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A Decrease in Crystallinity of Amobarbital by Mechanical Treatment in the Presence of the Diluents

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Amobarbital was ball-milled, triturated, mortar-ground or stamp-milled in the absence or in the presence of various kinds of the diluents, and influence of the mechanical treatment on the physical and chemical state of amobarbital powders was investigated.

Intensity of the signals of amobarbital in the X-ray diffraction diagram decreased by the mechanical treatment. The signal of amobarbital in the DTA thermogram was not influenced by the mechanical treatment in the absence of the diluent. But the signal branched off into more than two signals, shifted to the lower temperature, decreased in intensity and disappeared by the mechanical treatment in the presence of the diluents. These phenomena were influenced more remarkably by the kind of the diluents than by the kind of the mechanical treatment. These tendencies were remarkable in the presence of precipitated silica, carbon black, granules of activated charcoal or ethyl cellulose and for the mixtures containing small amount of amobarbital. Roughly speaking, the decrease in the melting point of amobarbital in the mechanically treated mixture was remarkable, when the intensity of the signals of amobarbital in the X-ray diffraction diagram decreased markedly.

It was suggested from the infrared spectra and the electron spin resonance spectra of various kinds of the samples that the interaction was caused between amobarbital and the diluent by the mechanical treatment.

Keywords——amobarbital; diluent; ball-milling; trituration; stamp-milling; the decrease in the intensity of the signals of amobarbital in the X-ray diffraction diagram; dropping of the melting point of amobarbital; particles smaller than 0.1 μ in diameter; disturbed layer; interaction of amobarbital with the diluent by mechanical treatment

In the previous paper were reported the change in crystallinity and solubilization of slightly soluble organic powders, such as chloranil, by ball-milling in the presence of polyvinylpyrrolidone.[2] Nakai *et al.* also reported the same phenomena by vibro-milling pharmaceutical powders, such as diphenylhydantoin, in the presence of microcrystalline cellulose.[3,4] But details concerning these phenomena have not been investigated and the mechanism has not been clarified yet.

In this paper, amobarbital was mechanically treated in the presence of various kinds of the diluents, and influence of the kind of the mechanical treatment and the diluent on the decrease in crystallinity of amobarbital was investigated, in order to clarify the mechanism of these phenomena.

Experimental

1) **Material**——Amobarbital was of JP IX grade and purchased from Nihon Shinyaku Co.. The diluents used were as follows; precipitated silica (Koso Chemicals Co.), carbon black (Hitachi Carbon Co.), methyl cellulose, 4000 cps (Wako Junyaku Co.), hydroxypropyl cellulose (HPC), 3—6 cps and 1000—4000

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[1] Location: *Hatanodai, 1-5-8, Shinagawa-ku, Tokyo.*
[2] N. Kaneniwa, A. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 2973 (1975).
[3] K. Yamamoto, M. Nakano, T. Arita, and Y. Nakai, *J. Pharmacokin. Biopharm.*, **2**, 487 (1974); K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai, *J. Pharm. Sci.*, **65**, 1484 (1976); K. Yamamoto, S. Matsuda, M. Nakano, T. Arita, and Y. Nakai, *Yakugaku Zasshi*, **97**, 367 (1970).
[4] Y. Nakai, E. Fukuoka, S. Nakajima, and K. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 3340 (1977).

cps (Wako Junyaku Co.), microcrystalline cellulose (MCC, for column chromatography, Funakoshi Yakuhin Co.), polyvinyl alcohol (PVA) 2000 (Koso Chemicals Co.), potato starch (JP IX grade, Sanko Seiyaku Co.), acacia powders (JP IX grade, Sanko Seiyaku Co.), sodium alginate (Koso Chemicals Co.), agar powders (Yako Junyaku Co.), dextran 10 and 2000 (Seikagaku Kogyo Co.), dextrin (Wako Junyaku Co.), polyethylene glycol 6000 (PEG 6000) (Soekawa Chemicals Co.), the granules of activated charcoal (guaranteed grade, Wako Junyaku Co.), ethyl cellulose, 100 cps (EC, Wako Junyaku Co.), stylene polymer (Koso Chemicals Co.), polyvinylpyrrolidone K90 (PVP K90 Wako Junyaku Co.) and gelatin (Wako Junyaku Co.). Sodium chloride, anhydrous dextrose, lactose, chloranil and phenothiazine were of guaranteed grade.

2) **The Way of the Mechanical Treatment**——Ball-milling: A stainless steel mill with the inside diameter of 10 cm and with the capacity of 900 ml and stainless steel balls of true density of 8.2 g/cm^3 were used. Amobarbital or the mixture of amobarbital and each of the diluents were inserted in the mill containing thirty balls in diameter of 1.9 cm and ten balls in diameter of 2.5 cm, and the mill was revolved at 0.7 times the critical velocity where the gravitational force working on the balls was equal to the centrifugal force. Ten grams of amobarbital or the mixture of carbon black containing 10 w/w % of amobarbital was ball-milled for 100 hours. In case of the other mixtures, 5 g of the sample was ball-milled for 30 hours and 10 g of the sample was ball-milled for 60 hours.

Trituration: Three grams of amobarbital or the mixture of amobarbital and each of the diluents was triturated by the Ishikawa's automatic triturator with the pestle and the mortar. During trituration, most of the samples moved to the upper side of the mortar where the pestle did not work. Therefore, trituration was stopped several times, the samples at the upper side were scraped down to the bottom of the mortar, then trituration was continued again, and the samples were effectively triturated for more than 30 minutes.

Mortar-grinding: Two grams of amobarbital or the mixture of amobarbital and each of the diluents was triturated for 30 min by the mortar-grinder (Mitamura Riken Kogyo Co.).

Stamp-milling: Five grams of amobrabital or the mixture of amobarbital and each of the diluents was stamp-milled at the rate of 40 times per minute for 30 min by the stamp-mill of Ikeda Rika Co. The weight of the part of the stamp-mill giving the impact stress to the sample was 7.3 kg, and the height of the position from which this part fell to the bottom of the mill was 14.5 cm.

3) **Analysis of the Samples**——X-Ray diffraction diagrams of the samples were obtained by a JEOL X-ray diffractometer (Model-7E). The differential thermal analysis of the samples was made by a thermal analyser (Model DT-20B) of Shimadzu Seisakusho. Infrared (IR) spectra of the samples were measured by a JASCO diffraction granting infrared spectrometer (Model IRA-2). Electron spin resonance spectra of the samples were measured in air at 23° by an electron spin resonance (ESR) spectrometer (Model JES-PE).

Results and Discussion

1. X-Ray Diffraction Diagrams of the Samples

Figure 1 shows the X-ray diffraction diagrams of the mixtures of methyl cellulose and amobarbital. The intensity of the signals of amobarbital in the mixture containing 30 w/w % of amobarbital decreased and the signals for the mixture containing 10 w/w % of amobarbital disappeared by ball-milling. The similar tendency was also observed for the other mixture[2-4] The results are summarized in Table I, where R_x is the ratio of the area of the signal of amobarbital at 16° of 2θ for the mechanically treated mixture to the area for the physical mixture. Signals were observed around 16° of 2θ in the X-ray diffraction diagrams of anhydrous dextrose, phenothiazine and lactose, though no signal was observed in case of the other diluents. R_x was obtained by the signal of 12.5° of 2θ for the mixture of anhydrous glucose or phenothiazine, and by the signal of 8° of 2θ for the mixture of lactose. The value

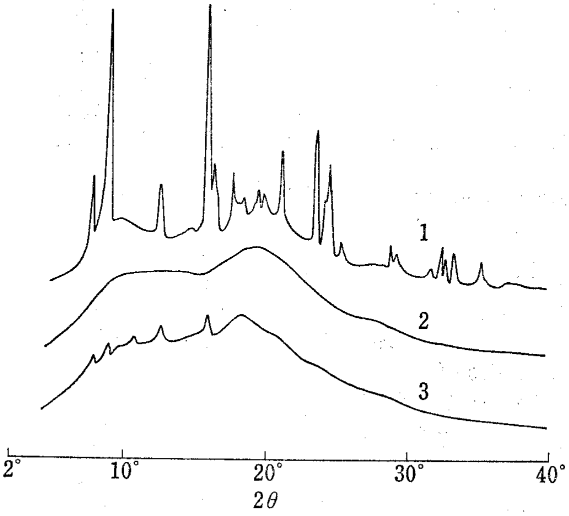

Fig. 1. Influence of Ball-Milling in the Presence of Methyl Cellulose on X-Ray Diffraction Diagrams of Amobarbital

1, physical mixture of amobarbital and methyl cellulose in the ratio of 3: 7 by weight.
2, the mixture of amobarbital and methyl cellulose in the ratio of 1: 9 by weight ball-milled for 60 hours.
3, the mixture of amobarbital and methyl cellulose in the ratio of 3: 7 by weight ball-milled for 60 hours.

of R_x for the mixture of anhydrous dextrose or phenothiazine was 190—320%. A large error may be inevitable, as R_x was obtained by the small signal of amobarbital between the large signals of the diluent. Though, in the other cases, it is also probable that R_x has comparatively large error, R_x is useful to compare roughly the extent of the decrease in the intensity of the signals of amobarbital in the X-ray diffraction diagrams by mechanical treatment.

R_x for amobarbital mechanically treated in the absence of the diluent was around or larger than 50%. R_x was small for the mixture of precipitated silica, carbon black, the

Table I. Influence of Mechanical Treatment in the Presence of Diluents on Crystallinity of Amobarbital, (A)

Diluent	Content of A (w/w %)	Ball-milling[a]		Trituration		Mortar-grinding		Stamp-milling[b]	
		R_x (%)	mp (°)	R_x (%)	mp (°)	R_x (%)	mp (°)	R_x (%)	mp (°)
- (Absent)	100	49	$T_1=157$	48	$T_1=157$	87	$T_1=158$	78	$T_1=157$
Precipitated silica	10	0	—	0	$T_1=135$	0	—	0	—
Carbon black	10	0	—	0	$T_1=114$	0	—	19	—
Sodium chloride	10	2	$T_1=156$, $T_2=144$	55	$T_1=151$, $T_2=146$	c)	$T_1=157$	0	$T_1=155$
Methyl Cellulose	30	11	$T_1=138$, $T_2=125$	52	$T_1=143$	37	$T_1=135$	4	$T_1=135$
HPC, 3-6 cps	30	31	—	c)	—	c)	—	24	$T_1=103$
HPC, 1000-4000 cps	30	36	—	26	—	c)	—		
MCC	10	0	—	25	$T_1=148$	46	$T_1=156$, $T_2=150$	31	$T_1=153$
PVA 2000	10	33	$T_1=147$	55	$T_1=151$, $T_2=146$	c)	$T_1=157$	26	$T_1=156$
Potato starch	10	c)	—			95	$T_1=159$	11	$T_1=156$
Potato starch	30	29	$T_1=145$, $T_2=127$	24	$T_1=157$				
Acacia powders	10	14	$T_1=148$	11	$T_1=156$	72	$T_1=159$	3	$T_1=156$
Acacia powders	30	30	$T_1=157$, $T_2=137$						
Sodium alginate	30	22	$T_1=157$, $T_2=148$	31	$T_1=155$	22	$T_1=155$	8	$T_1=156$
Agar powders	10	0	—	27	$T_1=157$	23	$T_1=159$	12	$T_1=158$
Dextran 2000	10	0	—	33	$T_1=151$	27	$T_1=155$	11	—
Dextrin	10	0	—	131[d]	$T_1=156$	80	$T_1=156$	11	$T_1=152$
PEG 6000	10	43	—	17	—	30	—	9	—
Lactose	10	55	e)	51	e)	61	e)	20	e)
Anhydrous dextrose	10	248[d]	e)	315[d]	e)	305[d]	e)	278[d]	e)
Granules of activated charcoal	10	0	—	0	—	0	—	0	$T_1=158$
Ethyl cellulose	10	0	—	0	—	8	—	12	—
Stylene polymer	10	0	$T_1=146$, $T_2=110$	c)	—	c)	$T_1=156$	20	$T_1=153$
PVP K90	10	0	—	0	—			c)	—
Gelatin	10	0	—	19	$T_1=156$	20	$T_1=157$	31	$T_1=158$
Chloranil	10	3	$T_1=151$	7	$T_1=147$	11	$T_1=152$	6	$T_1=150$
Phenothiazine	10	152[d]	$T_1=123$	215[d]	$T_1=136$	114	$T_1=137$	197[d]	$T_1=137$

a) Amobarbital and the mixture of carbon black or dextran 2000 were ball-milled for 100 hours, and the other samples were ball-milled for 60 hours.

b) The mixture of silica was stamp-milled for 20 minutes and the mixture of carbon black for 15 minutes. The other samples were stamp-milled for 30 minutes.

c) X-ray diffraction diagrams of the samples could not be obtained, for the sample became blocky or the granular sample was not crushed by application of mechanical treatment.

d) Abnormally large value of R_x was obtained, though it was not clear whether the value was due to experimental errors.

e) The value of mp of amobarbital could not be obtained by DTA, for the signal of amobarbital was overlapped by the large signal of the diluent.

Table II. Influence of the Content of Amobarbital, A, in the Mixture on Variation in Crystallinity of Amobarbital by Ball-Milling

Diluent	Content of A (w/w %)	W_s–T_b[a] (g-hr)	R_x (%)	mp (°)
Precipitated silica sands	10	10—65	0	—
	20	10—61	0.8	$T_1=128$
	40	5—32	7	$T_1=150$, $T_2=137$
	60	5—32	21	$T_1=153$, $T_2=147$
	80	5—32	33	$T_1=149$
Methyl cellulose	30	10—63	11	$T_1=138$, $T_2=125$
	40	5—32	26	$T_1=143$, $T_2=127$
	60	5—32	32	$T_1=148$, $T_2=133$
	80	5—32	37	$T_1=153$, $T_2=141$
	80	0[b]	100	$T_1=154$
Microcrystalline cellulose	10	10—61	0	—
	20	5—30	32	$T_1=152$, $T_2=136$
	40	5—33	24	$T_1=152$, $T_2=143$
	60	5—33	28	$T_1=154$, $T_2=145$
	80	5—30	39	$T_1=154$, $T_2=150$
Agar powders	10	10—61	0	—
	20	5—31	0	$T_1=147$, $T_2=143$
	40	5—31	24	$T_1=150$, $T_2=146$
	60	5—31	44	$T_1=152$
	80	5—31	32	$T_1=153$
Ethyl cellulose	10	10—62	0	—
	20	10—64	0	—
	40	10—60	36	$T_1=136$, $T_2=126$, $T_3=104$
	60	10—61	24	$T_1=145$, $T_2=130$
	80	10—61	24	$T_1=151$, $T_2=129$

a) W_s is the weight amount of the mixture, and T_b is the ball-milling time. For example, 10—60 means that 10 g of the mixture was ball-milled for 60 hours.
b) Physical mixture.

granules of activated charcoal or ethyl cellulose. But R_x for the mixture of PVA 2000 or lactose was a little smaller than the value for amobarbital mechanically treated in the ansence of the diluent. Stamp-milling and ball-milling seemed to be more effective than trituration and mortar-grinding for the decrease in R_x for the mixture of sodium chloride, methyl cellulose, dextran or dextrin. But the decrease in R_x was influenced more remarkably by the kind of the diluent than by the kind of the mechanical treatment.

As shown in Table II, R_x was small for the mixture containing small amount of amobarbital.

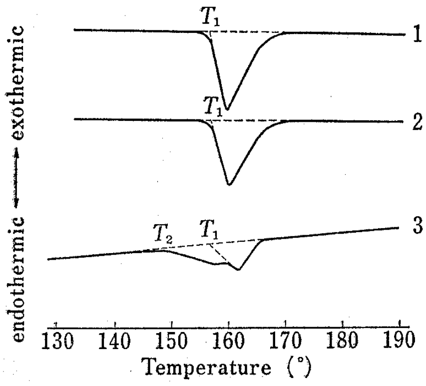

Fig. 2. Differential Thermal Analysis of Amobarbital

1, original amobarbital (Range; ±100 μV).
2, amobarbital ball-milled for 100 hours (Range; ±100 μV).
3, the mixture of amobarbital and sodium arginate in the ratio of 3:7 by weight ball-milled for 61 hours (Range; ±50 μV).

2. DTA

As shown in Fig. 2, the signal in the DTA thermogram of amobarbital in the mixture branched off into more than two signals, shifted to lower temperature, decreased in the intensity and disappeared by mechanical treatment in the presence of the diluents.[3,4] The melting points of amobarbital in the mechanically treated mixtures obtained by the DTA thermogram, T_1, T_2, ···, are summarized in Table I and II. The melting point of

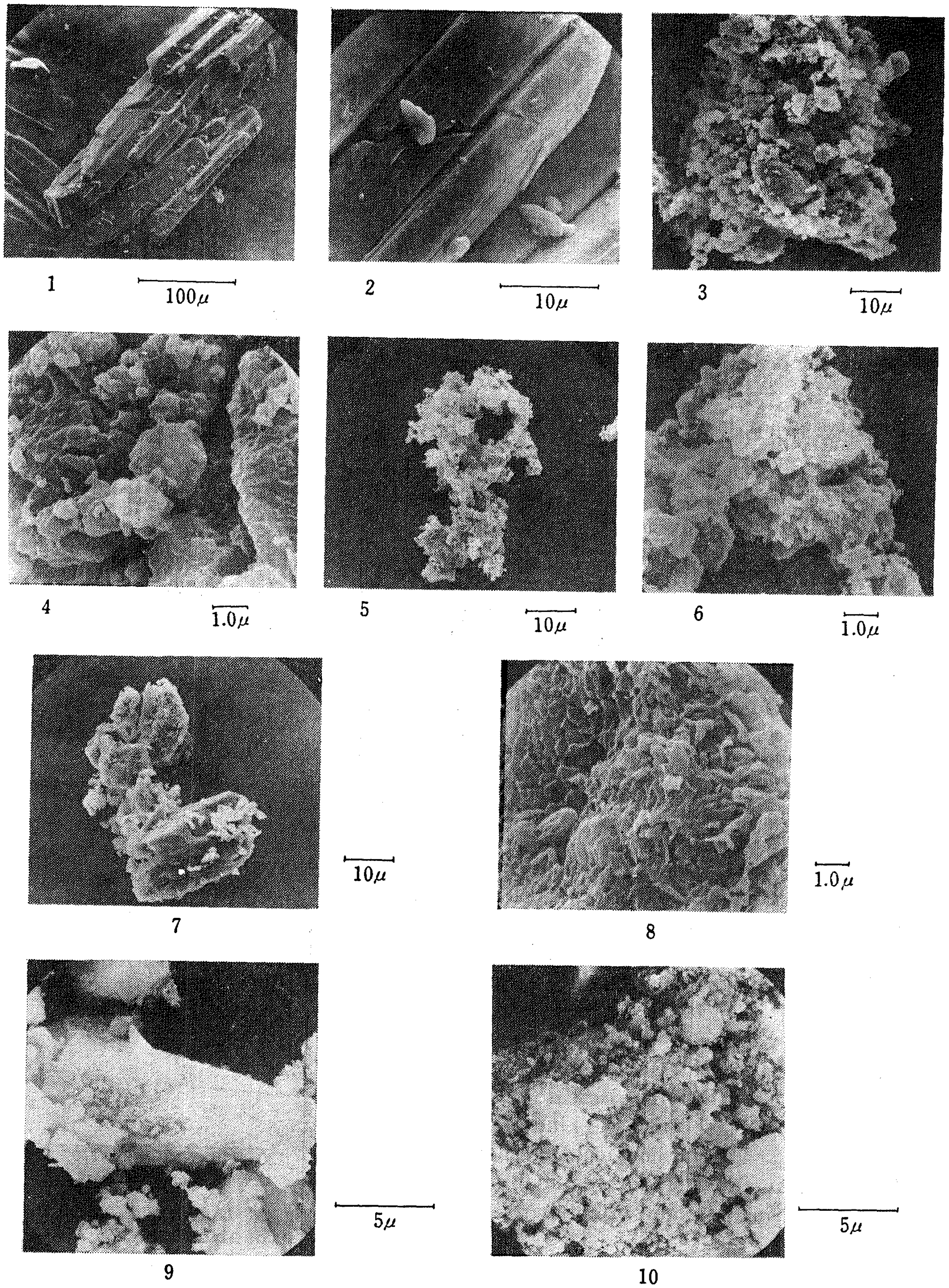

Fig. 3. Scanning Electron Microscopic Photographs of Amobarbital and the Ball-Milled Mixture of Precipitated Silica

Samples[a]	Magnification	Samples[a]	Magnification
1, original amobarbital	× 300	6, triturated amobarbital	×10000
2, original amobarbital	× 3000	7, stamp-milled amobarbital	× 1500
3, ball-milled amobarbital	× 1500	8, stamp-milled amobarbital	×10000
4, ball-milled amobarbital	×10000	9, original precipitated silica	× 6000
5, triturated amobarbital	× 1500	10, the ball-milled mixture of precipitated silica	× 6000

a) referred to Table I.

amobarbital was not influenced by the mechanical treatment in the absence of the diluent, though R_x was between 48% and 87%. It is known that the line broadening is observed for the signals in the X-ray diffraction diagrams of the particles smaller than 0.1 μ.[5] Fig. 3 shows the scanning electron microscopic photographs of original or the mechanically treated amobarbital and the ball-milled mixture of precipitated silica. Small particles of ball-milled and triturated amobarbital agglomerated each other, but the particles smaller than 0.1 μ in diameter were scarcely observed. It was considered from Fig. 3 that the particle size of amobarbital did not decrease remarkably by stamp-milling, but the surface of the stamp-milled particles was markedly rough compared with the surface of original amobarbital. Probably, the disturbed layer is formed on the surface of amobarbital particles by stamp-milling in the absence of the diluents. The decrease in the intensity of the signals of amobarbital in the X-ray diffraction diagrams by the mechanical treatment in the absence of the diluents may be due to the formation of the disturbed part in the crystal structure.

Roughly speaking, the dropping of the melting point of amobarbital in the mechanically treated mixture was remarkable, when R_x was small. It was clarified by the scanning electron microscopic observation that the particles of the mechanically treated powders tend to agglomerate each other more remarkably than the particles of the original powders (Fig. 3). It is suggested from this observation that the size of amobarbital particles decreases more markedly or that formation of the disturbed layer in the surface of the particles is more remarkable by the mechanical treatment in the presence of the diluents than by the treatment in the absence of the diluents.

It has been discussed theoretically by Hayakawa *et al.* that the melting point of the fine powders was lower than that of the large particles by the difference of the surface energy between them, and this fact was confirmed experimentally for the particles of approximately 250 Å in diameter.[6,7] Nakai *et al.* reported that the signals of the medicinals such as benzoic acid in the X-ray diffraction diagrams and in the DTA thermograms disappeared and that solubility of these medicinals increased by vibro-milling in the presence of microcrystalline cellulose (MCC). They also found that the pores of 30—40 Å in diameter in the particles of MCC in the vibro-milled mixture of benzoic acid increased by releasing benzoic acid from the mixture. They considered that medicinals dispersed in the cellulose matrix in the ground mixture as molecules or micro-assemblies of molecules bound by hydrogen-bonding with MCC.[4] Kaneniwa *et al.* discussed the increase in solubility of the particles smaller than 0.1 μ in diameter with the decrease in the size due to the increase in the surface free energy.[8] But, the results of Nakai *et al.* may also be considered to be due to the covering of the pores in the MCC particles by the thin coating films of benzoic acid. On the other hand, it was reported that the dissolution rate of crystal silica decreased, the heat of transition in the phase state varied, and the line broadening and the decrease in the intensity of the signals in the X-ray diffraction diagram were observed by crushing, and these findings were attributed to the formation of the disturbed layer in the surface of the particles by crushing, though the size of the crushed particles were around or smaller than 5 μ.[6,9]

Though details are not investigated in this paper, the following three possibilities are suggested from the above facts to the decrease in the intensity of the signals in the X-ray diffraction diagrams and dropping of the melting point of amobarbital by mechanical treatment in the presence of the diluents; a large portion of the particles of amobarbital in the mechanically treated mixture are smaller than 0.1 μ in diameter, the surface of the diluent

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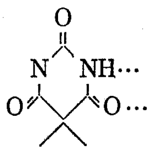
5) H. Akamatsu, "Jikken Kagaku Koza, 4, Kotai Butsurikagaku," Maruzen 1956, p. 224.
6) M. Hori and S. Hayakawa, *Nihon Butsurigakkaishi*, **20**, 396 (1964).
7) Yu. I. Petrov, *Fiz. Tverdogo Tela*, **6**, 2160 (1964).
8) N. Kaneniwa, *Funsai*, **15**, 48 (1970); N. Kaneniwa and K. Imagawa, *Funsai*, **22**, 18 (1977).
9) P.B. Dempster and P.D. Ritchie, *Nature*, **169**, 538 (1952); *idem*, *J. Appl. Chem.*, **2**, 31, 42 (1952); 3, 182, 213 (1953); G. Nagelschmidt, R.L. Gordon, O.G. Griffin, *Nature*, **169**, 39 (1952): **175**, 1135 (1955).

particles is covered with the coating film of amobarbital in thickness thinner than 0.1 μ, or a thick disturbed layer is formed in the surface of the amobarbital particles, though the particles are larger than 0.1 μ in diameter.

3. IR Spectra

Change *et al.* characterized the interaction between polyethylene glycol (PEG) and barbituric acid derivatived by comparison of the IR spectra of the complex between them with the spectra of the physical mixture. A free NH streching absorption at 3310 cm^{-1} region disappeared and the intermolecular hydrogen-bonded NH streching absorption of phenobarbital near 3200 cm^{-1} and 3080 cm^{-1} shifted to higher frequency by the interaction with PEG. The similar phenomenon was also observed in the spectra of pentobuthetal, probarbital, butarbital, cyclobarbital and buthethal, though a free NH streching absorption at 3310 cm^{-1} region was not observed in these spectra. This shift was considered to be due to the hydrogen-bonding between PEG and barbiturates. The 2-carbonyl streching absorption at the region of 1780—70 cm^{-1} shifted to the lower frequency and the 4,6-carbonyl out of phase streching absorption at 1720—10 cm^{-1} region and symmetric in phase streching absorption at 1680—70 cm^{-1} region shifted to the higher frequency in these spectra by complexation with PEG. Chang *et al.* considered from the above facts that the conformation of hydrogen-bonding sites in the phenobarbital crystal was as in I, the conformation in the other barbiturates as in II, and that the conformation became as in III on complexation.[10]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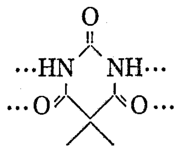
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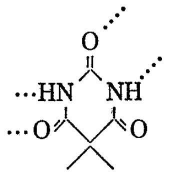
III

Mesley compared the IR spectra of barbituric acid derivatives and their salts, including many polymorphic modifications, and found two major differences in the spectra of phenobarbitone IV, V and VI and nealbarbitone from the other barbiturates; the peak near 3200 cm^{-1} was significantly stronger than the peak at 3100 cm^{-1}, the latter being shifted from its usual position of 3080 cm^{-1}, though the two bands of the other barbiturates were of approximately equal intensity, and the highest frequency carbonyl band was missing, leaving a single broad band centered around 1705 cm^{-1} in which no individual peaks were dissolved. Mesley considered this finding to be due to the hydrogen-bonding of the 2-carbonyl group with an NH group, presumably at the expence of either the 4- or 6-carbonyl group. The support for this was also found in the N–H region, where all of these compounds showed the evidence of a second broad band near 800 cm^{-1}, which would be consistent with a weaker hydrogen-bond.[11]

Now, the IR spectra of mechanically treated amobarbital were investigated. The absorption at 3200 cm^{-1} was a little stronger than the absorption at 3080 cm^{-1} for amobarbital mechanically treated in the absence of the diluent. The N–H absorption of triturated amobarbital shifted from 850 cm^{-1} to a lower frequency and a broad signal was observed between 850 cm^{-1} and 815 cm^{-1}, as shown in Fig. 4. Mesley observed two signals at 850 cm^{-1} and 815 cm^{-1} in the spectra of amylobarbitone (amobarbital) I, and 841 cm^{-1} and 822 cm^{-1} in the spectra of type II, and that the band near 1220 cm^{-1} was split in type II, but not in type I.[11] But the absorption at 850 cm^{-1} and 815 cm^{-1} of original amobarbital was identical with the absorption of amobarbital mechanically treated by the method other than trituration.

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10) B.L. Chang, N.O. Nuessle, and W.G. Haney, Jr, *J. Pharm. Sci.*, **64**, 1787 (1975).

11) R.J. Mesley, *Spectrochimica Acta.*, **26A**, 1427 (1970).

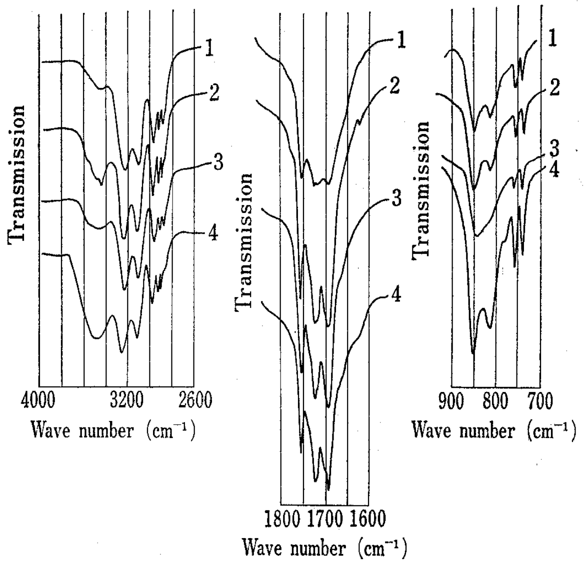

Fig. 4. Influence of Mechanical Treatment on IR Spectra of Amobarbital

1, original amobarbital.
2, amobarbital ball-milled for 100 hours (W_s=10 g).
3, triturated amobarbital (W_s=3 g).
4, amobarbital stamp-milled for 30 minutes (W_s=5 g).

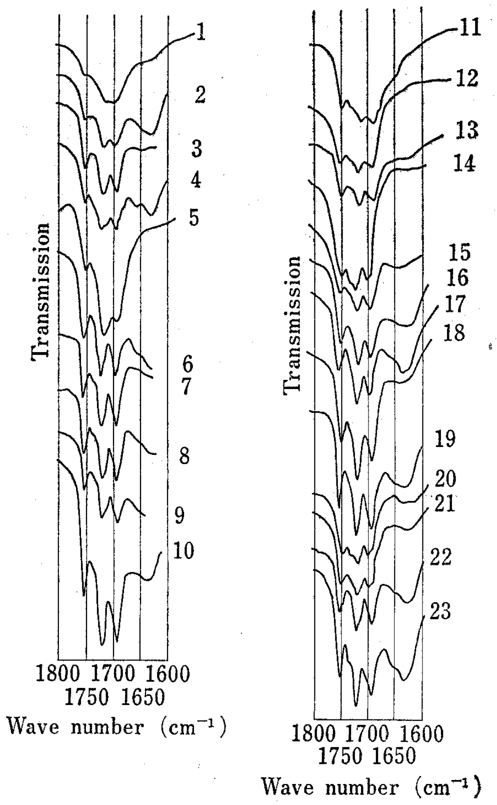

Fig. 5. Influence of Mechanical Treatment in the Presence of Diluent on IR Spectra of Amobarbital in the Carbonyl Streching Regions

Samples; Referred to Table I

	Diluent	Mechanical treatment
1,	precipitated silica	ball-milling
2,	microcrystalline cellulose	ball-milling
3,	PVA 2000	ball-milling
4,	dextrin	ball-milling
5,	stylene polymer	ball-milling
6,	acacia powders	trituration
7,	precipitated silica	trituration
8,	microcrystalline cellulose	trituration
9,	acacia powders	stamp-milling
10,	dextrin	stamp-milling
11,	methyl cellulose	physical mixture
12,	methyl cellulose	ball-milling
13,	hydroxypropyl cellulose	ball-milling
14,	ethyl cellulose	ball-milling
15,	agar powders	ball-milling
16,	potato starch[a]	ball-milling
17,	dextran 10	ball-milling
18,	PEG 6000	ball-milling
19,	anhydrous dextrose	ball-milling
20,	ethyl cellulose	trituration
21,	ethyl cellulose	stamp-milling
22,	precipitated silica	stamp-milling
23,	dextran 10	stamp-milling

a) content of amobarbital; 10 w/w %

Signals were observed at the range of 3000—4000 cm^{-1} and 700—900 cm^{-1} region, but no signal was observed at the range of 1600—1800 cm^{-1} in the IR spectra of most of the diluents. Then, the carbonyl absorption at the range of 1600—1800 cm^{-1} of amobarbital in the mechanically treated mixture was investigated. As shown in Fig. 5, two types of the difference was observed between the spectrum of original amobarbital and the spectra of the mechanically treated mixture.

1; The absorption at 1750 cm^{-1} was remarkably weak, as shown for the ball-milled mixture of precipitated silica, MCC or stylene polymers.

2; The absorption at 1720 cm^{-1} is stronger than the absorption at 1750 cm^{-1} and 1680 cm^{-1}, as shown for the mechanically treated mixture of ethyl cellulose. The absorption of amobarbital at 1680 cm^{-1} shifted to the higher frequency by ball-milling and trituration in the presence of ethyl cellulose.

The spectrum of the physical mixture of phenothiazine was identical with the spectra of the mechanically treated mixtures. But, in case of the other mixtures, the difference in the carbonyl absorption was observed only for the mechanically treated mixtures. These findings were considered to be due to hydrogen-bonding of the 2-carbonyl groups and the hydrogen-bonds of NH weakened by the mechanical treatment in the presence of the diluent, though it was not clear whether the hydrogen-bonding was between amobarbital molecules or between amobarbital and the diluent.

4. ESR Spectra

Signals were not observed in the ESR spectra of amobarbital powders ball-milled or stamp-milled in the absence of the diluent. But, as shown in Fig. 6, a signal was observed in the spectrum of amobarbital triturated in the absence of the diluent.

The line width of the signals in the spectra of the mechanically treated mixtures of carbon black or chloranil was narrower than the width for these diluents mechanically treated in the absence of amobarbital. This finding is probably due to the exchange narrowing caused by

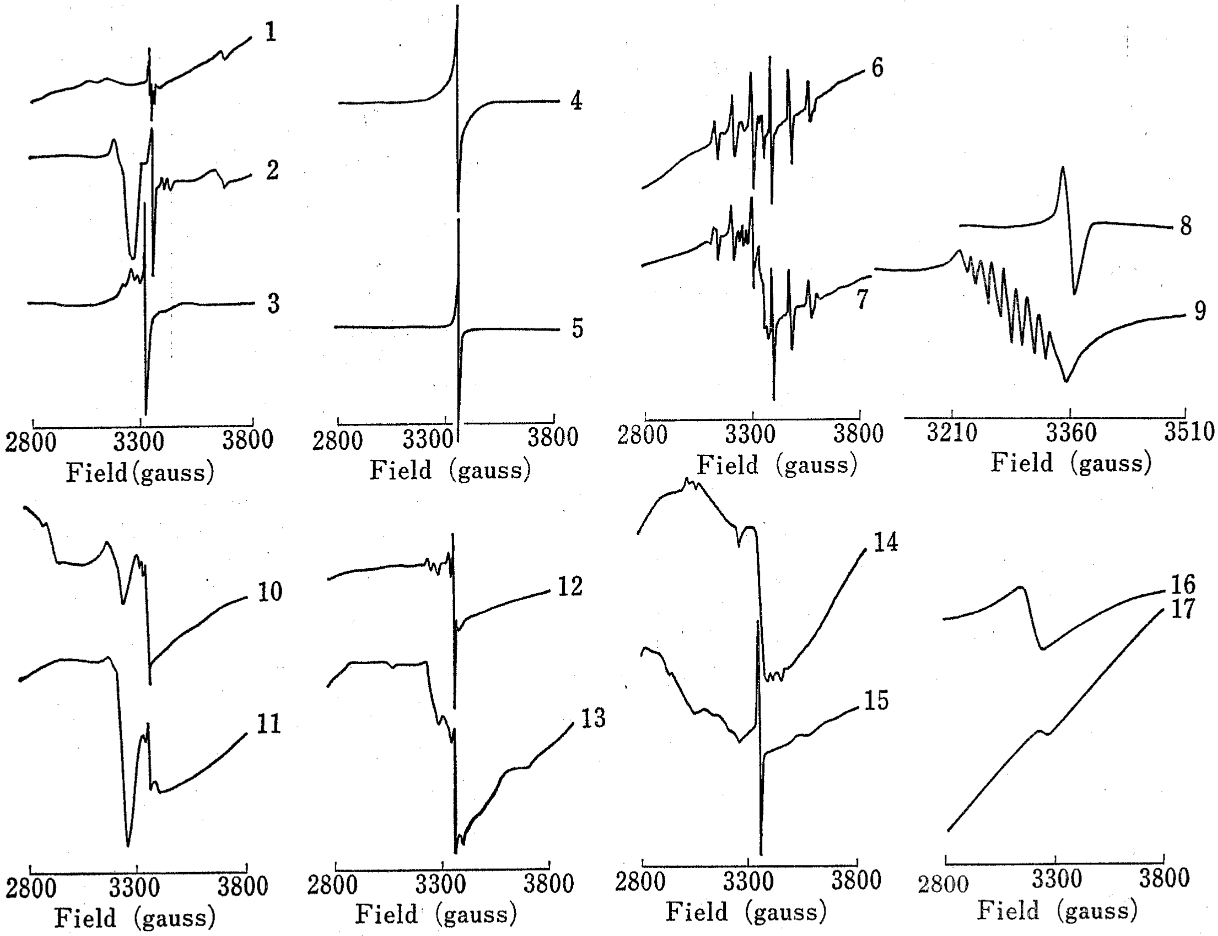

Fig. 6. ESR of the Mechanically Treated Mixtures of Amobarbital, A, and Diluents

	Diluent	Content of A (w/w %)	Treatment	Modulation width (gauss)	Amplitude
1,	—	100	trituration	0.63×10	10^3
2,	precipitated silica	0	trituration	0.63×10	10^3
3,	precipitated silica	10	trituration	0.63×1	8.9×10
4,	carbon black	0	trituration	0.63×1	2.1×10 a)
5,	carbon black	10	trituration	0.63×1	2.0×10 a)
6,	sodium chloride	0	trituration	0.63×10	3.2×10^2
7,	sodium chloride	10	trituration	0.63×1	5.0×10^2
8,	PVA 2000	0	trituration	0.63×10	7.9×10^2
9,	PVA 2000	10	trituration	0.63×10	7.9×10^2
10,	lactose	0	trituration	0.63×10	8.9×10^2
11,	lactose	10	trituration	0.63×10	2.0×10^2
12,	PVP K90	0	trituration	0.63×10	3.2×10^2
13,	PVP K90	10	trituration	0.63×10	15^3
14,	chloranil	0	trituration	0.63×10	5.0×10^2
15,	chloranil	10	trituration	0.63×10	5.6×10^2
16,	chloranil	0	ball-milling	0.63×1	2.0×10^2
17,	chloranil	10	ball-milling	0.63×1	2.0×10^2

a) The spectra of these samples were measured by inserting in a sample tube of quartz glass in diameter of 4 mm a Pyrex tube in diameter of 0.8 mm in which the sample was closely packed. The spectra of the other samples were measured by inserting the sample directly in the sample tube.

the interaction between them by the mechanical treatment.[12] Fujimoto *et al.* found that the spin densities in carbon black increased by the mechanical or the chemical treatment of its surface, and proposed a distribution model in which electron spin scarcely existed on the surface but most of them collectively existed in 5—6 Å inner part of the carbon black particles. There was practically no contribution of electron spins to the chemical reaction of the rubber and carbon black. However, a variation in the restriction of electron spins and an increase in the number of electron spins were observed when there was a chemical reaction on the surface of carbon black.[13] Yokokawa found that the line width of the signals for some kinds of coals was narrower in ethylene diamine than in air. This author also found that the signal was of the Gaussian type in air and that the signal varied toward the Lorenzian type in ethylene diamine. The spin concentration of low-rank coals increased in a basic medium and this might be considered to result from the formation of semiquinone type anion radicals.[14] Toyoda found that the line width of the signals for coals decreased with the increase in the carbon content, when the content was larger than 90 w/w%, and considered this finding to be due to the exchange narrowing caused by the interaction between delocalized spin centers which resulted from the increase in the aromatic nuclei.[15]

The spectrum of the triturated mixture of precipitated silica, sodium chloride, PVA 2000, dextran 10, lactose or PVP K90 was different from the superposition of the spectrum of triturated amobarbital and that of the triturated diluent, respectively. Signals were observed for the stamp-milled mixtures of anhydrous dextrose or precipitated silica and for the ball-milled mixture of PVP K90, but signals were not observed for ball-milled PVP K90 or for the stamp-milled powders of anhydrous dextrose or precipitated silica. Signals were not observed for the mechanically treated mixtures of acacia powders, phenothiazine or potato starch, though signals were observed for these diluents mechanically treated in the absence of amobarbital. These phenomena may also be due to the interaction between amobarbital and the diluent caused by the mechanical treatment.

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