—Regular Articles—

Coloration of Phenothiazines with Metal-containing Drugs

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We studied the color change of phenothiazines and metal-containing drugs after compound formation, followed by use of FT-Raman spectrocopy to observe any structural changes in them. When 6 phenothiazines (thioridazine hydrochloride, prochlorperazine maleate, levomepromazine maleate, chlorpromazine phenolphthalinate, fluphenazine maleate and perphenazine fendiate) formed compounds with natural aluminum silicate, the color change was accompanied by a shift of FT-Raman signals. These changes could be attributed to the structural changes of phenothiazines. This present observation can be then used in advance to avoid coloration of phenothiazines during preparative procedures with metal-containing drugs such as antacids.

Key words——coloration; phenothiazines; metal-containing drugs; Fourier transform Raman spectroscopy (FT-Raman)

INTRODUCTION

Phenothiazines are widely used as psychotropics and antihistaminics in the clinical field.[1] The typical adverse effects of phenothiazines are gastro-intestinal disorders such as diarrhea, nausea, vomiting, and constipation,[2] often resulting in the administration of metal-containing antacids such as natural aluminum silicate.

At our hospital, an outpatient consulted a pharmacist about the coloration of thioridazine hydrochloride, which had been mixed together with natural aluminum silicate at another hospital. The patient was concerned when the mixed compound turned pale blue white in color.

Regards to the coloration of phenothiazines, there are few reports from clinical fields but a report from Inada *et al*.[3] They reported the coloration after addition of magnesium oxide to chlorpromazine phenolphthalinate. A trace amount of phenolphthalein contaning chlorpromazine phenolphthalinate was thought to occurred the coloration. On the other hand, El-Kommos *et al*.[4] reported that phenothiazines gave violet, blue or green products with the reagent in the presence of Fe^{3+}.[4] The detailed mechanism for coloration of phenothiazines with natural aluminum silicate have been still open questions.

It is for this type of reason why we performed the compounding test, using a variety of phenothiazines in the presence of the metal-containing drugs or acidic and basic reagents.

Thioridazine hydrochloride has a conjugated system in its phenothiazine structure that is electron-rich and the coloration can be attributed to the influence of metal ions contained in natural aluminum silicate on the phenothiazine structure.

FT-Raman spectroscopy was also performed to observe any structural changes and to gain a deeper understanding of the causes of the coloration of the compound.

EXPERIMENTAL

1. Materials Sixteen kinds of phenothiazines and drugs with the similar structure and 10 kinds of metal-containing drugs were tested. They are used frequently on clinic, and are shown in Tables 1 and 2, respectively.

In this experiment, both 10% hydrochloric acid (Shioe) and ammonium chloride (Nacalai Tesque) were used as the acidic reagents. Sodium hydroxide (Wako Pure Chemical Industries), calcium hydroxide (Nacalai Tesque) and sodium carbonate

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Table 1. Phenothiazines and Drugs with the Similar Structure

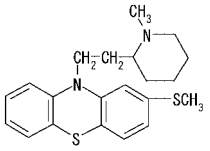
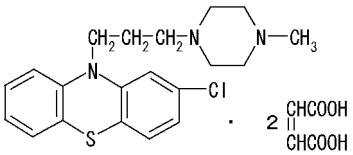
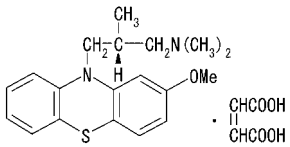
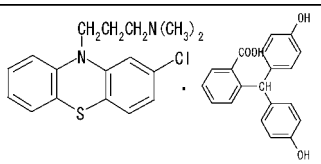
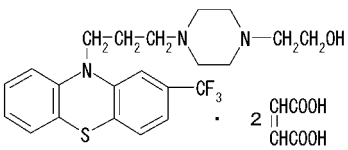
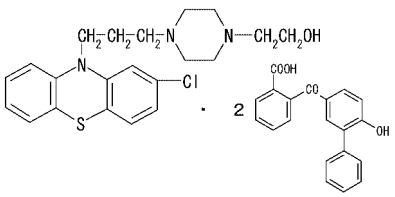
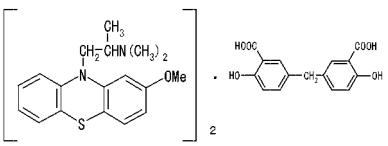
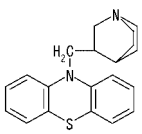
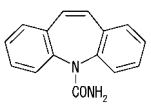
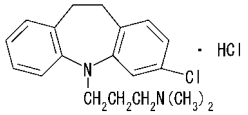
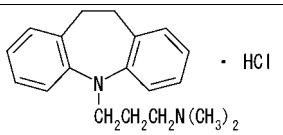
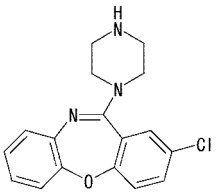
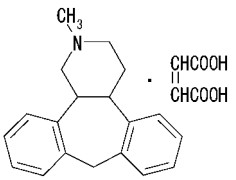
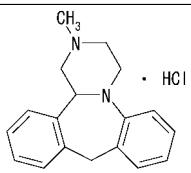
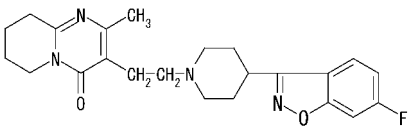
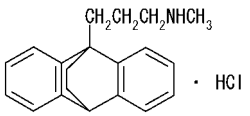
Classicafition	General name	Commercial name (Manufacturer)	Structure	Dosage form (dose)
Phenothiazine	Thioridazine hydrochloride	Melleril® (Novartis)		Tablet (10 mg/T)
Phenothiazine	Prochlorperazine maleate	Novamin® (Shionogi)		Tablet (5 mg/T)
Phenothiazine	Levomepromazine maleate	Levotomin® (Welfide)		Powder (100 mg/g)
Phenothiazine	Chlorpromazine phenolphthalinate	Wintermin® (Shionogi)		Fine granule (100 mg/g)
Phenothiazine	Fluphenazine maleate	Flumezin® (Welfide)		Powder (2 mg/g)
Phenothiazine	Perphenazine fendiate	PZC® (Welfide)		Powder (10 mg/g)
Phenothiazine	Promethazine methylenedisalicylate	Pyrethia® (Shionogi)		Fine granule (100 mg/g)
Phenothiazine	Mequitazine	Nipolazin® (Azwell)		Tablet (3 mg/T)
Dibenzazepine	Carbamazepine	Tegretol® (Novartis)		Fine granule (500 mg/g)
Dibenzazepine	Clomipramine hydrochloride	Anafranil® (Novartis)		Tablet (10 mg/T)

Table 1. (continued).

Classicafition	General name	Commercial name (Manufacturer)	Structure	Dosage form (dose)
Dibenzazepine	Imipramine hydrochloride	Tofranil® (Novartis)		Tablet (10 mg/T)
Dibenzoxazepine	Amoxapine	Amoxan® (Wyeth Lederle)		Capsule (25 mg/Cap)
Dibenzocyclohep-tane	Setiptiline maleate	Tecipul® (Mochida)		Tablet (1 mg/T)
Piperazino azepine	Mianserin hydrochloride	Tetramide® (Organon)		Tablet (10 mg/T)
Benzisoxazol	Risperidone	Risperdal® (Janssen Kyowa)		Tablet (1 mg/T)
Dibenzo-bicyclo-octadiene	Maprotiline hydrochloride	Ludiomil® (Novartis)		Tablet (25 mg/T)

(Nacalai Tesque) were used as the basic reagents.

2. Compounding Test

1) Preparation of Compound Prior to the test, each capsule was first cleaved, then the tablet was crush and sieved. Following this, 0.25 g was weighed out and used for the test.

Each phenothiazine was then mixed with metal-containing drugs or reagents, and then packed in cellophane polylaminate paper. For the control, each of the drugs was similarly packed in the cellophane polylaminate paper.

2) Conditions of Storage and Observation Each compound packed into a light-resistant bag for shading was stored at a temperature range of 22–27℃ and a relative humidity of 40–54%. The coloration change was macroscopically observed 1 day, 3 days, 7 days, 14 days, 21 days and 28 days after the initial mixing by 3 persons.

3) Judgment Criteria The judgment of coloration was done according to Table 3.

3. Compounding Test with Acidic and Basic Reagents The compounding test with acidic or basic reagents was done for the following 8 kinds of phenothiazines (thioridazine hydrochloride, prochlorperazine maleate, levomepromazine maleate, chlorpromazine phenolphthalinate, fluphenazine maleate, perphenazine fendiate, promethazine methylenedisalicylate, and mequitazine).

In order to assess the effect of strong acids and bases on coloration, an aliquot of 10% hydrochloric acid or 1 mol/l sodium hydroxide solution was combined with each phenothiazine. Furthermore, 0.25 g of ammonium chloride, calcium hydroxide, or sodium carbonate was added to each phenothiazine. Ob-

Table 2. Metal-containing Drugs

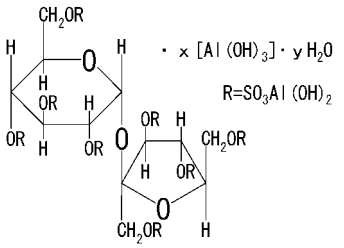
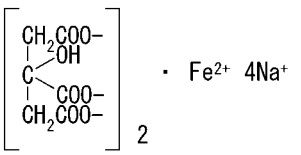
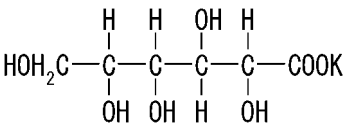
Metal	General name	Commercial name (Manufacturer)	Structure	Dosage form (dose)
Al^{3+}	Natural aluminum silicate	Adsorbin® (Sankyo)	$Al_2O_3 \cdot xSiO \cdot yH_2O$	Powder
Al^{3+}	Sucralfate	Ulcerlmin® (Chugai)		Fine granule (900 mg/g)
Al^{3+}	Drid aluminum hydroxide gel	Drid aluminum hydroxide gel (Shioe)	$Al(OH)_3$	Fine granule
Mg^{2+}	Magnesium oxide	Magnesium oxide (Shioe)	MgO	Fine granule
Ca^{2+}	Precipitated calcium carbonate	Precipitated calcium carbonate (Kenei)	$CaCO_3$	Powder
Ca^{2+}	Calcium lactate	Calcium lactate (Merck Hoei)	$[CH_3CH(OH)COO^-]_2Ca^{2+} \cdot 5H_2O$	Fine granule
Fe^{2+}, Na^+	Sodium ferrous citrate	Ferromia® (Eisai)		Tablet (470.9 mg/T)
Na^+	Sodium chloride	Sodium chloride (Otsuka)	NaCl	Powder
Na^+	Sodium bicarbonate	Sodium bicarbonate (Shioe)	$NaHCO_3$	Powder
K^+	Potassium gluconate	Gluconsan K (Kaken)		Fine granule (937 mg/g)

Table 3. Judgment Criteria of Macroscopic Observations

Judgment criteria	Macroscopic observations
−	No change in coloration
+	Slight coloration
++	Some coloration
+++	Definite coloration

servations of the color changes were according to the instructions given in 2. 1), 2) and 3).

4. FT-Raman Spectrometry FT-Raman spectra of the phenothiazine-compounds colored 14 days after mixing with a metal-containing drug were recorded on a JASCO FT-IR800 H instrument.

1) Preparation of compound Each phenothiazine was weighed and mixed with a metal-containing drug to make the mass ratio 9 : 1, phenothiazine to metal-containing drug. If no change was observed at that condition, each phenothiazine and drug were mixed at a mass ratio of 1 : 1, followed by a re-examination for any coloration.

2) Judgment Criteria The FT-Raman spectra were measured with a microscopic assessment for the coloration of the compounds. Initially, the spectral change was determined by the difference between the spectrum of mixed compound and that of a metal-containing drug. Next, the obtained spectral changes

were compared with the spectrum of phenothiazine itself. The judgment criteria are shown in Table 4.

RESULTS AND DISCUSSION

1. Compounding test Table 5 shows the color changes for each phenothiazine-compound 28 days after mixing with a metal-containing drug. The following compounds showed a marked color change after mixing with natural aluminum silicate: thioridazine hydrochloride (bluish white), prochlorperazine maleate (reddish white), levomepromazine maleate (purplish white), chlorpromazine phenolphthalinate (pale reddish white), fluphenazine maleate (pale yellowish white), and perphenazine fendiate (pale reddish white). Among these drugs, the time course of the color change was examined from the time of initial mixing to 28 days after mixing with natural aluminum silicate or magnesium oxide (Table 6). The phenothiazines were particularly susceptible to coloration when compounded with natural aluminum silicate.

Thioridazine hydrochloride and prochlorperazine maleate were the most susceptible to natural aluminum silicate, showing coloration only 1 day after initial mixing, and levomepromazine maleate and chlorpromazine phenolphthalinate showed colorlation 3 days after initial mixing. Neither promethazine methylenedisalicylate nor mequitazine exhibited coloration although they have a conjugate cyclic structure, similar to the other phenothiazines described above. This may be attributed to the differences in the structures of substituents. With regards to chlor-

Table 4. Judgment Criteria of FT-Raman Spectra

Judgment criteria	FT-Raman spectra
−	No change
+	Some change
++	Definite change

Table 5. Color Changes for Compounds 28 Days after Mixing; Keys (−, +, ++, and +++) as in Table 3

	Natural aluminum silicate	Sucralfate	Drid aluminum hydroxide gel	Magnesium oxide	Precipitated calcium carbonate	Calcium lactate	Sodium ferrous citrate	Sodium chloride	Sodium bicarbonate	Potassium gluconate
Thioridazine hydrochloride	+++ (Bluish white)	−	−	−	−	−	−	−	−	−
Prochlorperazine maleate	+++ (Reddish white)	−	−	−	−	−	−	−	−	−
Levomepromazine maleate	+++ (Purplish white)	−	−	−	−	−	−	−	−	−
Chlorpromazine phenolphthalinate	++ (Pale reddish white)	−	−	++ (Pale reddish white)	−	−	−	−	−	−
Fluphenazine maleate	+ (Pale yellowish white)	−	−	−	−	−	−	−	−	−
Perphenazine fendiate	+ (Pale reddish white)	−	−	−	−	−	−	−	−	−
Promethazine methylenedisalicylate	−	−	−	−	−	−	−	−	−	−
Mequitazine	−	−	−	−	−	−	−	−	−	−
Carbamazepine	−	−	−	−	−	−	−	−	−	−
Clomipramine hydrochloride	−	−	−	−	−	−	−	−	−	−
Imipramine hydrochloride	−	−	−	−	−	−	−	−	−	−
Amoxapine	−	−	−	−	−	−	−	−	−	−
Setiptiline maleate	−	−	−	−	−	−	−	−	−	−
Mianserin hydrochloride	−	−	−	−	−	−	−	−	−	−
Risperidone	−	−	−	−	−	−	−	−	−	−
Maprotiline hydrochloride	−	−	−	−	−	−	−	−	−	−

Table 6. Color Changes of Compounds from the Time of Initial Mixing to 28 Days after Mixing; Keys (−, +, ++, and +++) as in Table 3

Phenothiazines	Metal-containing drugs	Initial	1 day	3 days	7 days	14 days	21 days	28 days
Thioridazine hydrochloride	Natural aluminum silicate	Slight gray	++ (Slight bluish white)	+++ (Pale bluish white)	+++ (Pale bluish white)	+++ (Bluish white)	+++ (Bluish white)	+++ (Bluish white)
Prochlorperazine maleate		Slight gray	++ (Slight reddish white)	++ (Slight reddish white)	+++ (Pale reddish white)	+++ (Pale reddish white)	+++ (Reddish white)	+++ (Reddish white)
Levomepromazine maleate		Slight gray	−	+ (Slight purplish white)	++ (Slight purplish white)	+++ (Pale purplish white)	+++ (Pale purplish white)	+++ (Purplish white)
Chlorpromazine phenolphthalinate		Slight gray	−	+ (Slight reddish white)	+ (Slight reddish white)	+ (Slight reddish white)	+ (Slight reddish white)	++ (Pale reddish white)
Fluphenazine maleate		Slight gray	−	−	−	−	−	+ (Pale yellowish white)
Perphenazine fendiate		Slight gray	−	−	−	−	−	+ (Pale reddish white)
Chlorpromazine phenolphthalinate	Magnesium Oxide	Slight gray	−	−	+ (Slight reddish white)	+ (Slight reddish white)	++ (Pale reddish white)	++ (Pale reddish white)

promazine phenolphthalinate mixed with magnesium oxide, coloration was observed 7 days after initial mixing.

The coloration of these compounds 14 days after initial mixing is shown in Fig. 1. There is no definite correlation between the structures of phenothiazines and the coloration.

2. Compounding Test with Acidic and Basic Reagents In order to clarify the effect of pH on these colorations, 10% hydrochloric acid and 1 mol/l sodium hydroxide solution were added to 6 kinds of phenothiazines, promethazine methylenedisalicylate and mequitazine.

Table 7 shows the effect of acidic or basic reagents on the coloration of the 8 kinds of phenothiazines. One drop of 10% hydrochloric acid caused the following to exhibit coloration: thioridazine hydrochloride (blue), prochlorperazine maleate (yellow), levomepromazine maleate (pale yellow), chlorpromazine phenolphthalinate (slight red), perphenazine fendiate (slight red) and mequitazine (slight red). No change in colorlation in fluphenazine maleate and promethazine methylenedisalicylate was observed. The application of one drop of 1 mol/l sodium hydroxide solution resulted in the coloration of chlorpromazine phenolphthalinate to red and perphenazine fendiate to pale yellow. Using liquid reagents, the pH change gave rise to the coloration of the 6 phenothiazines.

When compounding 8 phenothiazines with ammonium chloride, calcium hydroxide, or sodium carbonate, only the color of chlorpromazine phenolphthalinate changed to pale reddish white 7 days after initial mixing (Table 8); the other 7 compounds showed no changes throughout the 28 day testing period.

The coloration after addition of the basic solid reagents is caused by a trace amount of phenolphthalein contained in chlorpromazine phenolphthalinate, as pointed out by Inada *et al.*[3] Compounding metal-containing drugs such as natural aluminum silicate or magnesium oxide caused coloration in 6 kinds of phenothiazines, such as thioridazine hydrochloride, prochlorperazine maleate, levomepromazine maleate, chlorpromazine phenolphtalinate, fluphenazine maleate and perphenazine fendiate. However, with the exception of chlorpromazine phenolphthainate, the coloration of all phenothiazines did not occur upon addition of acidic or basic solid reagents.

El-Kommos *et al.*[4] reported that phenothiazines, ie., thioridazine hydrochloride, methotrimeprazine and chlorpromazine hydrochloride, gave violet, blue or green products with 3-methylbenzothiazolin-2-one hydrazone in the presence of Fe^{3+}. The reaction is thought to proceed via preliminary oxidation of the phenothiazine nucleus to a phenothiazinyl radical follwed by coupling of the reagent in the 3-position. Borg *et al.*[5] reported that phenothiazines, i.e., chlor-

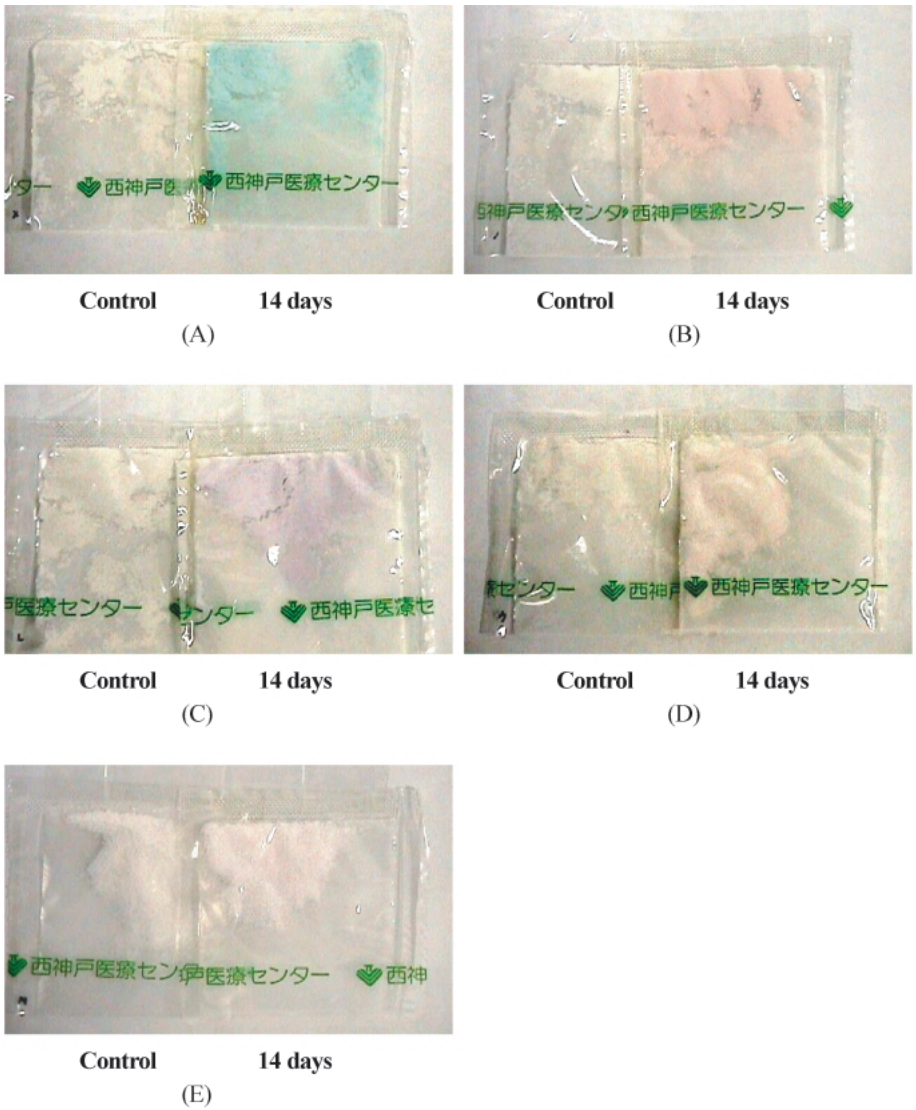


Fig. 1. Coloration of Compounds 14 Days after Initial Mixing

(A) Thioridazine hydrochloride+Natural aluminum silicate, (B) Prochlorperazine maleate+Natural aluminum silicate, (C) Levomepromazine maleate+Natural aluminum silicate, (D) Chlorpromazine phenolphthalinate+Natural aluminum silicate, (E) Chlorpromazine phenolphthalinate+Magnesium oxide.

Table 7. Effect of Acidic or Basic Reagents on the Coloration; Keys (−, +, ++, and +++) as in Table 3

	Thioridazine hydrochloride	Prochlor-perazine maleate	Levome-promazine maleate	Chlorpromazine phenolphthalinate	Fluphenazine maleate	Perphenazine fendiate	Promethazine methylenedi-salicylate	Mequitazine
10% HCl	+++ (Blue)	+++ (Yellow)	++ (Pale yellow)	+ (Slight red)	−	+ (Slight red)	−	+ (Slight red)
1 mol/l NaOH	−	−	−	+++ (Red)	−	++ (Pale yellow)	−	−

promazine, prochlorpromazine, trifluoperazine and promethazine produce rose-red colored products in the presence of Mn^{3+}, Fe^{3+} and Co^{3+}, not produce the colored products in the presence of Ni^{2+}, Cu^{2+}, Zn^{2+}, Al^{3+}, Cr^{3+}, Ca^{2+} and Mg^{2+}.[5] Minakata *et al*.[6] reported that phenothiazines changed to different colored radicals following their oxdation with the reagent and the radicals produced were stable.

The difference between the coloration of the phenothiazines prior to and after mixing with either

Table 8. Color Changes of Compounds from the Time of Initial Mixing to 28 Days after Mixing; Keys (−, +, ++, and +++) as in Table 3

Phenothiazines	Reagents	Initial	1 day	3 days	7 days	14 days	21 days	28 days
Chlorpromazine phenolphthalinate	NH_4Cl	White	−	−	−	−	−	−
	$Ca(OH)_2$	White	−	−	++ (Pale reddish white)	++ (Pale reddish white)	+++ (Pale reddish white)	+++ (Pale reddish white)
	Na_2CO_3	White	−	−	++ (Pale reddish white)	++ (Pale reddish white)	+++ (Pale reddish white)	+++ (Pale reddish white)

Table 9. Changes in Color and FT-Raman Spectra (Phenothiazine: Metal-containing Drug, 9 : 1); Keys (−, + and ++) as in Table 4

Phenothiazines	Metal-containing drugs	Initial	1 day	2 days	3 days	5 days	7 days	10 days
Thioridazine hydrochloride	Natural aluminum silicate	− (White)	+ (Slight bluish white)	++ (Pale bluish white)	++ (Pale bluish white)	++ (Pale bluish white)	++ (Pale bluish white)	++ (Pale bluish white)
Prochlorperazine maleate		− (White)	− (Slight reddish white)	+ (Slight reddish white)	++ (Pale reddish white)	++ (Pale reddish white)	++ (Pale reddish white)	++ (Pale reddish white)
Levomepromazine maleate		− (White)	− (White)	− (White)	− (Slight purplish white)	− (Slight purplish white)	− (Slight purplish white)	− (Slight purplish white)
Chlorpromazine phenolphthalinate		− (White)	− (White)	++ (Slight reddish white)	++ (Slight reddish white)	++ (Slight reddish white)	++ (Slight reddish white)	++ (Slight reddish white)
Fluphenazine maleate		− (White)	− (White)	− (white)	− (White)	− (White)	− (White)	− (White)
Perphenazine fendiate		− (White)	− (White)	− (White)	− (Slight reddish white)	− (Slight reddish white)	− (Pale reddish white)	− (Pale reddish white)
Chlorpromazine phenolphthalinate	Magnesium oxide	− (White)	++ (White)	++ (White)	++ (White)	++ (White)	++ (White)	++ (White)

metal-containing drugs or acidic and basic reagents could possibly involve radicals.

As to be shown in Fig. 1, there is no definite correlation between the structures of phenothiazines and the coloration. On the other hand, sucralfate and dried aluminum hydroxide gel, both commercial products of antacids, contain Al^{3+} as well as natural aluminum silicate, but these two antacids resulted in no coloration. This observation may be a result of the dosage form. Natural aluminum silicate is presented as a powder, while sucralfate and dried aluminum hydroxide gel exist as fine granules. The powder form is easily miscible with these phenothiazines, whereas the fine granules form is not.

3. FT-Raman spectrometry The changes in color and FT-Raman spectra are shown in Table 9, in which each phenothiazine and a metal-containing drug are compounded with mass ratio of 9 : 1. The three phenothiazines, thioridazine hydrochloride, prochlorperazine maleate and chlorpromazine phenolphthalinate, demonstrated both coloration and changes in the FT-Raman spectrum 10 days after initial mixing with natural aluminum silicate. Levomepromazine maleate and perphenazine fendiate mixed with natural aluminum silicate demonstrated coloration but no significant changes in the FT-Raman spectra. Chlorpromazine phenolphthalinate mixed with magnesium oxide demonstrated no coloration but showed changes in the FT-Raman spectra.

Three kinds of phenothiazines, levomepromazine maleate, perphenazine fendiate, and fluphenazine maleate, demonstrated no changes in FT-Raman spectrum even 10 days after mixing with a metal-containing drug at a mass ratio of 9 : 1. The mass ratio of these phenothiazines to natural aluminum silicate was then readjusted and increased to 1 : 1. Table 10 shows the changes of these three phenothiazines in color and FT-Raman spectra, after readjustment to a 1 : 1 phenothiazine to natural aluminum silicate mass ratio.

Table 10. Changes in Color and FT-Raman Spectra (Phenothiazine: Metal-containing Drug, 1 : 1); Keys (−, + and ++) as in Table 4

Phenothiazines	Metal-containing drugs	Initial	1 day	2 days	3 days	5 days	7 days	10 days
Levomepromazine maleate	Natural aluminum silicate	− (White)	+ (Slight purplish white)	++ (Purplish white)	++ (Purplish white)	++ (Purplish white)	++ (Purplish white)	++ (Purplish white)
Fluphenazine maleate		− (White)	− (White)	− (White)	− (White)	− (White)	− (White)	− (White)
Perphenazine fendiate		− (White)	− (White)	− (Slight reddish white)	− (Slight reddish white)	− (Slight reddish white)	+ (Slight reddish white)	+ (Slight reddish white)

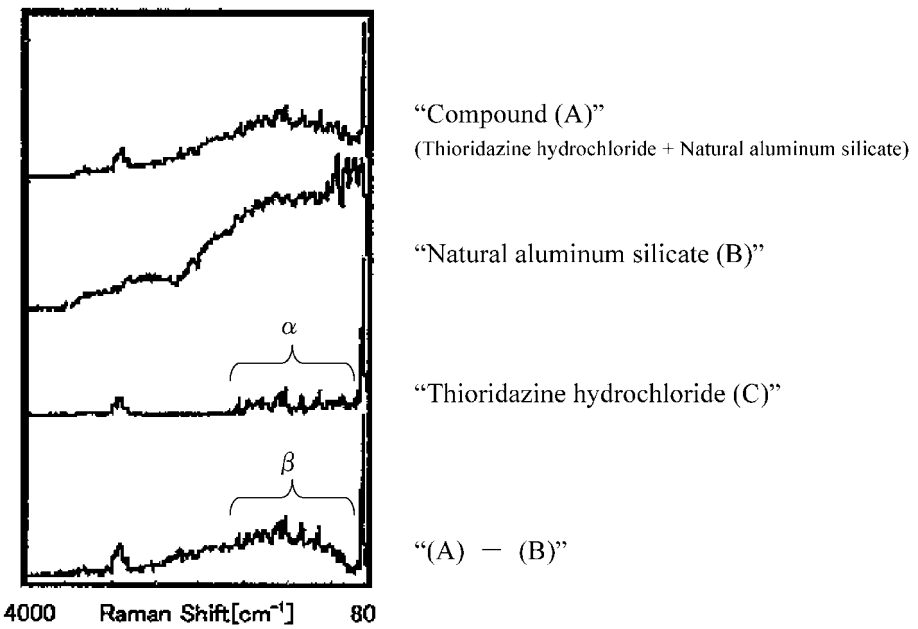


Fig. 2. Thioridazine Hydrochloride+Natural Aluminum Silicate (9 : 1, 1 Day)

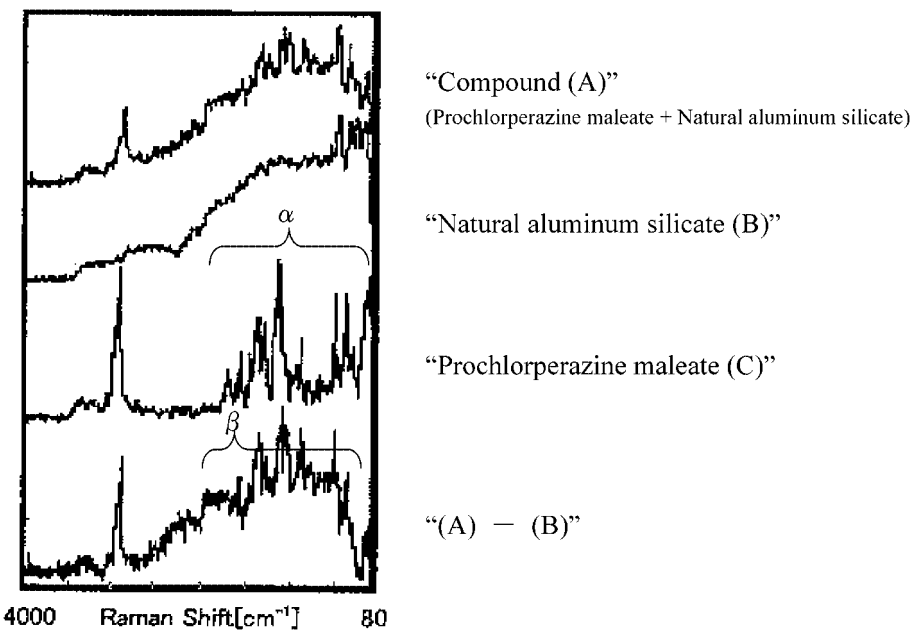


Fig. 3. Prochlorperazine Maleate+Natural Aluminum Silicate (9 : 1, 2 Days)

Levomepromazine maleate and perphenazine fendiate showed both coloration and changes in their FT-Raman spectra while fluphenazine maleate did not. Among the six kinds of phenothiazines, only these demonstrated a significant change in both coloration and FT-Raman spectra.

The Raman spectra of each compound (A) of a phenothiazine and a metal-containing drug, metal-containing drug (B), phenothiazine (C), and the difference {(A)−(B)} are shown in Fig. 2 to 7.

In Fig. 2, 3, 6 and 7, the area (β) on the difference {(A)−(B)} represents a significant Raman spectral change in compare with the area (α) on the phenothiazine (C). The area of Fig. 2, 3, 6 and 7, we observed the spectral change in the shape and the intensity ratio of peeks. The compound (A) in Raman spectra in Fig. 4 and 5 represents a more significant Raman spectral change, the peek originally found in the phenothiazine (C) were lost; however, the new peeks, not found in the phenothiazine (C), appeared.

With the exception of fluphenazine maleate, coloration was noted in all the compounds when mixed

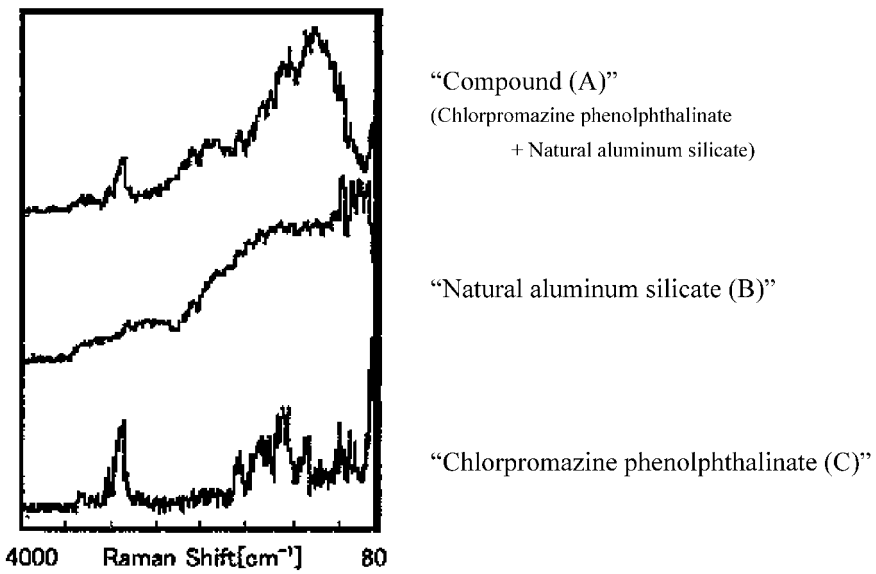


Fig. 4. Chlorpromazine Phenolphthalinate+Natural Aluminum Silicate (9 : 1, 2 Days)

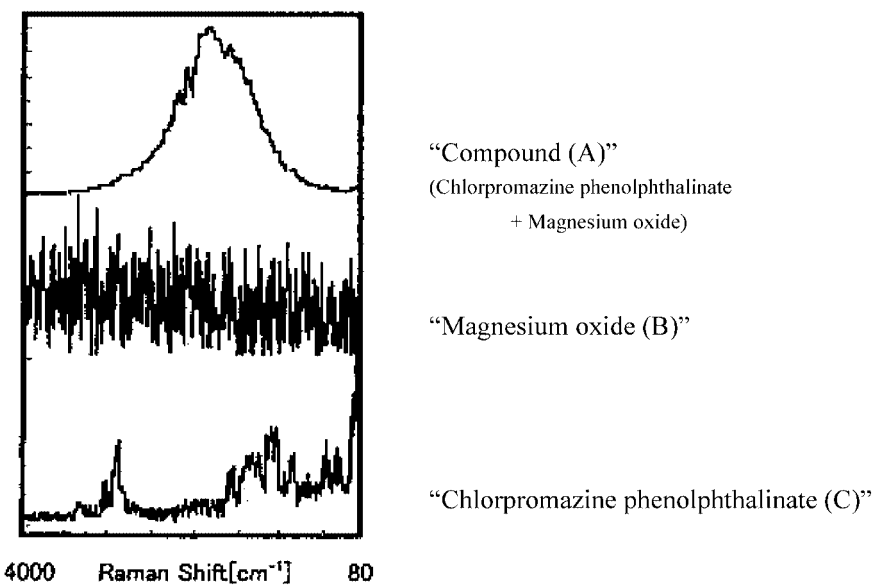


Fig. 5. Chlorpromazine Phenolphthalinate+Magnesium Oxide (9 : 1, 1 Day)

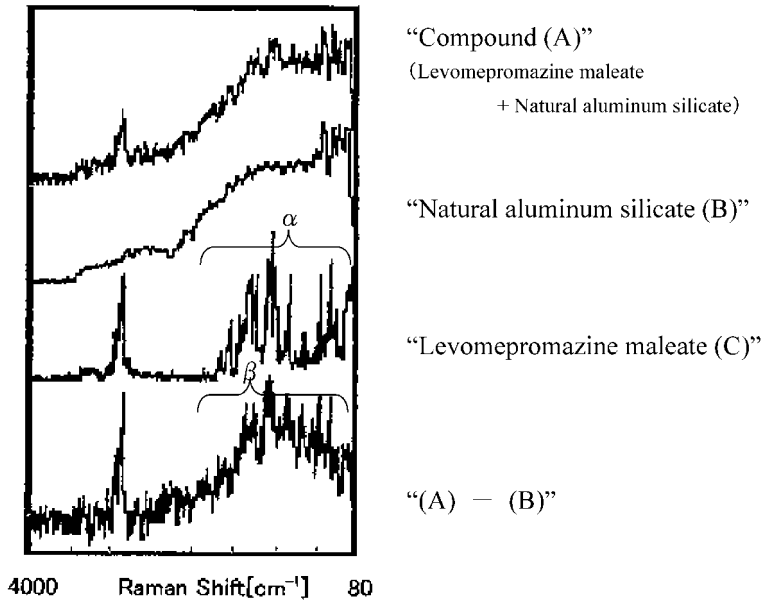


Fig. 6. Levomepromazine Maleate+Natural Aluminum Silicate (1 : 1, 1 Day)

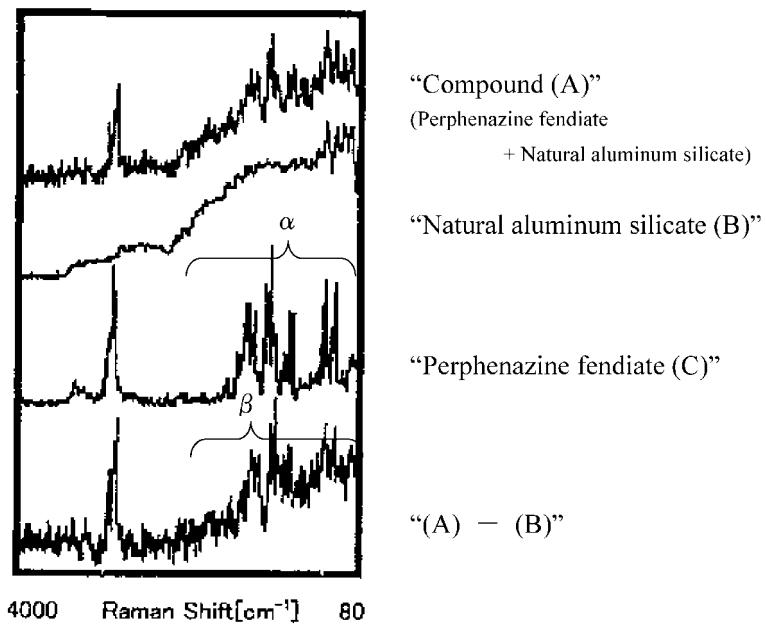


Fig. 7. Perphenazine Fendiate+Natural Aluminum Silicate (1 : 1, 7 Days)

with natural aluminum silicate. We observed a strong correlation between the coloration of each phenothiazine and the change in FT-Raman spectra.

It is important to note that the shift of FT-Raman signals were observed with compounds that demonstrated coloration. It is suggested that structural changes due to radicals with a metal ion, probably Fe^{3+}, are involved in the coloration.

CONCLUSION

In the clinical field, the coloration of a drug may decrease a patient's compliance with drug prescriptions and instructions. Therefore, it is of importance to avoid compounding the studied six kinds of phenothiazines and metal-containing drugs such as natural aluminum silicate or magnesium oxide to ensure patients will follow drug prescriptions safely and

without problems.

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