraction intensity is half the maximum intensity at the line.

mixture to the value for the physical mixture of amobarbital ball-milled for 60 h in the absence of any diluents, a mixture whose crystallinity was assumed to be 0.82.[2)] The results are shown in Figs. 3, 4, 5, and 6. Some of the values of C_{III} could not be obtained for the mixture with MCC containing 10 w/w% of amobarbital, as diffraction lines were observed in the diagram of MCC at the first stage of ball-milling. However, in all cases, Crystal I decreased remarkably at the first stage of ball-milling, while the amorphous part increased gradually upon ball-milling.

Table 1 suggests that the line-width of amobarbital increases upon ball-milling with diluents; this is probably a result of the increase in the lattice imperfection.

Heat of Fusion. The heat of fusion of amobarbital, ΔH_{obsd}, decreased remarkably upon ball-milling with diluents, as is shown in Fig. 7. In a previous paper, Eq. 2 was applied to the relation between ΔH_{obsd} and x_{cr}:[2)]

$$\Delta H_{\text{obsd}} = 29.3\,x_{\text{cr}} + 5.0\,(1-x_{\text{cr}}). \qquad (2)$$

The crystallinity which is obtained by Eq. 2 using the data of ΔH_{obsd} is defined as $x_{\text{cr heat}}$ in this paper. The data of $x_{\text{cr heat}}$ are shown in Figs, 3, 4, 5, and 6 by the triangles. In the case of the mixture with MC, $x_{\text{cr heat}}$ was much smaller than x_{cr} even for the physical mixture. This phenomenon is considered to be due to the interaction between amobarbital and MC. However $x_{\text{cr heat}}$ and x_{cr} were nearly identical for the other mixtures.

Melting Point. As is shown in Fig. 8, the peak of fusion of amobarbital was broadened and caused to branch into two peaks by ball-milling with diluents. In Fig. 8, T_1 is the temperature at which amobarbital begins to fuse, T_2 and T_3 are the melting points for the two peaks, T_3* is the temperature at the beginning of the shoulder, and T_4 is the temperature at which the fusion comes to an end. Table 2 shows the numerical values of these temperatures. T_1 was lowered by ball-milling with diluents. In each case, T_1 was lower when x_{cr} was smaller, as is shown in Fig. 9. These results suggest that the lowering of T_1 by ball-milling is due to the increase in the amorphous part. The relations between T_1 and x_{cr} were influenced by the kind of diluent. The lowering of T_1 was more remarkable for the mixture with MC than for the other mixtures, and T_1 was lowered even by physically mixing amobarbital with MC. In the case of the mixtures with dextran or MCC, T_4 was not influenced and T_3 was lowered slightly by ball-milling, but T_3 and T_4 were lowered by ball-milling the mixture with MC. A signal was observed in the DTA thermograms of the mixture with dextran or MCC when the sample was heated from room temperature to 200 °C, left alone at room temperature, and then heated again immediately after cooling, and the signal was nearly identical with the signal by heating for the first time. However, in the case of the mixture with MC, no signal was observed upon the same preparation, while only a small signal was observed when the sample was set aside for more than a day at room temperature after heating to 200 °C. This phenomenon was more remarkable for the mixture ball-milled for a long time. It can be considered, on the basis of the above facts, that interaction occurs between amobarbital and the diluents and that the interaction with MC is more remarkable than the interaction with the other diluents. It has also been reported that MC prevented the amorphous noboviocin from crystallization in the aqueous suspension.[4)]

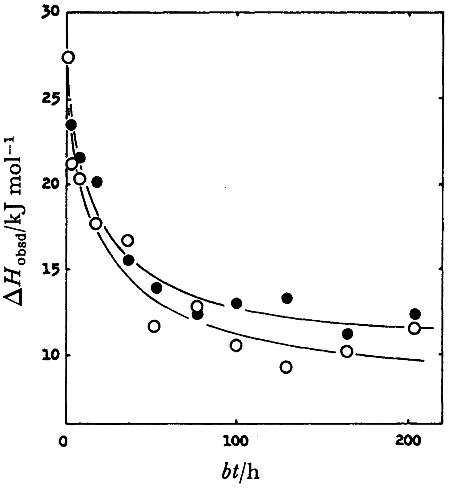

Fig. 7. Decrease in the heat of fusion of amobarbital by ball-milling with diluents.
The content of amobarbital: 30 w/w%, diluent: ●; dextran, ○; MCC.

Particle Size. Variation in the particle size of amobarbital with ball-milling in the presence of dextran

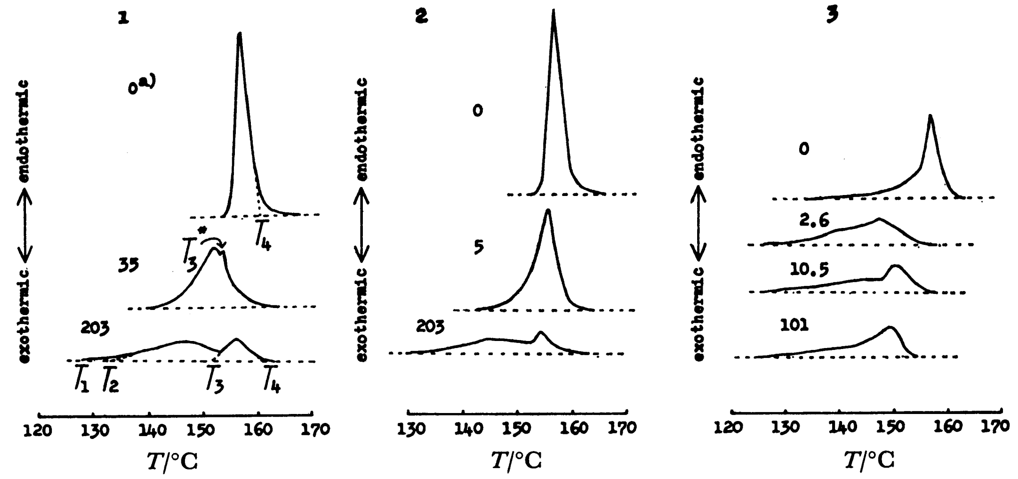

Fig. 8. Influence of ball-milling with diluents on DTA thermograms of amobarbital.
The content of amobarbital in the mixture with MCC is 30 w/w%. Diluent: **1**; dextran, **2**; MCC, **3**; MC. a) The figure on each of the curves is the ball-milling time/h.

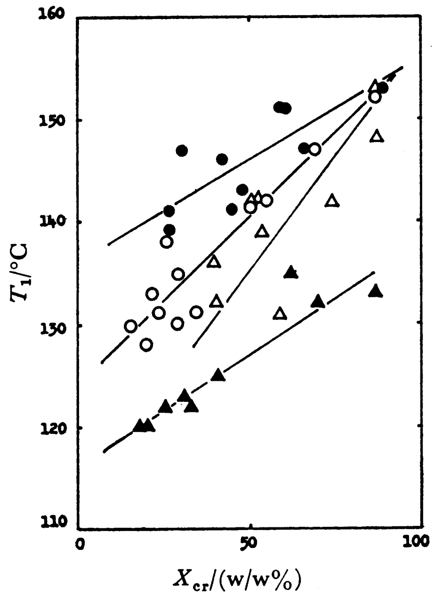

Fig. 9. Relation between T_1 and x_{cr}.
Ball-milling condition.

	Diluent	C_a[a)] (w/w %)
△	Dextran	30
●	MCC	10
○	MCC	30
▲	MC	40

a) C_a is the content of amobarbital in the mixture.

TABLE 2. BROADENING OF THE PEAK OF FUSION OF AMOBARBITAL IN THE DTA THERMOGRAM UPON BALL-MILLING WITH DILUENTS

Diluent	C_a[a)] (w/w%)	bt h	T_1 °C	T_2 °C	T_3 °C	T_3* °C	T_4 °C
—	100	0	153		155		159
		60	149		154		159
Dextran	30	0	153		153		159
		2	148		153		158
		35	142	146	154		158
		203	132	139	154		158
MCC	10	0	153		155		159
		1	147		154		159
		10	141		146		158
		15	141	145		154	159
MCC	30	0	152		154		159
		2	147		152		158
		5	142		151		158
		8	142	151		155	158
		36	135	143		153	158
		203	128	133	153		158
MC	40	0	133		156		159
		0.17	135		147		160
		2.6	123		134		154
		10	126	130	143		154
		30	122	128	141		154
		101	120	124	140		152

a) C_a is the content of amobarbital in the mixture.

or MC was also investigated. In Figs. 10 and 11, D_{50} is the median diameter by weight base, and $W_{0.3}$ is the weight percentage of the particles smaller than 0.3 μm in diamter. In Fig. 10, D_{50} decreased remarkably in the first stage of ball-milling. $W_{0.3}$ increased gradually, and it stayed nearly constant after ball-milling for more than 2 h for the mixture with MC. For the mixture with dextran, D_{50} was at a minimum at a ball-milling time between 17 and 100 h. A similar phenomenon has also been reported for many kinds of inorganic powders.[5)] As is shown in Figs, 2, 10, and 11, the change in C_{III} with the ball-milling time was parallel to the decrease in D_{50} at the first stage of ball-milling. It is considered that the transformation of Crystal I into Crystal III is remarkable when the particles are broken at nearly the center. In Figs. 3, 6, 10, and 11, the increase in the amorphous part with ball-milling is parallel to the increase in $W_{0.3}$ at a ball-milling time within 50 h. It is suggested that the amorphous part increases markedly when the particles are broken at the edge. It is also probable that the agglomeration rate is larger than the rate of decrease in the particle size when the amorphous

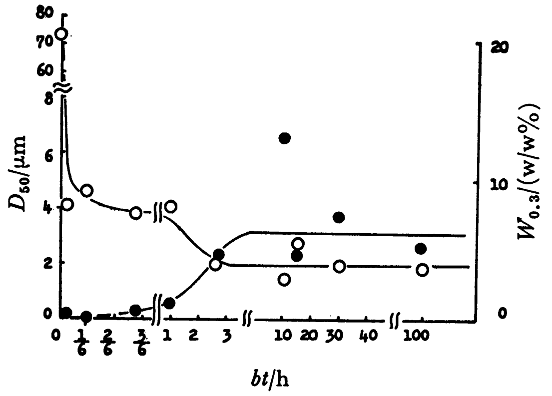

Fig. 10. Variation in the particle size of amobarbital by ball-milling with MC.
○: D_{50}, ●: $W_{0.3}$.

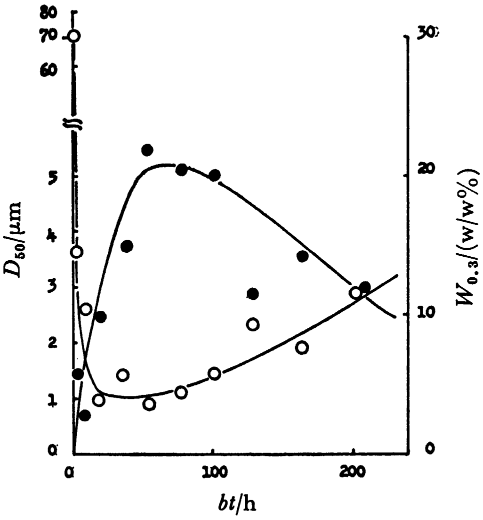

Fig. 11. Variation in the particle size of amobarbital by ball-milling with dextran.
○: D_{50}, ●: $W_{0.3}$.

part increases slightly after ball-milling for more than 100 h in the case of a mixture with dextran.

Solubility. In the case of the mixture with MC, the concentration of amobarbital in the filtrate of the suspension of the KH_2PO_4–Na_2HPO_4 buffer solution increased gradually with shaking, and then it stayed nearly constant after shaking for more than 2 h. However the concentration was at a maximum at the shaking time of 5 min for the other mixtures. In Figs. 12, 13, and 14, $c_{5\,\text{min}}$, $c_{2\,\text{h}}$, and c_{e} are the concentrations for the suspension shaken for 5 min, for 2 h, and set aside at 30 °C for a week after shaking for 2 h, respectively. The values of $c_{2\,\text{h}}$ or $c_{5\,\text{min}}$ for amobarbital in the ball-milled mixture were larger than the values for amobarbital ball-milled in the absence of the diluent. In Fig. 12, the $c_{5\,\text{min}}$ value for the mixture with dextran was at a maximum at a ball-milling time around 30—70 h; this was probably attributable to the fact that the surface energy of the amobarbital particles was at a maximum at this stage. In Figs. 10 and 11, D_{50} for the mixture with MC was larger than that for the mixture with dextran, but $c_{2\text{n}}$ and c_{e} for the mixture with MC were larger than $c_{5\,\text{min}}$ for the mixture with dextran. To judge from this fact, it does not seem that the surface energy is the main reason for the increase in the solubility of amobarbital.

The amorphous part in the amobarbital particles in the ball-milled mixtures was larger than the part for amobarbital ball-milled in the absence of diluents. In Figs, 3, 4, 6, 12, 13, and 14, the increase in $c_{5\,\text{min}}$ upon ball-milling with dextran or MCC at the first stage and the increase in c_{e} for the mixture with MC were parallel to the increase in the amorphous part. These facts suggest that the increase in the solubility of amobarbital upon ball-milling is due to the increase in the amorphous part. The solubility of amobarbital in the ball-milled mixture is expected to be 6—8.5 times as high as that of the original amobarbital, from the thermodynamical consideration using the data of ΔH_{obsd} and T_2, if the solid state of amobarbital in the ball-milled mixture is equilibrated with amobarbital in the solution.[2]

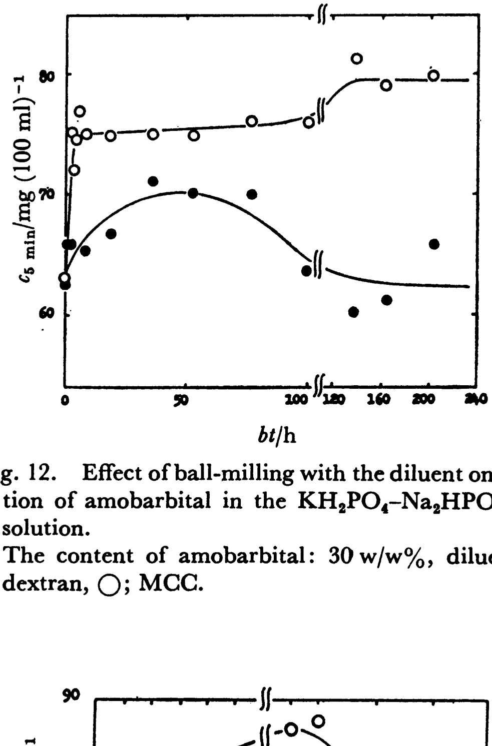

Fig. 12. Effect of ball-milling with the diluent on dissolution of amobarbital in the KH_2PO_4–Na_2HPO_4 buffer solution.
The content of amobarbital: 30 w/w%, diluent: ●; dextran, ○; MCC.

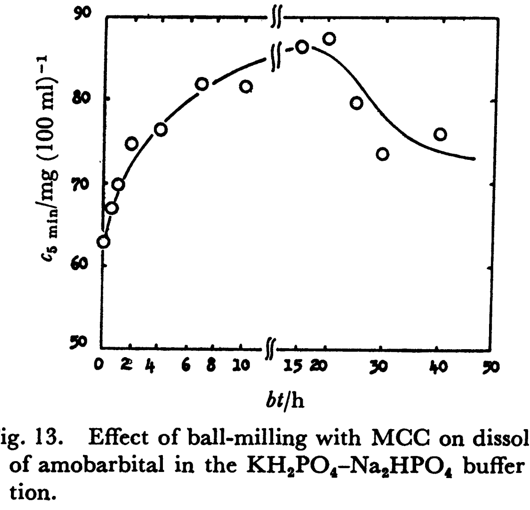

Fig. 13. Effect of ball-milling with MCC on dissolution of amobarbital in the KH_2PO_4–Na_2HPO_4 buffer solution.
The content of amobarbital: 10 w/w%.

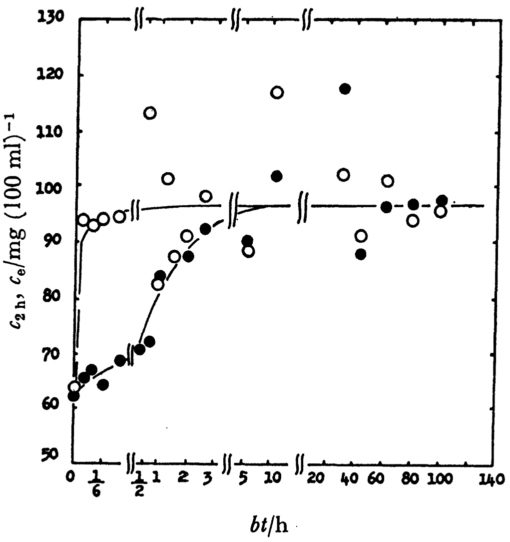

Fig. 14. Effect of ball-milling with MC on dissolution of amobarbital in the KH_2PO_4–Na_2HPO_4 buffer solution.

○: $c_{2\,h}$, ●: c_e.

In Figs, 3, 4, 5, and 6, the percentage of the amorphous part in amobarbital for the mixture with MC is nearly equal to the percentage for the mixture with MCC, though the percentage for the mixture with dextran is a little smaller than the percentage for the other mixtures. However, the c_{2h} for the mixture with MC was larger than the $c_{5\,\mathrm{min}}$ for the other mixtures. For the mixture with MC, c_e was nearly identical with c_{2h}, but for the other mixtures c_e was smaller than $c_{5\,\mathrm{min}}$ and nearly identical with the solubility of the original amobarbital. This fact suggests that the interaction of amobarbital with the diluent caused by ball-milling is one of the important reasons for the increase in the solubility. More details will be reported in another paper concerning this problem.

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