

Effect of Grinding on Physical and Chemical Properties of Crystalline Medicinals with Microcrystalline Cellulose. II. Retention of Volatile Medicinals in Ground Mixture

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Volatile medicinals, naphthalene, *d*-camphor, and *p*-cresol became amorphous during grinding with microcrystalline cellulose. The medicinal of interest was retained in the ground mixture even when the mixture was heated at moderately high temperature *in vacuo*. The close relationship was noticed between the retentivity and the state of the medicinals (amorphous or not) in the ground mixture. The amount of the medicinal remaining in the ground mixture was influenced by the medicinal content, the grinding time, and the amount of water adsorbed. The medicinals were very rapidly released from the ground mixture into water.

The mechanism for these results was discussed, based on the structure of the ground mixture proposed in the previous paper as follows: the molecules of the volatile medicinals are enclosed by the cellulose molecules that were bound by hydrogen bonds between hydroxyl radicals. The system was regarded as an "entropy frozen solution" of the medicinal in cellulose molecules. By adding water to the ground mixture, the hydrogen bonds are weakened and the medicinal molecule obtains the ability of molecular movement.

Keywords—microcrystalline cellulose; naphthalene; *d*-camphor; *p*-cresol; mechanochemistry; grinding; dissolution rate; crystallinity; volatilization; retention of volatile medicinals

In the previous paper,²⁾ it was recognized by X-ray diffraction and thermal measurements that grinding with microcrystalline cellulose (M.C.C.) turned crystalline medicinals into the amorphous. The grinding resulted in a rapid releasing rate of a medicinal from the ground mixture and a high bioavailability of the medicinal.³⁾ On the basis of the results, the following mechanism for the phenomena was proposed: medicinals were dispersed in cellulose as a molecule or an assembly of a small number of molecules. The ground mixture may be regarded as a solution of the medicinal in cellulose without having molecular translation movement (an "entropy frozen solution").

In the present report, volatile materials, naphthalene, *d*-camphor, and *p*-cresol, were ground with M.C.C. respectively and retention of the volatile materials in the ground mixture was studied. The factors affecting the retention were examined.

Experimental

(1) **Materials**—M.C.C.: M.C.C.⁴⁾ was stored in a well closed container. Water content was 6.4%. Dried M.C.C.: M.C.C. was dried at 60° for 5 hr *in vacuo*. Ground M.C.C. (noncrystalline cellulose): M.C.C.

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was ground for 3 hr and halo pattern was observed on the X-ray diffractogram in the same manner as reported in the previous paper.⁵⁾ Water content was 7.1%. Naphthalene, *d*-camphor, and *p*-cresol were of reagent grade. Weight loss percent of M.C.C. during heating at 60° *in vacuo* for 5 hr was used as water content (%).

(2) **Grinding of Mixture of M.C.C. and Medicinals**—A stainless steel shaker mill⁶⁾ was used. The procedures were the same as those reported in the previous paper.²⁾ Grinding time was 3 hr unless indicated otherwise.

(3) **X-Ray Diffraction (Powder Method)**—The apparatus and the procedures were the same as those reported in the previous paper.⁵⁾

(4) **Thermal Measurements**—The weight loss due to volatilization of medicinals was measured either by TG under the conditions of an increasing temperature of 5°/min and a nitrogen flow of 200 ml/min or by weighing the sample periodically in heating at a constant temperature of 80° in a vacuum system. The melting temperature and the heat of fusion were measured by a differential thermal analyzer (DTA)⁷⁾ and a differential scanning calorimeter (DSC).⁸⁾ Scanning speed ranged from 1 to 5°/min.

(5) **Measurement of Dissolution Rate**—The apparatus and procedures were similar to those reported in the previous paper.²⁾ Amount of water was 300 ml for *d*-camphor and 500 ml for naphthalene. The solution was stirred at 200 rpm by a two-wings glass stirrer at 20° for *d*-camphor and 23° for naphthalene. In the dissolution test of naphthalene, the concentration was continuously measured with an ultraviolet (UV) spectrophotometer by circulating the solution through a flow cell.

(6) **Analysis of Medicinals in a Ground Mixture**—Naphthalene and *p*-cresol were completely released in a 90% ethanol solution from the ground mixture. Distilled water was used for *d*-camphor. The solutions were subjected to Millipore filtration (0.45 μ) and the concentrations were measured spectrophotometrically at 276 nm for naphthalene, 280 nm for *p*-cresol and 285 nm for *d*-camphor. For the concentration measurement of *d*-camphor released from the ground mixture, the photometric absorption was corrected by subtracting the absorption intensity due to M.C.C. solution since the absorption of M.C.C. could not be neglected as compared to the absorption due to *d*-camphor.

Results

Each ground mixture of 5% *d*-camphor, 3% naphthalene, and 5% *p*-cresol with M.C.C. showed halo patterns on the X-ray diffractograms and also showed no heat of fusion on DTA and DSC curves. These were the same results as reported in the previous paper.²⁾

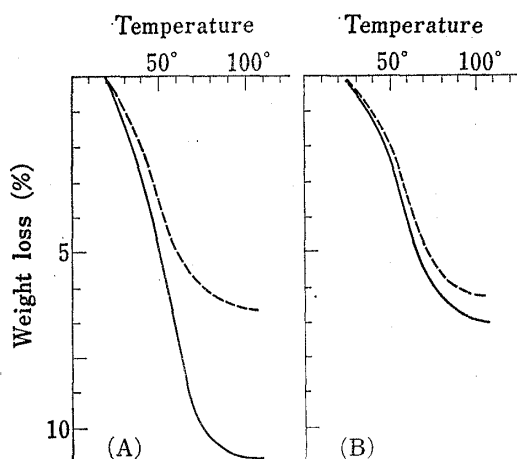


Fig. 1. TG Curves for Ground and Physical Mixtures of 5% *d*-Camphor and 95% M.C.C.

- (A) physical mixture —, M.C.C. alone —.
 (B) 3 hr ground mixture —, 3 hr ground M.C.C. alone —.

The volatilization of *d*-camphor from the physical and ground mixture was examined by TG under the conditions of increasing temperature of 5°/min and a nitrogen flow. Fig. 1(A) shows the TG curves of M.C.C. (broken line) and the physical mixture of 5% *d*-camphor (solid line). The decrease in weight of M.C.C. at the elevated temperature is due to water evaporation. The physical mixture decreased in weight more than M.C.C., and this difference is attributed to the volatilization of *d*-camphor from the mixture. From the chemical analysis, it was recognized that *d*-camphor was completely lost from the mixture after the thermal running. Fig. 1(B) shows the result of the ground mixture of 5% *d*-camphor (solid line) and that of the ground M.C.C. of the reference (broken line). The weight loss of the ground mixture was nearly the same as that of the ground M.C.C. This result showed that a

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 6) Yanagimoto Seisakusho, Co., Ltd.
 7) Shimadzu Seisakusho DT-20B.
 8) Perkin Elmer DSC-1B.

greater part of *d*-camphor remained in the ground mixture after heating at 100°. The same results were obtained from the ground mixture of naphthalene and of *p*-cresol with M.C.C.

The remaining amounts were also measured for the ground mixtures during heating at constant temperature of 80° *in vacuo*. Fig. 2(A) shows the results with the ground mixture (solid line) and the physical one (broken line) of 5% *d*-camphor. More than 90% of *d*-camphor remained in the ground mixture even after 3 hr heating, while the physical mixture completely lost *d*-camphor within 10 min. Fig. 2(B) shows the result with the ground mixture of 3% naphthalene. Nearly all amount of naphthalene remained in the ground mixture. The same results were obtained from the ground mixture of *p*-cresol.

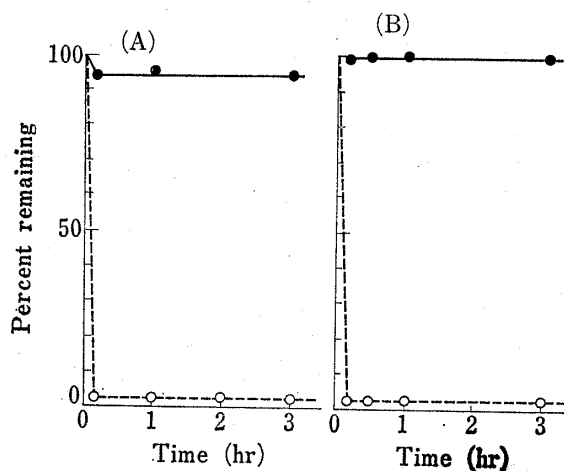


Fig. 2. Remaining Amount of *d*-Camphor and Naphthalene in Ground (—●—) and Physical (---○---) Mixtures as a Function of Heating Time at 80° *in vacuo*

- (A) mixture of 5% *d*-camphor and 95% M.C.C.
 (B) mixture of 3% naphthalene and 97% M.C.C.

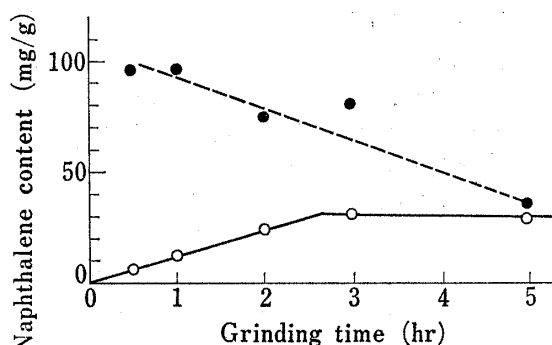


Fig. 3. Effect of Grinding Time on Naphthalene Contents before (---●---) and after (—○—) Heating at 80° for 3 hr *in vacuo*.

A mixture of 10% naphthalene and 90% M.C. C. was ground for a definite lapse of time. Naphthalene contents in the ground mixture before and after heating were determined spectrophotometrically.

Effect of grinding on retention of naphthalene in the ground mixture was examined as a function of grinding time. The results are shown in Fig. 3. When a large amount of naphthalene (10%) was added to M.C.C., the content of naphthalene in the ground mixture decreased with increasing grinding time (broken line). It is supposed that this decrease may be due to the adherence of naphthalene to the inner surface of cell and the surface of balls as the result of separation of the components. X-Ray reflection peaks due to naphthalene were observed in the diffractograms of the ground mixtures. The ground mixtures at respective grinding times were heated at 80° *in vacuo* for 3 hr. The amount of remaining naph-

TABLE I. Relationship between the Amount of *p*-Cresol Added to M.C.C. and Remaining Amount in Ground Mixture after Heating

Amount of added <i>p</i> -cresol (mg/g M.C.C.)	Crystallinity of <i>p</i> -cresol ^(a)	Remaining amount after heating <i>in vacuo</i> at (mg/g M.C.C.)		
		40° 5 hr	80° 3 hr	130° 1 hr
60	Noncrystalline	60 (100) ^{b)}	60 (100)	60 (100)
100	Noncrystalline	100 (100)	100 (100)	91 (91)
200	Noncrystalline	179 (90)	145 (73)	95 (48)
300	Noncrystalline	164 (54)	119 (40)	88 (29)
600	Partly crystalline	135 (23)	53 (8.8)	41 (6.8)
1000	Partly crystalline	93 (9.3)	36 (3.6)	24 (2.4)

^{a)} Crystallinity of *p*-cresol in ground mixture was determined from X-ray diffractogram and DSC thermogram before heating the ground mixture.

^{b)} Percentage of remaining amount of *p*-cresol to the added amount shown in parenthesis.

thalene increased with grinding time and became constant after 3 hr (solid line). After heating the ground mixtures, they showed neither the X-ray reflection peaks nor the heat of fusion due to naphthalene crystals. These results indicate that the crystalline portion of naphthalene in the ground mixture was removed by heating *in vacuo*, while the noncrystalline naphthalene was retained in the ground mixture by negligible volatilization under the heating condition.

The amount of remaining *p*-cresol was examined for the 3 hr ground mixtures of various mixing ratios. Table I shows the amount of remaining in the ground mixtures after heating at 40°, 80°, and 130° *in vacuo*. Figures in parentheses show percentages of the remaining amount to the added *p*-cresol. In this table, crystallinity (crystalline or amorphous) of *p*-cresol contained in the ground mixtures was also shown that determined from X-ray diffractograms and thermograms of the mixtures before the temperature treatment. When a small amount of *p*-cresol such as 60 and 100 mg/g M.C.C. was added, *p*-cresol was found amorphous and nearly all amount was retained in the ground mixture under every temperature treatment. On the other hand, *p*-cresol remained partly crystalline and a great part of the medicinal was lost from the ground mixture when a large amount such as 600 and 1000 mg/g M.C.C. was added.

Effect of water content of M.C.C. on a remaining amount was examined for the ground mixture of naphthalene. M.C.C. was placed at various relative humidities about 2 months at 40°, then mixed with 10% naphthalene and ground for 3 hr. Fig. 4 shows the amount of remaining naphthalene in the ground mixture after heating at 80° *in vacuo* as a function of water content in M.C.C. The remaining amount decreased with increasing water content of M.C.C. and became constant above the water content of 120 mg/g M.C.C..

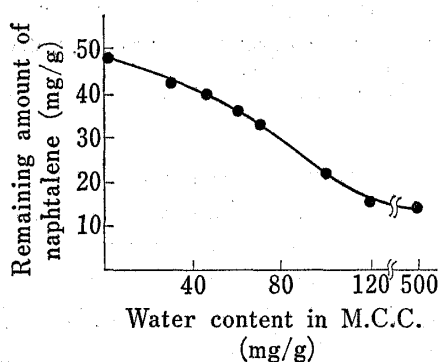


Fig. 4. Relationship between Water Content in M.C.C. and Amount of Naphthalene Remaining in 3 hr Ground Mixture after Heating

mixing ratio: naphthalene 10%, M.C.C. 90%
heating condition: at 80°, 3 hr *in vacuo*.

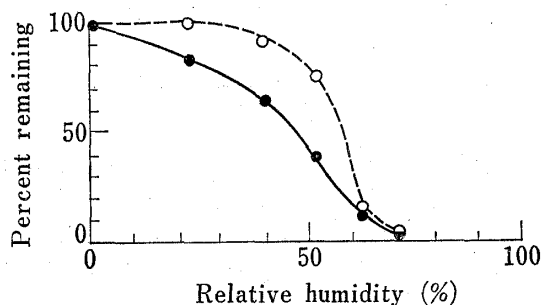


Fig. 5. Remaining Amount of *d*-Camphor and Naphthalene in 3 hr Ground Mixtures after Standing under Various Relative Humidities at 40° for 15 days

—○— ground mixture of 3% naphthalene and 97% M.C.C.
—●— ground mixture of 5% *d*-camphor and 95% M.C.C.

The effects of water content on the retention of naphthalene and *d*-camphor were further investigated. Ground mixtures of 3% naphthalene or 5% *d*-camphor with M.C.C. were heated at 80° *in vacuo* for 3 hr, then the ground mixtures were placed at various relative humidities at 40°. The remaining amount was measured after 15 days. Fig. 5 shows the percentage of remaining *d*-camphor (solid line) and naphthalene (broken line) as a function of relative humidity. The remaining amount gradually decreased with increasing relative humidity up to 50%, then fell and was completely lost at 70% of relative humidity.

Effect of water adsorption on the amount of remaining naphthalene was also studied at 100% relative humidity as a function of time. The ground mixture of 10% naphthalene was heated at 80° *in vacuo*. The heat treated ground mixtures not containing crystalline portion of naphthalene were placed at 100% relative humidity at 30°. Samples were taken

out from the stored ground mixture in time course and subjected to measurements of weight, X-ray diffraction, and DSC. The remaining amount of naphthalene was chemically measured after heating the samples at 80° *in vacuo* for 3 hr. Table II shows the effect of water adsorp-

TABLE II. Effect of Water Adsorption on Recrystallization of Amorphous Naphthalene and on Remaining Amount after Heating

Standing time ^{a)} (hr)	Water content (%)	Crystallinity ^{b)}	Percent remaining ^{c)}
0.5	1.2	Noncrystalline	95
1.5	2.9	Noncrystalline	86
5.0	8.2	Partly crystalline	51
21	12.9	Partly crystalline	2.0

a) The 3 hr ground mixture of 10% naphthalene and 90% M.C.C. was kept at 100% R.H. and at 30°.

b) Crystallinity was determined from X-ray diffractogram and DSC thermogram.

c) The ground mixture was heated at 80° for 3 hr *in vacuo*, then, the amount of naphthalene was measured spectrophotometrically.

tion on recrystallization of amorphous naphthalene and on remaining amount after heating treatment. The amount of remaining naphthalene decreased being inversely proportional to the degree of water adsorption and only 2% was retained in the ground mixture of 12.9% water content (standing for 21 hr). The crystallization of naphthalene was examined from X-ray diffractograms and DSC thermograms with respective ground mixtures. The crystallization was recognized for the ground mixture containing 8.2% of water (standing for 5 hr). These results show that naphthalene molecules obtain their translational movement by water adsorption and the molecular movement results in the crystallization and volatilization of the medicinal.

The release of *d*-camphor and naphthalene from the ground mixture was measured in water as shown in Fig. 6(A) and (B), respectively. Broken lines and solid lines in the figures are the releasing patterns from the physical and ground mixtures, respectively. The medicinals were released by far the more rapidly from the ground mixture than from the physical one similarly as the results reported in the previous papers.^{2,3)} Especially at the initial stage of the releasing, the dissolution rate was very high.

Discussion

Volatile medicinals, naphthalene, *d*-camphor, and *p*-cresol, became amorphous in the respective ground mixtures with M.C.C. same as reported in the previous paper.²⁾ A large portion of the medicinals was retained in the ground mixture even when mixture was heated at the elevated temperature *in vacuo* (Fig. 1 and 2) and percentage of the remaining medicinal increased with decreasing amount of the added volatile medicinal (Table I) and with the increase of grinding time (Fig. 3).

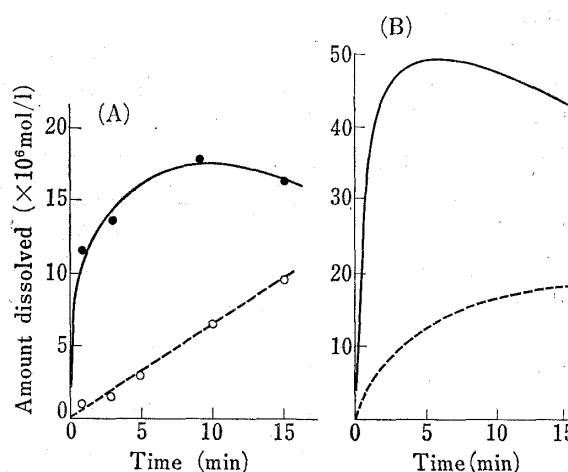


Fig. 6. Releasing Patterns of *d*-Camphor and Naphthalene from 3 hr Ground (—) and Physical (---) Mixtures

(A) mixtures of 5% *d*-camphor and 95% M.C.C.

(B) mixtures of 3% naphthalene and 97% M.C.C.

Volatilization and subsequent intertablet migration of nitroglycerin were examined in many experiments.⁹⁻¹²⁾ It was reported that additives such as PEG 400 in nitroglycerin tablets resulted in a decrease in an intertablet migration⁹⁻¹¹⁾ and the role of the stabilizing additives was not to minimize the migration effect by slowing the rate of volatilization, but was to lower the vapor pressure.¹⁰⁾ Nitroglycerin tablets containing M.C.C. showed the retention of nitroglycerin in tablets.^{12,13)} The mechanism responsible for the retention was explained by the hydrogen bonds between cellulose and nitroglycerin.¹²⁾

In the present experiment, volatile crystalline medicinals were retained in the ground mixture with M.C.C.. The hydrogen bonds between cellulose and medicinals, suggested in the nitroglycerin tablet,¹²⁾ may not be applicable for the ground mixture of nonpolar molecules such as naphthalene. Intermolecular hydrogen bonds of OH- π type were reported for benzyl alcohol and ethylbenzene in cyclohexane system.¹⁴⁾ A definite steric position of OH radical to π electron system is necessary for the hydrogen bonds. In the ground mixtures with M.C.C., the possibility to take the definite position between OH of cellulose and π electron system of naphthalene must be very small, if any at all, since the molecular translational movement of naphthalene is probably not allowed in the ground mixture.

The close relationship was found between the degree of retentivity of volatile medicinals and the state of medicinals (amorphous or not) in the ground mixture; only amorphous medicinals were retained (Table I and II). Therefore, the reason for the retention of volatile medicinals must be the same as described in the previous paper²⁾; that is, the molecules of the medicinals are enclosed by cellulose molecules and cannot move away from the structure.

The amount of remaining naphthalene or *d*-camphor decreased with increasing the amount of water adsorbing on the ground mixture (Fig. 4 and 5, Table II). These results also strongly support the proposed structure of ground mixture responsible for the retention of molecules in the mixture. It was reported in the previous paper²⁾ that water molecules adsorbed on cellulose of a ground mixture. The water adsorption probably results in weakening of hydrogen bonds between the cellulose molecules enclosing volatile molecules. Thus, the volatile molecules obtain the ability of molecular movement and volatilize from the ground mixture. When the ground mixture of naphthalene was placed at a saturated water vapor pressure at 30° for 5 hr, crystallization of naphthalene occurred in the mixture (Table II). Moreover, the crystallization occurred rapidly in the ground mixture when few drops of water were added to the mixture. Reflection peaks due to naphthalene crystals were clearly recorded on the X-ray diffractograms. This rapid crystallization phenomenon can be observed microscopically when a small amount of water was added to the ground mixture on the plate glass.

Based on the proposed structure²⁾ of the ground mixture, the rapid crystallization can be explained as follows: when water vapor adsorbs on the cellulose of the mixture at a high water vapor pressure or some drops of water are added to the ground mixture, hydrogen bonds between cellulose molecules are probably broken and a great number of the molecules of interest would obtain the ability of translational movement. However, the number of medicinal molecules released is far larger than the number necessary to saturate the small amount of the added water with the medicinal (supersaturation), so a lower free energy is attained by separation in two phases (crystallization).

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Naphthalene and *d*-camphor were rapidly released from the ground mixture in water (Fig. 6). When a large amount of water is added to a ground mixture, the medicinal molecules can obtain simultaneously molecular movement in the mixture, exchanging their places with water molecules (dissolution) immediately after water penetrates into the ground mixture. Therefore, the mechanism responsible for medicinal releasing from a ground mixture is thought to be different from the general dissolution mechanism that was characterized by the molecular diffusion from a solid surface. Only molecules present at the solid-water interface can diffuse into water at a definite time in the case of dissolution of a solid, while every molecule simultaneously obtain the ability to exchange its place with water molecules, releasing from the ground mixture.