RESEARCH PAPER

On Preventing Sugar-Coated Tablets from Browning

Y. Tomida[1,]* and M. Saeki[2]

[1]*Production Division, Takeda Chemical Industries Ltd., Osaka 540-8645, Japan*
[2]*Pharmaceutical Production Division, Yoshitomi Pharmaceutical Industries Ltd., Fukuoka-ken 871-0011, Japan*

ABSTRACT

The phenomenon of browning occurs gradually in the white sugar-coating layer (comprised of sucrose, talc, and powdered acacia) when the coating is applied on a large scale. We found that this phenomenon is negligible on sugar-coated tablets when they are prepared on a small scale. The smoothing layer prepared on a small scale is nearly as opaque as the subcoating layer. Conversely, the smoothing layer produced on a larger scale is semitransparent. In large-scale operations, the conditions required to make the smoothing layer opaque were established, and it was demonstrated that this method can restrict the browning phenomenon. It is considered that the nitrogen-containing contaminants in powdered acacia may react with heat-inverted sucrose (the Maillard reaction) to make brown substances in the smoothing layer and that the opaque appearance of the layer conceals the color accumulation of the brown substances in the smoothing layer and therefore restricts the browning phenomenon.
Key Words: *Sugar-coating scale; Smoothing layer; Browning prevention; Acacia.*

INTRODUCTION

Sucrose, talc, and powdered acacia are frequently used as ingredients for conventional tablet sugar-coating layers because of the ease with which they can be made into a round shape (1). However, the browning phenomenon occurred in white tablets with the elapse of a day. The fact that this phenomenon was not observed when povidone was used in place of powdered acacia may mean that the Maillard reaction (2) between nitrogen-containing contaminants in powdered acacia (3) and heat-inverted (4) sucrose is responsible for the formation of

* To whom correspondence should be addressed.

brown substances in the sugar-coating layer. The replacement of powdered acacia with another binder, the concealment of the color using titanium dioxide, or using deep coloring would solve this browning problem. However, a procedure for preventing white sugar-coated tablets from deteriorating by the browning phenomenon without changing the formula for the coating layer was investigated.

MATERIALS AND METHODS

Lactose Japanese Pharmacopeia (JP), cornstarch JP, hydroxypropyl cellulose JP, magnesium stearate JP, talc JP, powdered acacia JP, sucrose JP, carnauba wax JP, and bee wax JP were used in this work.

Tablet Preparation

Lactose tablets (diameter 9 mm, thickness 4.3 mm, convex 7.5 mm (radius), weight 240 mg) consisting of lactose, cornstarch, hydroxypropyl cellulose, and magnesium stearate were used as cores for the sugar-coating processes. The bulk tablets were subcoated with a dusting mixture of talc (97 parts) and powdered acacia (3 parts) and a binder suspension, under the same formulation and conventional operating conditions (subcoating layer 135 mg). The binder suspension used throughout the experiments was prepared as follows. Sucrose (90 parts) followed by powdered acacia (11.5 parts) was dissolved in deionized water (45 parts) heated up to 98°C, and then talc (60 parts) was suspended in the solution. The same binder suspension formulation was used for the smoothing processes (smoothing layer 50 mg). The smoothed tablets were coated using sucrose solution and were then polished with carnauba wax and bee wax using a conventional method (syrup layer 30 mg).

Coating Equipment and Conditions

Several lots of subcoated tablets were smoothed using various sizes of sugar-coating pans (Kikusui Seisakusho Ltd., Kyoto, Japan; diameters 30.5, 40.6, 76.2, 101.6, 132.1, or 195.6 cm) and using various smoothing process conditions; the pan revolving speed was either 10/8, 12, 25, 30, or 40 rpm. Air, at a temperature of about 60°C, was applied to the surface of the tablet bed for 2 or 5 min after manually pouring binder suspension onto the tablets. This hot air supply was used to dry the smoothing layer and was continued for 18, 28, or 25 min. The tablet temperature was maintained at approximately 40°C during the smoothing process for all experiments. The subcoating operation was repeated 10 times.

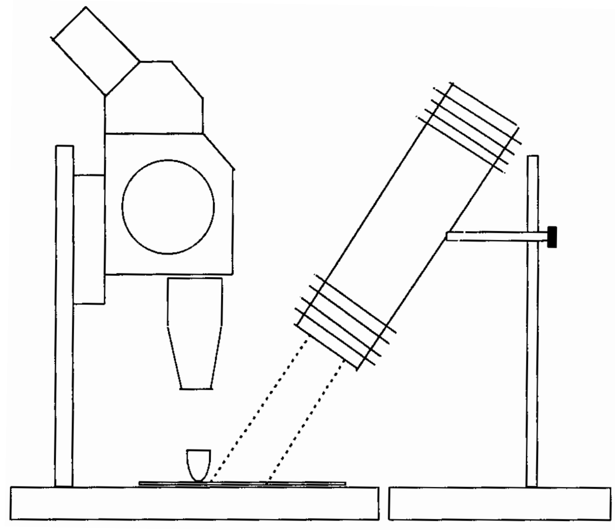

Figure 1. Microscopic observations of the smoothing layer by the red background method.

Transparency of the Smoothing Layer

A sugar-coated tablet was cut vertically with a knife and the undamaged cross-section was illuminated directly from above or against a red background, as shown in Fig. 1, and was observed with the aid of a microscope (Measure Scope, Nikon). The cross-section was also observed using a scanning electron microscope (model S-2300, Hitachi) to investigate the disposition of the crystallized sucrose.

Degree of Browning Phenomenon

Sugar-coated tablets were stored at either 25, 40, 50, or 60°C, and their appearance was periodically observed and compared with that of the initial tablets as a reference (Tables 1 and 2). The browning phenomenon was also measured as a color difference, E, obtained from the following equation using a Color Difference Meter (model SM-5, Suga Test Instruments Co. Ltd.):

$$\Delta E = \{(a - a_0)^2 + (b - b_0)^2 + (L - L_0)^2\}^{1/2} \quad (1)$$

where a_0, b_0, and L_0 are the initial values and a, b, and L are the values after aging.

Smoothing Layer Thickness

The thickness of the smoothing layer was measured as a difference between the mean thickness of 20 smoothed tablets and that of 20 subcoated tablets using a dial gauge (model G, Peacock Co.).

RESULTS AND DISCUSSION

Browning Phenomenon

The appearance of white sugar-coated tablets prepared on a large scale turned pale brown at 60°C after 2 weeks, whereas those prepared on a small scale at the formulation study stage stayed white. The layer causing the browning phenomenon was investigated after the in-process materials and the finished product had been stored at 60°C for 2 weeks.

As Fig. 2 shows, smoothed tablets and sugar-coated tablets turned pale brown more than did the subcoated tablets. The replacement of powdered acacia for a dusting mixture and binder suspension with povidone could solve the browning problem. It was considered that this browning phenomenon might stem from the Maillard reaction between heat-inverted sugar and the nitrogen-containing contaminants of acacia.

Deep coloring or an opacifier such as titanium dioxide may be effective in concealing this phenomenon. However, the browning change of sugar-coated tablets prepared on a small scale using the same formulation and without deep coloring or an opacifier was small under the same conditions, as shown in Table 1. Therefore, the cause of the difference in the browning phenomenon between sugar-coated tablets that were coated on a small and a large was investigated.

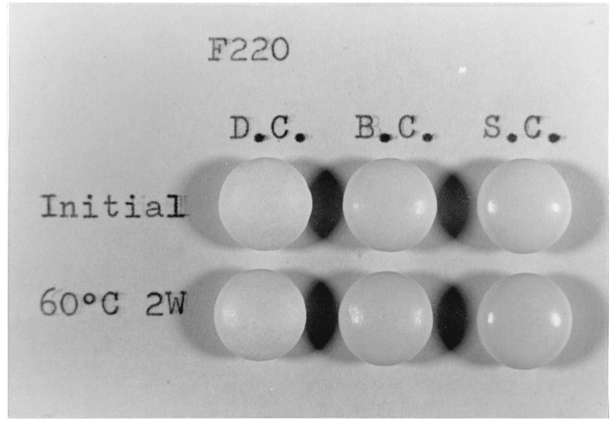

Figure 2. Browning phenomenon of subcoated (D.C.), smoothed (B.C.), and sugar-coated (S.C.) Tablets prepared on a large scale.

Opaqueness of the Smoothing Layer

Each sugar-coated tablet, prepared on a small or a large scale, was cut vertically into two pieces with a knife and each undamaged cross-section was observed with the aid of a microscope. As shown in Fig. 3, it was found that the smoothing layer was close to the subcoating layer in the case of those coated on a small scale. Conversely, the smoothing layer was closer to the outer sugar-coating layer in the case of those coated on a large scale. The transparency of the smoothing layers was examined using light penetration against a red background, and the smoothing layer of a tablet coated on a large scale was found to be much more transparent than that of one coated on a small scale, as shown in Fig. 4. Through the same investigation on each of 20 representative samples,

Table 1

Smoothing Conditions, Transparency of Smoothing Layer (SL), and Browning Phenomena

Sample No.	Interval for Spreading and Drying (min)	Pan Size Diameter (cm)	Pan Revolving Speed (rpm)	Transparency of SL	Browning Phenomena 60°C 2 weeks
MS-1	5–25	30.5	30	Op.	−
MS-2	5–25	40.6	30	Op.	−
MS-3	5–25	76.2	40	Semi-op.	+
MS-4	5–25	101.6	30	Semi-trans	+

Op, opaque; Trans, transparent; −, almost unchanged; +, distinguishable without a reference.

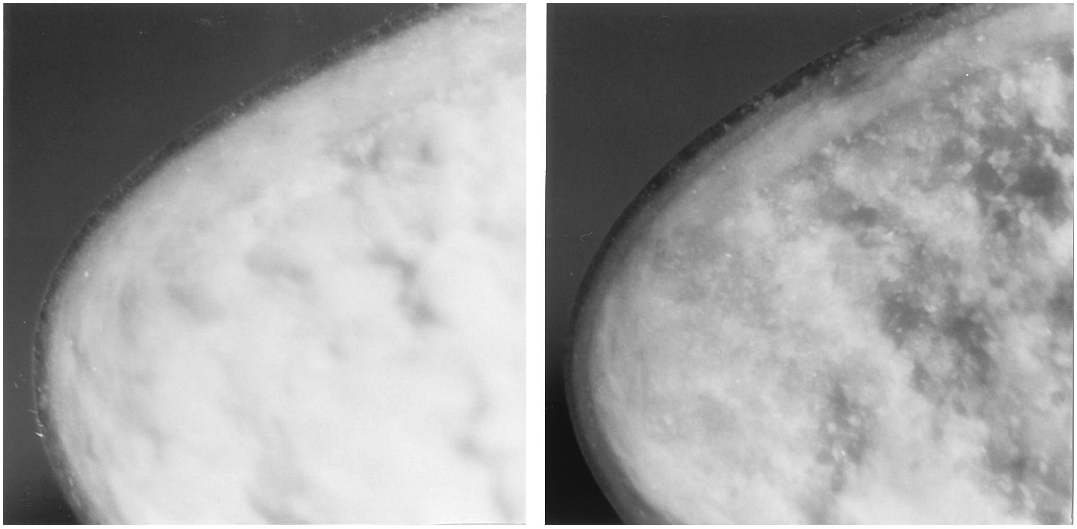

Figure 3. Cross-section of sugar-coated tablets. Left: Prepared on a small scale (sample no. MS-1). Right: Prepared on a large scale (sample no. F-220).

no fluctuation in the transparency of the smoothing layers was observed within each batch.

Coating Condition for the Opaque Smoothing Layer

When finely ground, large transparent crystals generally become white and powdery in appearance because of diffuse reflection. It was expected that the sucrose crystal disposition in the smoothing layer of a tablet coated on a small scale would be more disordered than that on a tablet coated on a large scale. Therefore, except for the smoothing process, the formulation and conditions of the core lactose tablets, binder suspension, dusting powder, subcoating, sugar-coating, and polishing processes were kept the same throughout all experiments.

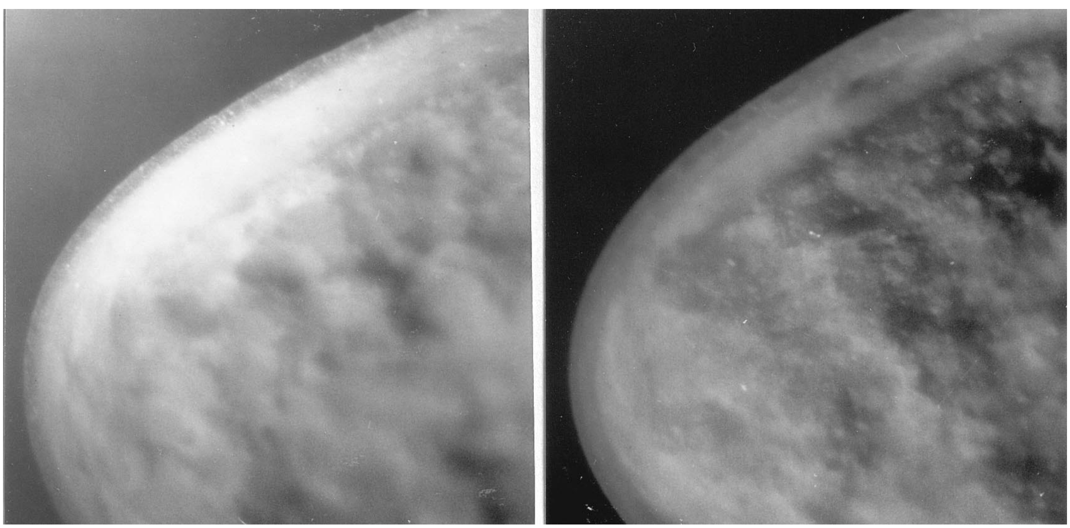

Figure 4. Sugar-coated tablet cross-section photographed using red background reflection. Left: Prepared on a small scale (sample no. MS-1). Right: Prepared on a large scale (sample no. F-220).

Table 2

Smoothing Conditions, Transparency of Smoothing Layer (SL), and Browning Phenomena

Sample No.	Interval for Spreading and Drying[a] (min)	Pan size Diameter (cm)	Pan Revolving Speed (rpm)	Transparency of SL	Browning Phenomena 60°C 2 weeks	Browning Phenomena 40°C 20 weeks
F110	5–25	101.6	30	Semi-trans.	++	++
N-11	2–18	102	30	Semi-op.	+	+
F320	2–18	102	30	Op.	±	±
F230	2–18	132	12	Op.	±	±
F700	2–18	196	10, 8[b]	Op.	±	±

The following sample groups coated under the same conditions showed the same transparency and browning phenomena: (1) F110, F120, F220; (2) F230, F240, F510, F520, F610, F620.

[a] Intervals for spreading binding suspension onto the surface of the tablets and for drying the smoothing layer buildup.

[b] Ten rpm for spreading the binding suspension and sequentially 8 rpm for the drying process.

Op., opaque; trans, transparent; ++, badly deteriorated; ± acceptable but distinguishable compared with reference.

The smoothing process conditions (excluding formulation) were varied to investigate the possibility of making the smoothing layer opaque when tablets are coated on a large scale (Table 2). To obtain the diffuse reflectivity (in other words, opaqueness) of the layer, the disordered deposition of crystallized sucrose in its layer and the reduction of tablet-to-tablet friction were taken into nconsideration. For these purposes, it was foreseen that the earlier the hot air supply was applied to the tablets after the uniform distribution of the binding suspension onto their surface and the lower the pan revolution speed, the more effective was the process. Consequently, the combination of the early hot air supply onto the wet surface of tablets and the low revolution speed of coating pan was effective in obtaining the appropriate level of opaqueness of the smoothing layer when tablets were coated on a large scale. Sugar-coated tablets were also stored under accelerated and stress conditions for 2 weeks or more to evaluate the stability of the appearance (i.e., the color change from white to pale brown) of the tablets. It was found that the browning phenomenon was restricted regardless the scale at which the coating was performed (Table 2 and Fig. 5) if they possessed an opaque smoothing layer rather than a semitransparent smoothing layer.

Figure 6 shows the cross-sectional semitransparent and opaque smoothing layers as seen with the aid of a scanning electron microscope.

The sucrose crystal and talc in the latter layer may be fixed more randomly than that in the former. The sugar-coating formulation, many ingredients, and the smoothing suspension manufacturing procedure were the same throughout all experiments. Therefore, it was concluded that the opaqueness of the smoothing layer interrupted the accumulation of the color generated during the accelerated and stress stability studies. The quantity of browning substance in the smoothing layer of each tablet, however, could not be determined. Accordingly, there is a possibility that the reaction between the nitrogen-containing contaminants in powder acacia and the heatinverted sucrose that produces the browning substances is greatly reduced by applying the hot air supply to the tablets as soon as possible after pouring the binder suspension onto the subcoated tablets. There was no difference in water content between

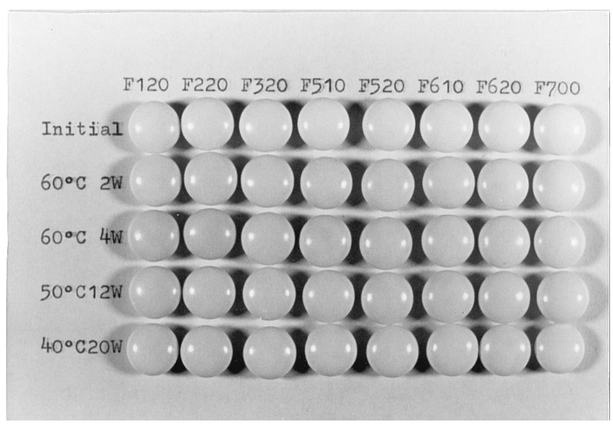

Figure 5. Browning phenomenon of sugar-coated tablets stored under various stress conditions.

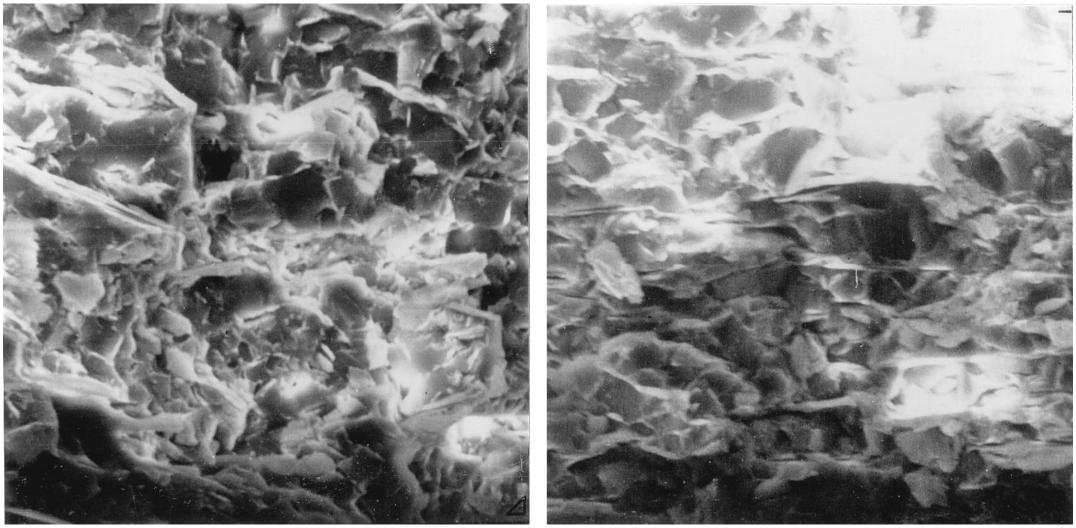

Figure 6. Scanning electron microscopic photograph of cross-sections of sugar-coated tablets. Left: Opaque smoothing layer (sample no. MS-1). Right: Semitransparent smoothing layer (sample no. F-220).

tablets with a semitransparent and an opaque smoothing layer.

Meanwhile, the relationship between the thickness of the smoothing layers and the degree of browning of the sugar-coated tablet stored for 2 weeks at 60°C was examined in which each smoothing layer was prepared semitransparently.

Each semitransparent smoothing layer of a different thickness was prepared on a large scale by increasing the pour times of the binder suspension on the same subcoated tablets. Three thousand of each smoothing tablet of different thicknesses were withdrawn from the large coating pan and were then syrup and wax coated in a small pan. As a result, the thicker the semitransparent smoothing layer, the deeper the color of the browning phenomenon (as was expected), and the semilogarithmic linear relationship between the thickness of the smoothing layer and the color difference was obtained (Fig. 7). This result demonstrates that the browning phenomenon of the white sugar-coated tablets comprising sucrose, talc, and powdered acacia was enhanced by the accumulation of discoloration in the semitransparent smoothing layer. However, the reason for the semilogarithmic linear relationship between the discoloration and the thickness of smoothing layer requires further investigation.

In the case of color sugar-coated tablets, the color of

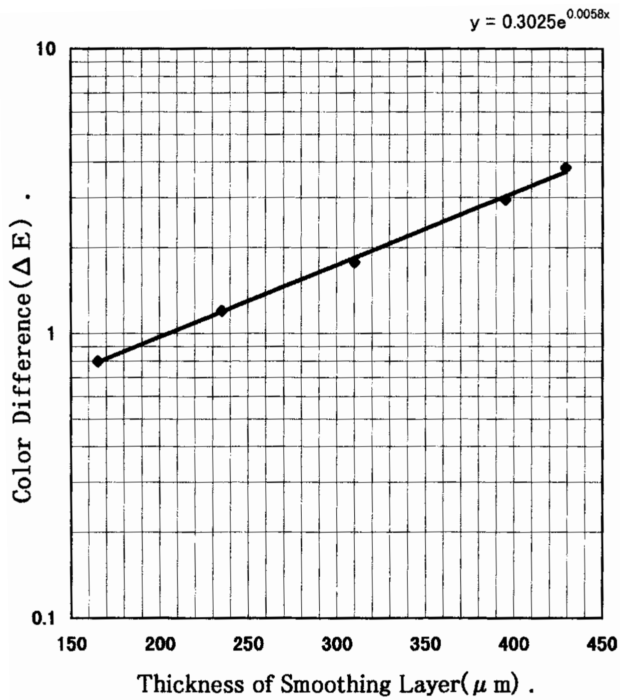

Figure 7. Relationship between the thickness of the smoothing layer and color difference in the browning phenomenon.

Table 3

Shock Resistiveness of Sugar-Coated Tablets

	Sample No.					
	F110	F210	F510	F520	F610	F700
Chipped tablets	0	1	0	0	0	2
Tested tablets	1560	1560	960	960	960	2400
Pan diameter (cm)	106.6	101.6	132.1	132.1	132.1	195.6
Transparency[a]	Trans.	Trans.	Op.	Op.	Op.	Op.

Experienced acceptance criteria; less than 2%.
[a] Trans., transparent; Op., opaque.

the tablets prepared using a large coating pan was deeper than that of those prepared using a small coating pan. This phenomenon is also considered to be due to a similar accumulation of color in the smoothing layer.

Strength of the Sugar-Coating Layer

Sugar-coated tablets prepared on a large scale to make them opaque were tested for shock resistivity. Each glass bottle was filled with 48 tablets and a piece of packing material. Filled bottles were placed into cartons (packaging cases). Tablets were inspected after shaking (frequency 600 cpm, amplitude 20 mm, time 20 sec; plus frequency 960 cpm, amplitude 2 mm, time 30 min.) and allowing to fall (height 70 cm, six times from six directions). As shown in Table 3, no difference was determined between the shock resistiveness of tablets with an opaque smoothing layer and those with a semitransparent smoothing layer.

Further Improvement of the Browning Phenomenon

Preventing sucrose from degrading to heat-inverted sucrose may be an effective way of restricting the browning phenomenon that occurs through the Maillard reaction. Accordingly, a lower temperature is considered to be preferable for the dissolution of sucrose.

REFERENCES

1. C. S. Porter, *Coating of Pharmaceutical Dosage Forms*, 18th ed., Mack Publishing Co., Easton, PA, 1994, pp. 1666–1675.
2. L. C. Maillard, Compt. Rend, 154, 66 (1911); Ann. Chim. 5, 258 (1916).
3. T. Kariyone, *Pharmacognosy*, Kadokawa Publishing, Tokyo, Japan, 1960, p. 279.
4. P. Honig, *Principles of Sugar Technology*, Vol. I, Elsevier, New York, 1953, pp. 7–13.