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RESEARCH PAPER

# Stability of the Powdered Dosage Form Prepared by Unsealing the Capsules: Water Vapor Sorption and Discoloration of the Powdery Contents of Clorazepate Dipotassium Capsules

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## ABSTRACT

*The hygroscopicity of the contents of clorazepate dipotassium (Mendon®) capsules (CM) was investigated by storage at various relative humidities (RHs). The CM adsorbed water vapor significantly at more than 75% RH. At the same time, a marked discoloration of CM from white to yellow was also observed during storage. On the basis of differential scanning calorimetry (DSC) and Fourier transform (FT) Raman spectroscopy, the discoloration seemed to be due to the change in clorazepate dipotassium to nordiazepam and other substances. It was found that, when opening of the Mendon capsule is necessary to prepare the powdered dosage form, the CM should be stored below 60% RH to avoid the adsorption of water vapor and discoloration.*

**Key Words:** *Clorazepate dipotassium; Color difference; Discoloration; FT-Raman spectrometry; Water adsorption.*

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## INTRODUCTION

In practical prescription work, there are many situations that require preparing a powdered dosage form (1), especially, in the case of medicines for internal use by children because infant patients have difficulty swallowing tablet or capsule medicines; taking into account the selection of the adequate dosage form and the simplicity of the dose, it is required that the powdered dosage not be tablets or capsules. However, for a medicine having high hygroscopy, preparation as a powdered dosage form is difficult (2,3), so the tablets and/or capsules must be prepared avoiding moisture adsorption. Consequently, when a small amount of medicine has to be utilized for infant patients, crushing of tablets and/or unsealing of capsules must be done to obtain the powdered dosage form. In such cases, the physical and chemical changes in the principal agents are important factors that must be considered.

Clorazepate dipotassium (Mendon® capsule, Dainippon Pharmaceutical Co., Ltd., Osaka, Japan) is an anxiolytic agent (4) used in the field of pediatrics and has been used as an anticonvulsant agent. To adjust the dosage amount and to prepare the powdered dosage form, the unsealing of Mendon® capsules has often been carried out.

Clorazepate dipotassium (CD) is well known to be absorbed and metabolized rapidly into nordiazepam (ND) and to produce an anxiolytic effect. The change of CD into ND occurs due to hygroscopy, and discoloration (i.e., a change in color) is observed. The discoloration of medicine seems to be unfavorable from a chemical point of view.

In the work reported here, we investigated the discoloration and hygroscopic behavior of CD under various preservation conditions.

## EXPERIMENTAL

### Materials

Mendon was purchased from Dainippon Pharmaceutical Company. CD was generously supplied by Dainippon Pharmaceutical. Potassium carbonate and talc were purchased from Wako Pure Chemical Industry (Osaka, Japan) and were used without further purification.

### Water Vapor Sorption Study

A definite amount of the contents of a Mendon capsule (CM), CD, or a physical mixture of potassium carbonate and talc ($K_2CO_3$:talc 9:1 weight ratio) were weighed into the weighing bottles and stored in a desiccator for humidification at 40°C. Phosphorous pentoxide and aqueous saturated salt solution were used to achieve specific relative humidities (RHs). The extent of water vapor sorption was monitored periodically by measuring the weight of the samples with an electrical balance (Shimadzu Libror AEG-120, Kyoto, Japan). A water vapor adsorption study was carried out using a microbalance system (VTI Co., Ltd., model MB-300G, Florida).

### Measurement of Color Difference

The discoloration of the samples was evaluated by the color difference. The color difference $\Delta E^*ab$ was defined and calculated as the change in Hunter's parameters of the sample using a Minolta colorimeter CR-300 (Osaka, Japan).

### Thermal Analysis

The DSC measurements of the samples were completed with a Du Pont TA9900 thermal analysis system under a stream of nitrogen gas using samples of about 2.0 mg each at a heating rate of 10°C/min. A liquid sample pan was used.

### Fourier Transform Raman Spectroscopy

The Fourier transform (FT) Raman spectroscopic measurements were carried out without any sample preparation on a Nicolet Raman 960 spectrophotometer (Wisconsin). The resolution was 4 $cm^{-1}$ and 256–1000 scans were averaged.

## RESULTS AND DISCUSSION

### Water Vapor Adsorption onto the Mendon Capsule

Figure 1 shows the water vapor adsorption patterns of the CM or a physical mixture of talc and potassium carbonate that are the excipients of Mendon capsules stored at various relative RHs at 40°C. The points shown are the average values of three measurements. In the case of CM shown in Fig. 1a, at 0%, 11%, 31.3%, and 61.5% RH, the water vapor adsorption patterns were similar, and the amount of adsorbed water was lower than 3.4%, meaning that water adsorption rarely occurred. At 79% RH, the amount of adsorbed water increased and became constant at 9.2%. In contrast, at 93.6% RH, significant water adsorption was observed, and the amount of ad-

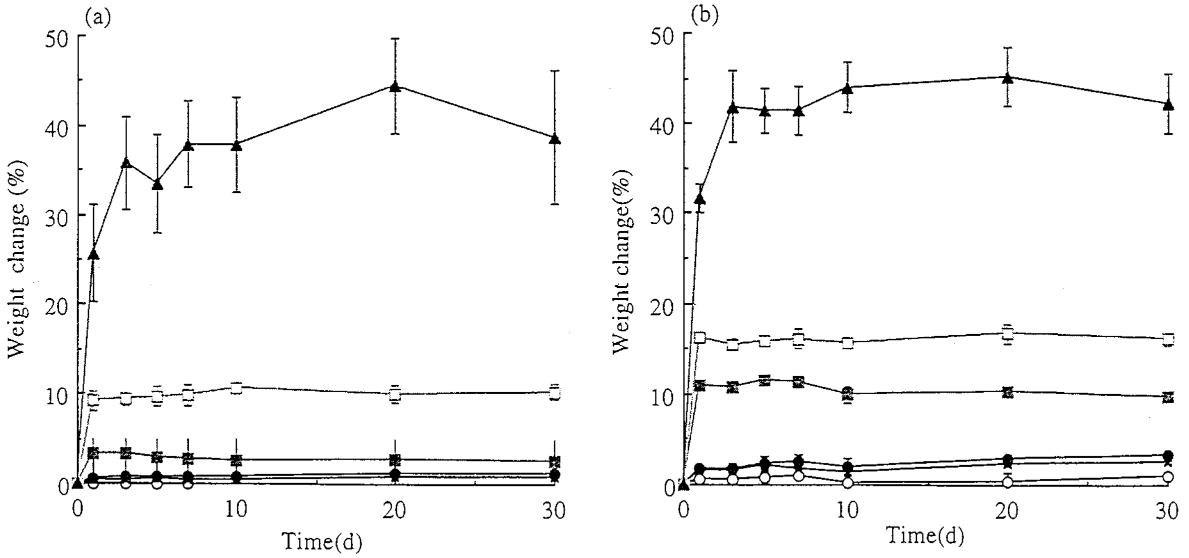

**Figure 1.** Water vapor sorption patterns of CM or its excipients stored under various RHs: (a) CM; (b) excipients of CM with ○ = 0% RH, × = 11% RH, ● = 31.3% RH, ■ = 61.5% RH, □ = 79% RH, ▲ = 93.6% RH. *Results shown were calculated as relative weight differences (%). **The data are the mean value of three experiments.

sorbed water increased with storage time and became steady at 37% after 7 days of storage. Figure 1b shows the water vapor adsorption patterns of the physical mixture (PM) of talc and potassium carbonate (9:1 weight ratio), which are the excipients of CM (4). The water vapor adsorption pattern of the PM shows a pattern similar to that of CM. The water adsorption of CM seems to be affected by the amount of excipients.

Figure 2 shows the water vapor adsorption isotherms of CM, CD crystals, potassium carbonate, and talc, the components of a Mendon capsule. Talc scarcely adsorbs water vapor throughout the RHs of this experiment. In the case of potassium carbonate, water vapor adsorption was observed above 10% RH; the weight change suddenly increased above 45% RH, which is result of deliquescence. The CD crystals started to adsorb water vapor at about 70% RH, indicating strong interaction between CD and $H_2O$. Therefore, above 70% RH, CD might be denaturalized. For CM, the trend of water adsorption was very similar to that of potassium carbonate up to 60% RH, followed by an accelerated increase. This accelerated increase could be attributed to interaction between CD and $H_2O$.

## Discoloration of the Mendon Capsules

In this study, a marked discoloration was observed during the water vapor adsorption study; the CM showed a color that varied from the initial white to yellow. Discoloration of pharmaceuticals, which is due to a chemical reaction between the medical agents and the excipients, has been reported (5). The discoloration observed in this study seems to be attributed to the interaction between CD and its excipients mediated by adsorbed water. To investigate the discoloration, the changes in color differences before and after the water vapor adsorption study

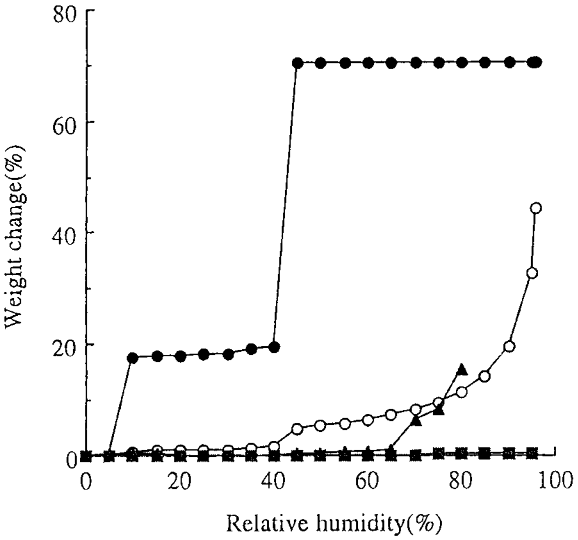

**Figure 2.** Water vapor adsorption isotherms of the CM and its excipients: ○ = CM; ▲ = CD crystals; ● = potassium carbonate; ■ = talc.

were measured. It has been reported that color difference measurements were attempted to evaluate the kinetic and forecasting of discoloration of solid medicinals (6–8).

Figure 3 shows the changes in color differences of CM stored at various RHs. At 0% RH, discoloration was not observed. Also, at 31.3% RH, the color difference increased with storage time, but this change could not be detected as visual discoloration by the human eye. On the contrary, at high RHs (e.g., 61.5% or 93.6% RH), discoloration was observed. Noguchi et al. demonstrated that if the $\Delta E^*$ value is more than 2, it can be detected as a change in color (9). The color difference of more than 2 was observed for the storage at both 61.5% and 93.6% RHs. As shown in Fig. 1, it was ascertained that the CM stored at 60% RH showed highest hygroscopicity within 24 hr, although the discoloration proceeded even after 30 days of storage. Once the CM was exposed to high RH, the discoloration seemed to be accelerated. The extent of discoloration corresponded to the amount of adsorbed water; thus, it seems unfavorable to expose CM to higher RH, even if the time of exposure is short.

## Differential Scanning Calorimetry

In the X-ray diffraction study, obvious changes in the diffraction patterns could not be observed (data not shown). Because the CD content was less than 0.2% of the CM, it seems that there was no detectable amount of CD, even if changes in crystalline state occurred in this study. Therefore, to investigate the thermal behavior of CD, a differential scanning calorimetry (DSC) measurement was attempted. Figure 4 shows the DSC curves for CD, CM, and CM stored under various RHs. On the DSC curve of CD crystals, a broad endothermic peak due to the melting of CD was observed at 236.6°C (peak top temperature). This endothermic peak was also observed as a sharp endothermic peak on the DSC curves of CM stored at 0%, 30%, and 61% RHs. However, the peak top temperature due to the melting of CD crystals shifted to lower temperature as the RH increased. The details for this phenomenon could not be understood in this study; it seems that some interaction between CD and its excipients has occurred during storage. In the case of the DSC curve of CM stored at 93.6% RH, the endothermic peak due to the melting of CD disappeared. Instead, three successive endothermic peaks were observed at 145.6°C, 155.7°C, and 188°C. As shown Fig. 5, according to the ''interview form'' of the Mendon capsule (4), CD is

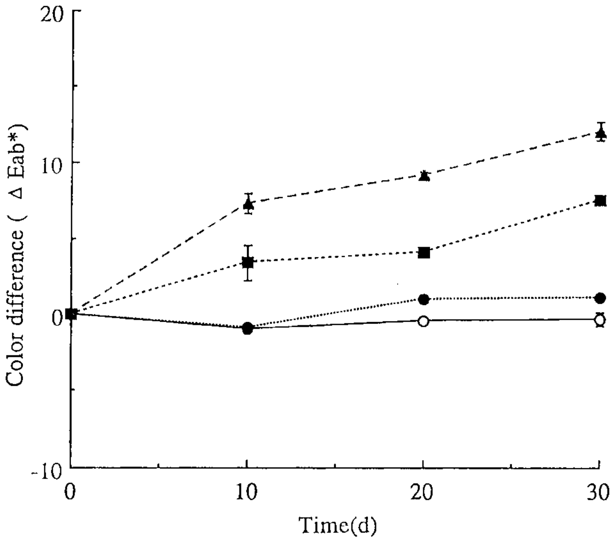

**Figure 3.** Color differences of CM stored under various RHs at 40°C: ○ = 0% RH; ● = 31.3% RH; ■ = 61.5% RH; ▲ = 93.6% RH.

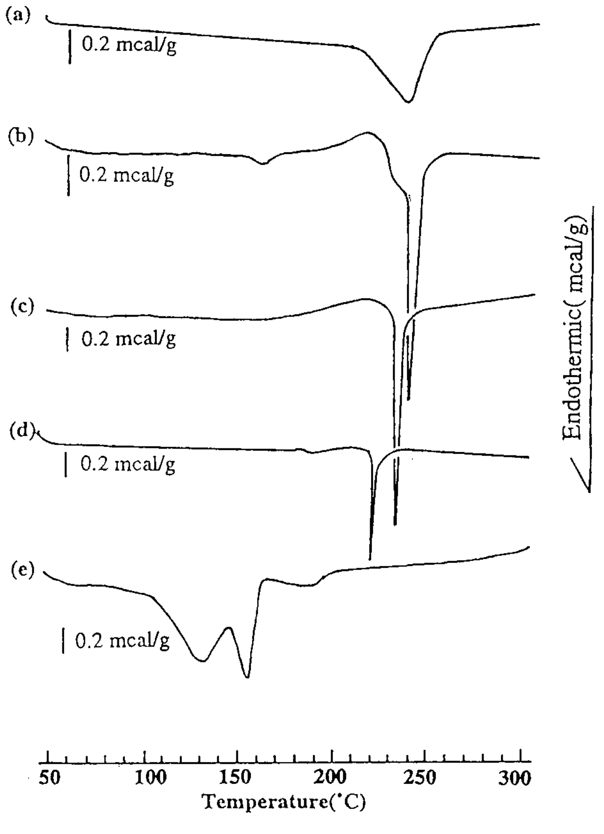

**Figure 4.** DSC curves of CM stored under various RHs at 40°C: (a) CD crystals; CM stored under (b) 0% RH, (c) 31.3% RH, (d) 61.5% RH, (e) 93.6% RH.

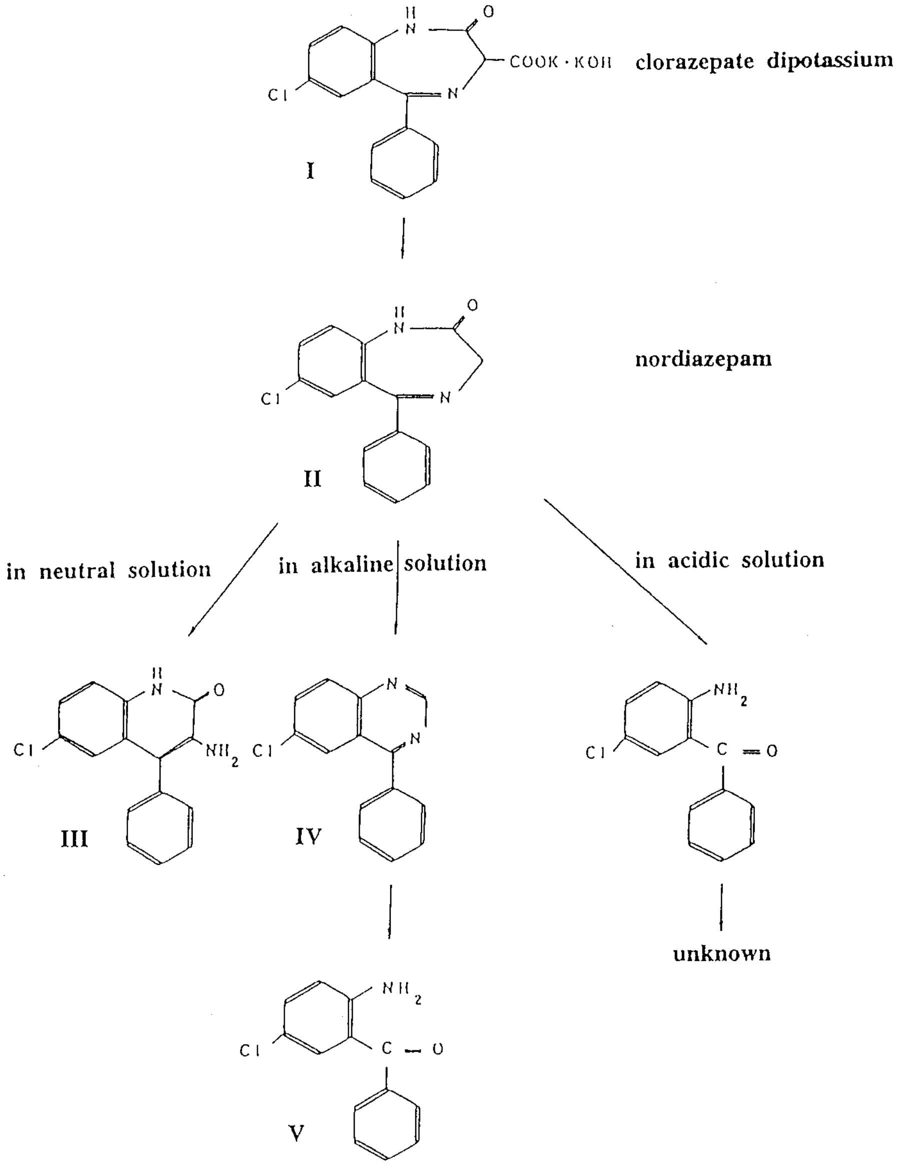

**Figure 5.** Structural change of CD in various reactions.

known to decompose to several substances under various conditions (4). Though detailed information on the changes observed in the DSC curve of CM stored at 93.6% RH was not obtained from this measurement, the change in the DSC curve seems attributable to the decomposition of the CD crystals into other substances.

## Estimation of the Colored Substances

In this study, it was impossible to isolate suspected substances individually. Therefore, to evaluate chemical change that is supposed to occur during storage, FT-Raman measurement was performed. FT-Raman spectrophotometry is useful for investigation of the chemical structure of a solid medicine (10). In addition, since an FT-Raman spectrum can be obtained as sharp peaks, it permits investigation of the chemical structure in preparations no matter how the excipients coexist (11).

Figure 6 shows the FT-Raman spectra of the CD crystals, CM stored at 0% RH, talc, and potassium carbonate. In the spectrum of CM stored at 0% RH, the bands observed at 1052, 677, 468–291, and 195 $cm^{-1}$ are due to

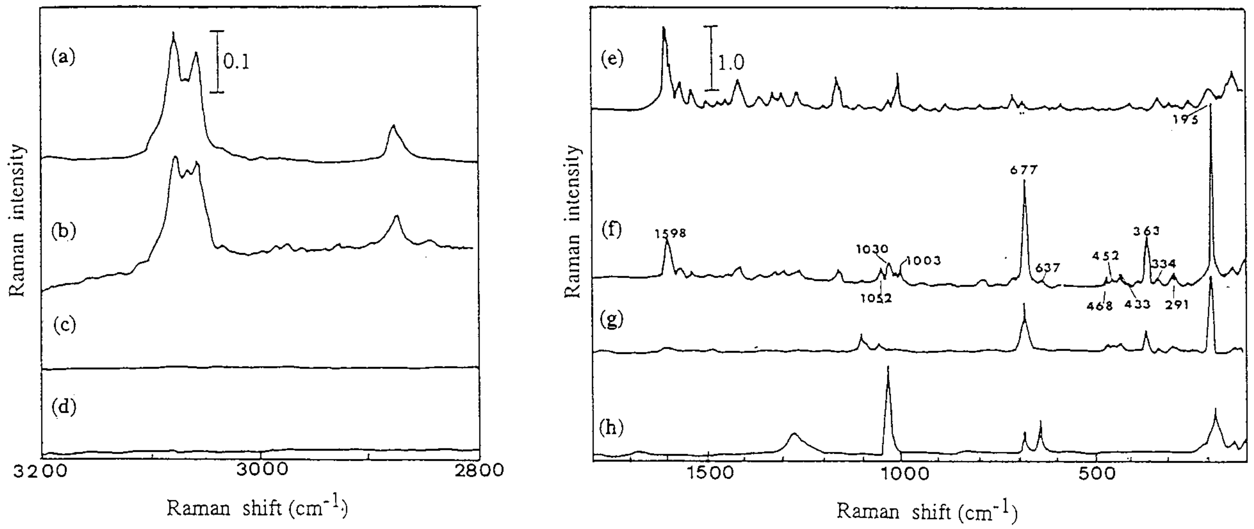

**Figure 6.** FT-Raman spectra of CM or its excipients: (a) and (e) CD crystals; (b) and (f) CM stored at 0% RH; (c) and (g) talc; (d) and (h) potassium carbonate.

talc. Furthermore, symmetric stretching and bending vibration bands of $CO_3^-$ due to potassium carbonate were observed at 1030 and 637 $cm^{-1}$. The other bands were similar to those of the CD crystals, which suggests that there was no molecular change in CM stored at 0% RH.

Figure 7 shows the FT-Raman spectra of CM stored under various RHs (0–90%) at 40°C for 30 days and of CD crystals. These peaks were normalized at 1598 $cm^{-1}$ as stretching vibration bands due to the aromatic ring. A spectrum at 1415 $cm^{-1}$ observed for CD is considered to be the symmetric stretching vibration band of carboxylate. In the spectra of CM stored at 30% RH, the peak strength of carboxylate observed at 1415 $cm^{-1}$ became slightly weak; it was suggested that the decarboxylation of CD occurred, resulting in the formation of ND.

In contrast to the spectrum of CM stored at 60% RH, the band of 1415 $cm^{-1}$ almost disappeared, indicating completion of the decarboxylation reaction in CD mole-

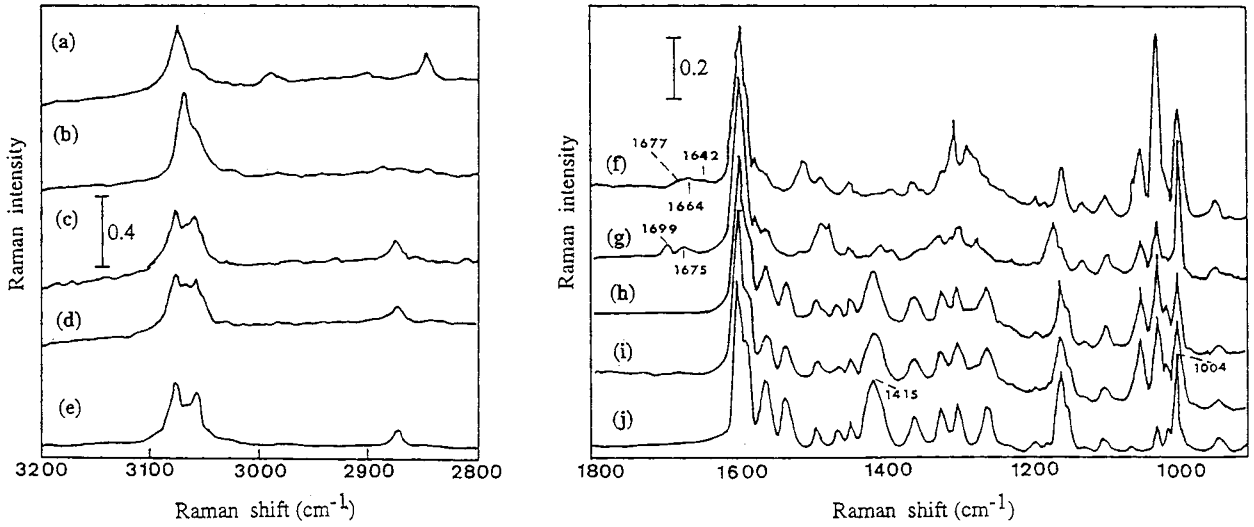

**Figure 7.** FT-Raman spectra of CM stored under various RHs at 40°C stored under (a) and (f) 93.6% RH; (b) and (g) 60% RH; (c) and (h) 30% RH; (d) and (i) 0% RH; (e) and (j) CD crystals.

cules. At the same time, the C—H stretching vibration band observed at 2880 $cm^{-1}$ for the CD also disappeared, suggesting that the changes from CD to III, IV, or V via ND can be assumed to occur together with the decarboxylation. The peaks observed at 1699 and 1675 $cm^{-1}$ can be assigned to amide I and the C=O stretching vibration band of a conjugated ketone, which is attributed to formation of III or V. In the case of CM stored at 93% RH, based on the fact that a new peak appeared below 3000 $cm^{-1}$ and that the peak height observed at 1004 $cm^{-1}$ assignable to skeletal vibration of a monosubstituted aromatic ring decreased, it could be concluded that cleavage of the aromatic ring occurred during storage, and that an alkene (C=C), in which bands were observed at 1664 and 1642 $cm^{-1}$, was newly formed. Furthermore, the appearance of new peaks at 3000–2800 $cm^{-1}$ suggest the formation of a saturated hydrocarbon.

In contrast, for the spectrum of CM stored at 90% RH, an amide I band at 1699 $cm^{-1}$ observed on the sample at 60% RH disappeared, indicating disappearance of substance III. Furthermore, the peak strength of the 1031-$cm^{-1}$ band, assignable to skeletal vibration of the 1,2-substituted aromatic ring, significantly increased. If 1,2-substituted aromatic ring forms, dechlorination of the aromatic ring is thought to occur. Thus, for the CM stored at 90% RH, the formation of both alkene (C=C) and a saturated hydrocarbon were considered to occur as a result of the disappearance of the monosubstituted aromatic ring, and dechlorination also occurred.

## CONCLUSION

In conclusion, discoloration of CM seems to be due to a chemical change from CD to ND and other substances. As far as the interview form of the Mendon capsule, even if the discoloration occurred during storage, it is considered that no problem exists concerning its therapeutic effect because CD is known to be absorbed by humans and metabolized rapidly into ND and to show an anxiolytic effect. In the pharmaceutical field, however, discoloration seems to be undesirable from a chemical point of view. Therefore, when opening of a Mendon capsule is necessary to prepare a powdered dosage form, CM should be stored below 60% RH to avoid the adsorption of water vapor and the discoloration.

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## REFERENCES

1. N. Tagami, M. Kaneko, S. Tsuruta, R. Matsushita, R. Iwaoku, and M. Nakano, Jpn. J. Hosp. Pharm., 21, 37 (1995).
2. K. Otaki, Y. Yamashita, N. Hayase, N. Kasahara, I. Takemoto, S. Akutsu, and T. Inagaki, Jpn. J. Hosp. Pharm., 23, 194 (1997).
3. S. Nagasako, A. Ishimura, E. Hirano, and K. Iwamoto, Jpn. J. Hosp. Pharm., 20, 466 (1994).
4. Dainippon Pharmaceutical Company, Limited, *‘‘Interview Form’’ of Mendon® Capsule*, Author, Osaka, Japan, 1975.
5. K. Hartauer and J. K. Guillary, Drug Ind. Pharm., 17, 617 (1991).
6. S. Kitamura, J. Tanabe, S. Koda, and Y. Morimoto, Yakuzaigaku, 46, 270 (1988).
7. Y. Matsuda, R. Akazawa, R. Teraoka, and M. Otsuka, Yakugaku Zasshi, 100, 953 (1980).
8. T. Hanawa, R. Ikoma, and M. Sugihara, Int. J. Pharm., 158, 249 (1997).
9. T. Noguchi, H. Takahshi, H. Abe, and T. Takeuchi, Yakuzaigaku, 59, 43 (1999).
10. H. Baranska, A. Labudzinska, and J. Terpinski, *Laser Raman Spectroscopy Analytical Applications*, Halsted, New York, 1987.
11. G. A. Neville and H. F. Shervell, J. Raman Spectrosc., 21, 9 (1990).