

Research papers

Preparation and characterization of sealed heated mixture of sublimable compound and porous calcium silicate II: Investigation of the interaction between maltol and porous calcium silicate surface

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Abstract

A sealed heated mixture of maltol (Mal) and porous calcium silicate (Florite® RE:FR) was prepared by heating the physical mixture in a sealed container. The amorphization of the Mal crystals in the sealed heated mixture (FR:Mal = 9:1 or 7:3) was observed by X-ray diffraction and differential scanning calorimetric measurements. At the same time, a marked discoloration was also observed in the sealed heated mixture, which showed a color change from initially white to yellow or light brown. On the basis of Fourier transform infrared spectroscopy, the discoloration seems to be due to the ionization of Mal molecules on the FR surface. The discoloration of the mixture during heating was accelerated by increasing the heating temperature and the heating time. The addition of colloidal silicon dioxide (Reolosil® QS-102:REO) affected the discoloration. It was found that an increase in an amount of REO added inhibited the discoloration during sealed heating. © 1997 Elsevier Science B.V.

Keywords: Maltol; Porous calcium silicate; Silicon dioxide; Discoloration; Sealed heating

1. Introduction

Florite® RE (FR) is well known as calcium silicate which has interesting properties due to its porous structure, and its use as a drug support material for controlled drug release have been

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examined (Hanawa et al., 1995a; Yuasa et al., 1994; Murakami and Yata, 1995).

In the previous paper, we reported that heating a mixture of FR and ethenzamide crystals in a sealed glass ampule, i.e., SH treatment, induced amorphization and improved the dissolution rate of ethenzamide (Hanawa et al., 1996). It was suggested that the sublimable feature of ethenzamide during heating is an important factor for adsorption of ethenzamide molecules onto the FR surface. The SH method is new and effective to adsorb drugs on a porous powder, as it is very simple and does not involve a dissolution process of drugs using any organic solvents. On the other hand, the FR surface shows basicity because FR involves calcium oxide as one of the constituents. The ionization of the carboxyl group of benzoic acid and/or flufenamic acid molecules was also reported (Ali et al., 1992a,b). Recently, Hartauer and Guillory (1991) reported that discoloration (i.e., change in color) observed in a mixture of aminophylline and lactose was due to the chemical reaction between ethylenediamine and lactose.

In the work reported herein, we selected maltol (Mal) as a model agent and heated it with FR in a sealed container. Mal is well-known as the flavoring agent imparting a 'freshly baked' odor and flavor to sweets and is also used to mask the acidic or bitter taste of medicine (Hodge and Nelson, 1961). Because Mal is sublimable at 93°C and displays a yellow color in alkaline environment (The Merck Index, 1996), it is appropriate to evaluate the interaction between Mal as an acidic agent and the FR surface during sealed heating. We therefore investigated the changes in crystalline states and molecular states of Mal during heating with FR in a sealed container using X-ray diffractometry, differential scanning calorimetry, Fourier transform infrared spectroscopy and measuring the color difference. Furthermore, to regulate the discoloration of the Mal in an sealed heated (SH) mixture, colloidal silicon dioxide (Reolosil® QS-102:REO) was initially mixed with the FR, and then Mal was added prior to the SH treatment. The effect of the addition of REO on discoloration was also investigated.

2. Experimental section

2.1. Materials

FR and REO were generously supplied by Tokuyama, (Yamaguchi, Japan). FR and REO were sieved through screens (149 μm) and used after drying under vacuum at 200°C for 6 h. Mal was purchased from Wako Pure Chemical Ind, (Osaka, Japan). Calcium oxide, silicon oxide and calcium hydroxide were of reagent grade and used without further purification.

2.2. Heating in a sealed container

A physical mixture of Mal and FR was prepared at definite weight ratios (FR:Mal = 9:1, 7:3 and 5:5) by simple blending with a mortar and pestle. The physical mixture (75 mg) was sealed in a 0.8 ml (i.d.; 10 mm, depth; 10.2 mm) aluminum container as shown in Fig. 1 (Hanawa et al., 1995b) and was then heated at a definite temperature (50–100°C) and time (0.5–6.0 h) in an oven (Shimadzu GC-7AG, Kyoto, Japan). We called this treatment the "SH treatment".

2.3. X-ray diffractometry

The X-ray diffraction patterns for the powdered samples were determined using a Rigakudenki 2027 diffractometer (Tokyo, Japan) under the following conditions; target Cu; filter, Ni; voltage, 30 kV; current, 5 mA; count range, 2000 cps; and scanning speed, 4°/min.

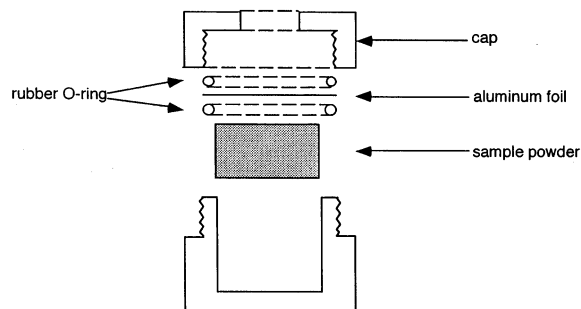


Fig. 1. Schematic side view of the aluminum container for sealed heating.

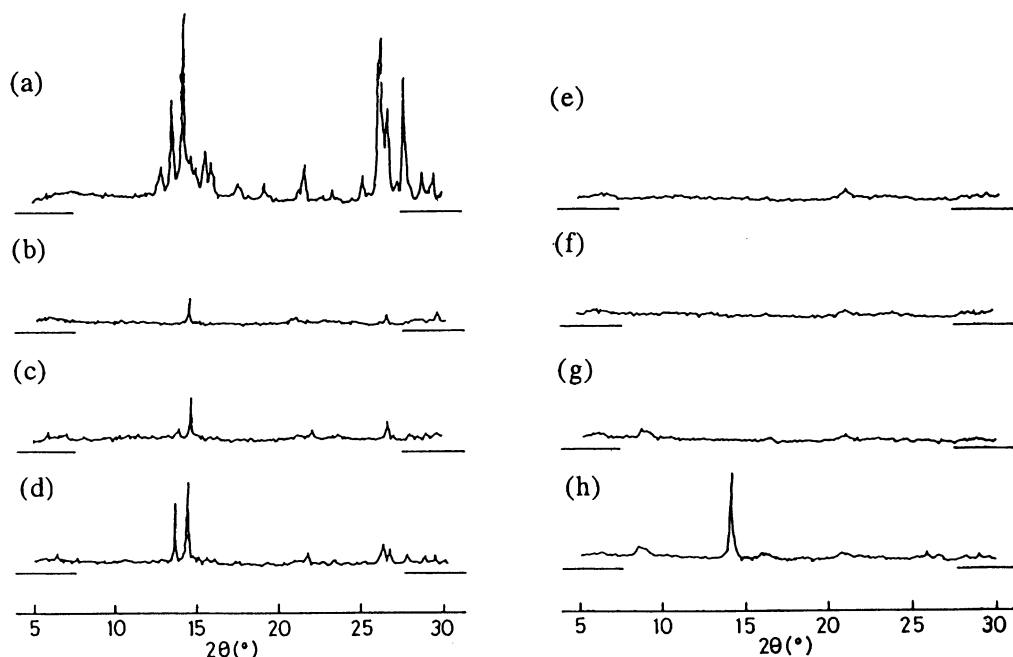


Fig. 2. X-ray diffraction patterns of physical and SH mixtures of FR and Mal: (a) Mal crystals; (b) physical mixture of FR and Mal (FR:Mal = 9:1); (c) physical mixture of FR and Mal (FR:Mal = 7:3); (d) physical mixture of FR and Mal (FR:Mal = 5:5); (e) FR, (f) SH mixture of (b), (g) SH mixture of (c), (h) SH mixture of (d).

2.4. Infrared (IR) absorption spectroscopy

The measurements were carried out on a Nicolet Fourier transform infrared (FTIR) spectrophotometer 5ZDX (WI, USA) using the diffuse reflectance method.

2.5. 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.

2.6. Measurement of the color difference

The discoloration of the mixture was evaluated by the color difference in the mixture before and after the SH treatment. The color difference, ΔE^*_{ab} , was defined and calculated as the change in Hunter's parameters for the sample using a Minolta Colorimeter CR-300 (Osaka, Japan).

3. Results and discussion

3.1. Physicochemical properties of the sealed heated mixture of FR and Mal

Fig. 2 shows the X-ray diffraction patterns of the mixtures of FR and Mal before and after SH treatment, which contained 10, 30 and 50% Mal, respectively. The diffraction patterns of the physical mixtures show the diffraction peaks due to Mal crystals at $2\theta = 13.5, 14.5$ and 26.5° . After heating at 100°C for 6 h, these X-ray diffraction peaks were still observed in the SH mixture containing 50% Mal. In contrast, for the SH mixtures containing 10 and 30% Mal showed halo X-ray diffraction patterns. Fig. 3 shows the DSC curves of the mixtures containing 10, 30 and 50% Mal before and after SH treatment. On the DSC curves of the physical mixtures, an endothermic peak due to the melting of Mal crystals was observed at 160°C. This endothermic peak was still observed in the SH mixture containing 50% Mal even after heating at 100°C for 6 h, whereas

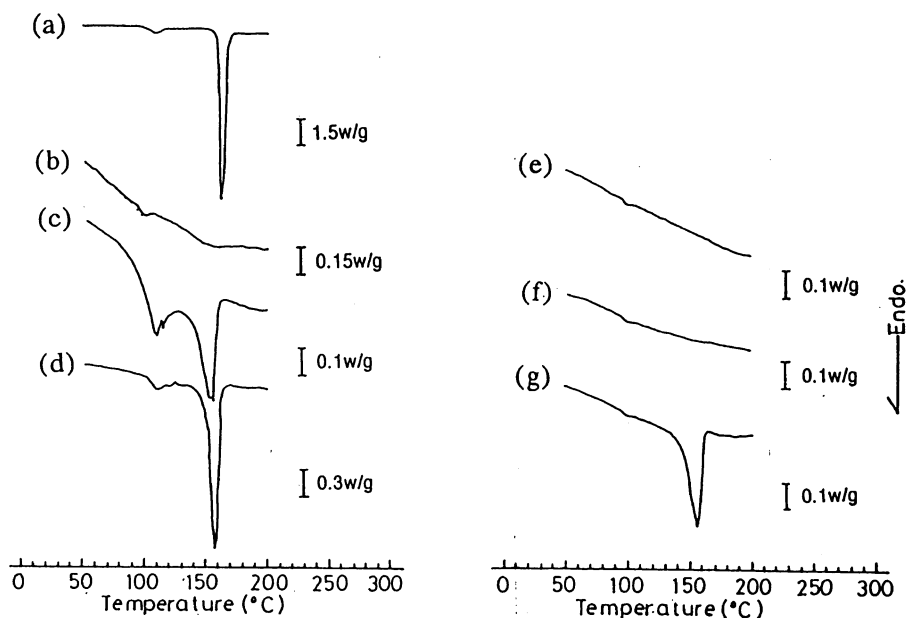


Fig. 3. DSC curves of physical and SH mixtures of FR and Mal: (a) Mal crystals; (b) physical mixture of FR and Mal (FR:Mal = 9:1); (c) physical mixture of FR and Mal (FR:Mal = 7:3); (d) physical mixture of FR and Mal (FR:Mal = 5:5); (e) SH mixture of (b); (f) SH mixture of (c); (g) SH mixture of (d).

this peak disappeared in the SH mixture containing 10 and 30% Mal. Another endothermic peak was also observed at 110°C in both DSC curves of physical and SH mixtures. Further details on this endothermic peak could not be revealed; therefore, be the subject of a future study. The X-ray diffraction and DSC studies of the SH mixture containing 10 and 30% Mal, Mal are considered to be in amorphous state in the mixture. In this study, because Mal is sublimable at 93°C (Hodge and Nelson, 1961), the amorphization of Mal seems to involve the adsorption of Mal into the porous FR particles through a gaseous phase during heating in the same manner previously reported (Hanawa et al., 1996).

3.2. Discoloration of the SH mixture of FR and Mal

Fig. 4 shows the photographs of the mixture of FR and Mal (FR:Mal = 9:1) before and after sealed heating at 100°C for 6 h. A marked discoloration was observed; the SH mixture had a color varying from initially white to yellow or light

brown. Discoloration of pharmaceuticals which is due to a chemical reaction between medicinal agents and excipients has been reported (Hartauer and Guillory, 1991). The discoloration observed in this study seems to be attributed to the interaction between Mal molecules and the FR surface. In order to investigate the discoloration during SH treatment, the changes in color differences before and after SH treatment were measured. It has been reported that color difference measurement was attempted to evaluate the kinetics and forecasting of discoloration of solid drugs (Kitamura et al., 1988; Matsuda et al., 1980). Fig. 5 shows the time courses for discoloration of the mixtures of FR and Mal (FR:Mal = 9:1) after sealed heating at various temperatures. With SH treatment, the surface of each sample gradually turned into yellow-brown; the value of color differences became greater with increased of heating time and temperature. To investigate the origin of the discoloration, calcium oxide and silicon dioxide, which are constituents of FR, were mixed with Mal and heated in a sealed container at 100°C for 6 h. Fig. 6 shows the changes in color

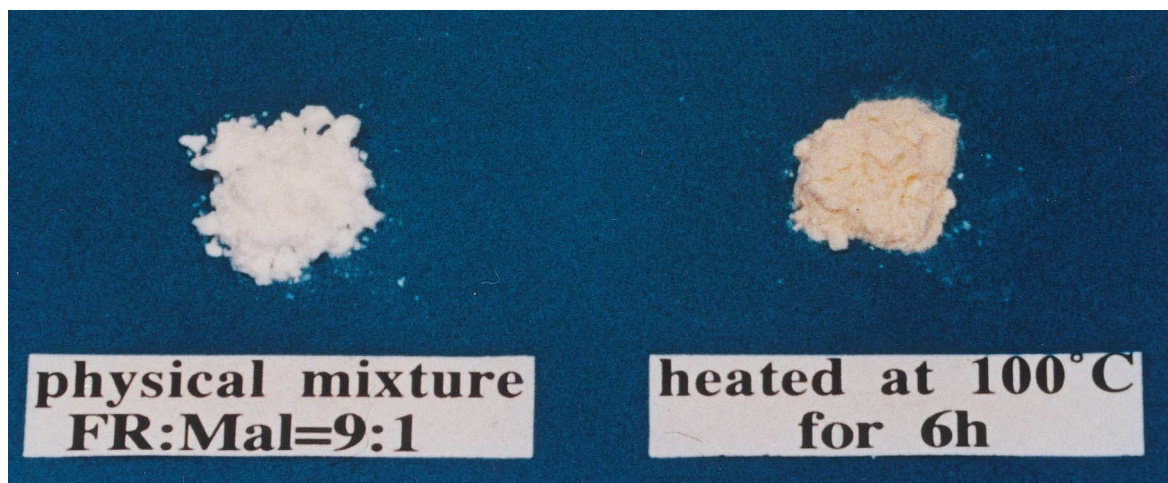


Fig. 4. Appearance of physical and SH mixture of FR and Mal

differences of SH mixture of Mal and calcium oxide or silicone dioxide. In the SH mixture with silicon dioxide and Mal, discoloration was not observed. On the contrary, in the case of the SH mixture with calcium oxide, discoloration was observed. Based on these results, the discoloration observed for the SH mixture of FR and Mal seems to be due to the presence of calcium oxide which provides basicity as a constituent of FR.

3.3. Identification of the colored substance resulting from sealed heating

To investigate the molecular states of Mal in the colored substance resulting from sealed heating of FR and Mal, IR measurement was performed. Fig. 7 and Fig. 8 shows the procedure for the isolation of the colored substance from the SH mixture of FR and Mal. The SH mixture was

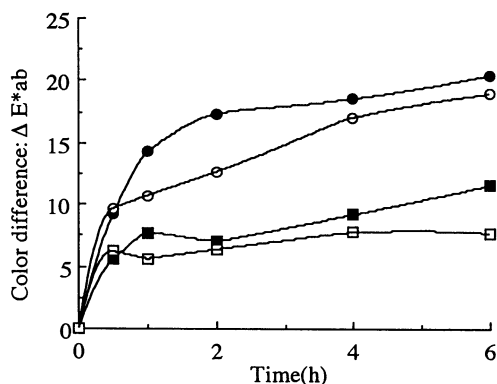


Fig. 5. Color differences between physical mixtures and SH mixtures of FR and Mal: □; SH at 50°C, ■; SH at 70°C, ○; SH at 90°C, ●; SH at 100°C.

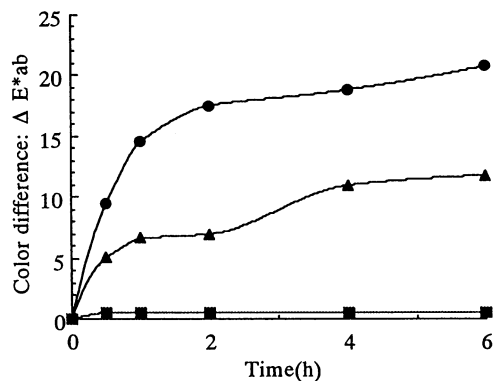


Fig. 6. Color Differences of SH mixture of FR and Mal, calcium oxide or silicone dioxide at 100°C: ●; SH mixture of Mal and FR, ▲; SH mixture of Mal and calcium oxide, ■; SH mixture of Mal and silicone dioxide.

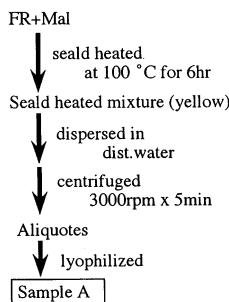


Fig. 7. Isolation of colored substance from the sealed heated mixture.

dispersed in distilled water, after centrifugation, and an aliquot was then lyophilized. We call this isolated product 'Sample A'. Furthermore, in order to investigate the role of calcium in discoloration, calcium hydroxide was refluxed with Mal and discoloration forming a yellow color occurred. The yellow-colored substance was obtained as 'Sample B' by filtering and lyophilizing of the refluxed mixture. When sample B was dissolved in hot water (90°C) and sulfuric acid was added to the solution, the yellow color of the solution faded and a white precipitate was produced. This solution was filtered and lyophilized, and 'Sample C' was then obtained. Fig. 9a shows the IR spectrum of the Mal crystals. The stretching vibration band due to the carbonyl group and the hydroxyl group of Mal was observed at 1651

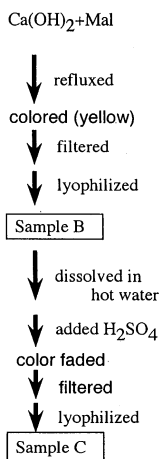


Fig. 8. Isolation of colored substances.

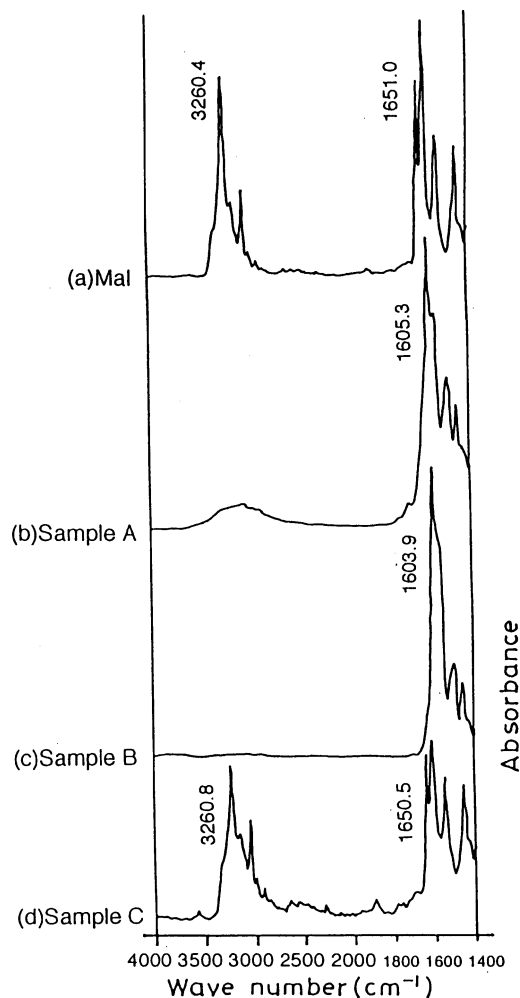


Fig. 9. Infrared spectra of Maltol crystals and discolored substances: (a) Maltol crystals; (b) sample A; (c) sample B; (d) sample C.

and 3260 cm^{-1} , respectively. In the IR spectrum of sample A or B, the carbonyl stretching vibration band shifted to a lower frequency of 1605 cm^{-1} which indicates ionization of the carbonyl group of the Mal molecule (Fig. 9b, c). At the same time, in sample A, the IR band at 3260 cm^{-1} became weaker and ultimately disappeared in sample B. With regard to sample C, with the addition of sulfuric acid to the solution of sample B, the carbonyl stretching vibration band shifted to a higher frequency at 1651 cm^{-1} and the hydroxyl stretching vibration band at 3260 cm^{-1}

appeared again. Based on these results, changes in the molecular states of Mal observed in sample A seemed to be attributed to ionization of carboxyl and hydroxyl groups. Furthermore, the fact that the white precipitate was observed on adding sulfuric acid to the solution of sample B suggested that the calcium ion was included in sample B as a constituent.

To characterize the complex formation between Mal and calcium, sample B were prepared stipulating that the stoichiometric $\text{Ca}(\text{OH})_2$:Mal were 1:1 (sample B-1) or 1:2 (sample B-2). From ICP emission spectrometry, the calcium content of the sample B-1 and sample B-2 were 17.4 and 13.3%, respectively (Table 1). The calcium content of sample B-2 was comparable to the theoretical data calculated from the suggested formula of the complex. On the contrary, in the case of sample A, the calcium content was 12.2%, which is comparable to that of sample B-2. Though the mechanism of discoloration of Mal is not yet fully understood in this study, it might be related to the ionization of Mal molecules and the formation of a complex between ionized Mal and calcium ion existing on the FR surface. In pharmaceutical fields, however, this discoloration seems to be undesirable from a chemical point of view.

3.4. Effect of the addition of silicon dioxide on discoloration of sealed heated mixture of FR and Mal

Gore and Banker (1979) demonstrated that aspirin stability was enhanced by the addition of colloidal silica at a high RH, and Yonemochi et al. (1991) also reported that the addition of colloidal silica on controlled pore glass affected the aspirin decomposition in the solid state. Further-

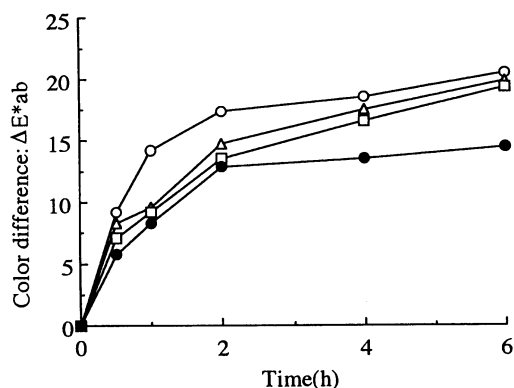


Fig. 10. Effect of adding the REO on color differences of sealed heated mixtures of FR and Mal: ○; FR:Mal = 90:10, △; FR:REO:Mal = 90:1.8:10, □; FR:REO:Mal = 90:3.6:10, ●; FR:REO:Mal = 90:9.0:10.

more, it is well known that phenovalin discolored with the coexistence of bases, such as magnesium oxide and sodium bicarbonate. Sakai (1988) demonstrated that the surface of magnesium oxide was coated by the simple blending with colloidal silica, Aerosil® R972, this resulted in the regulation of basicity and/or hygroscopy of magnesium oxide, consequently, in the inhibition of discoloration. In this study, we attempted to use REO for regulating the discoloration of Mal on the FR surface during SH treatment. REO is colloidal silicon dioxide; the specific surface area is generally estimated to be more than 200 m²/g, and it has no pore structure while it is in amorphous state, similar to FR. Various amounts of REO, 2, 4 and 10% based on the weight of FR, were physically mixed with the FR mixture, Mal was then added and the mixture was sealed and heated. Fig. 10 shows the comparison of the color differences with and without adding REO to the mixture of FR and Mal. By adding and increasing the amount of the REO, the discoloration could be regulated. After 1-h heating, the color differences of the SH mixtures with REO were about 8.3–9.5, that is about 58–67% lower than that without REO. Fig. 11 shows the color difference of SH mixtures of FR, REO and Mal at various heating temperatures. For all the heating temperatures, the discoloration could be regulated. Especially, the color difference of the mixture containing 10% REO added to the FR is about

Table 1
Calcium content in various samples

	Theoretical ^a (%)	Observed (%)
Sample A		12.2
Sample B-1	24.4	17.4
Sample B-2	13.7	13.3

^a The theoretical values were based on the assumed formula of the complex.

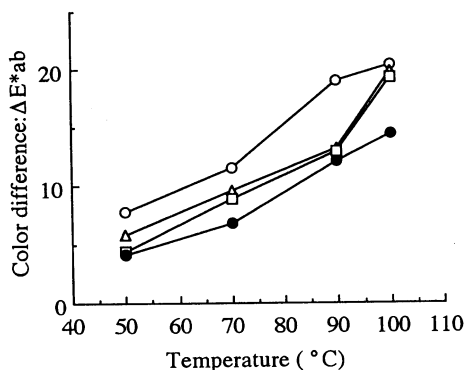


Fig. 11. Color differences of sealed heated mixtures of FR, REO and Mal at various heating temperature: ○; FR:Mal = 90:10, △; FR:REO:Mal = 90:1.8:10, □; FR:REO:Mal = 90:3.6:10, ●; FR:REO:Mal = 90:9.0:10.

55–70% lower than that of without REQ. In this study, the reason for the regulation of the discoloration with the presence of REO is not fully understood, but it might be the result of the fact that the FR surface was coated with REO, and the discoloration which seemed to be due to the chemical reaction between Mal molecules and the FR surface was inhibited.

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