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Whitening on deeply colored, sugar-coated tablets

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Among sugar coating technicians it is well known that partial whitening is often observed on the surface of colored, sugar-coated tablets packed in glass bottles during use in the user's home. This detracts from the appearance and incurs complaints from consumers. The sucrose of the tablet surface partially dissolves on exposure to relative humidity above the critical level. Microscopic examination revealed that recrystallization under rapid drying conditions of dissolved sucrose occurred disturbing a wax layer and generated the crystal texture enough to cause the defused light reflection. These were considered to result in the whitening. Tablets taken out of a glass bottle with wet fingers and then returned showed similar whitening. We took into consideration the factors likely to influence these wetting and drying processes and evaluated countermeasures that seem effective to prevent the whitening, that is, addition of four kinds of pharmaceutical excipients (additives), use of water-insoluble aluminum lake, and alteration of package forms. The only solution we found is the use of press-through packaging and strip packaging from which we can take out a tablet without touching it with fingers.

Key words: Coloration – Sugar-coated tablet – Whitening – Diffused light reflection – Press-through packaging – Water-soluble wax.

Deeply colored sugar-coated tablets packed in glass bottles sometimes show whitening during use, and gave rise to complaints from consumers. However, no solution to this problem has been reported. We, therefore, sought a method for preventing it. The cause is assumed to be dissolution of sugar layer in moisture, and subsequent rapid recrystallization of sucrose that produces a white appearance due to diffused light reflection. However, this whitening phenomenon does not occur when deeply colored sucrose-saturated solution (syrup) is applied to tablets in a coating pan and then slowly dried in a thin-cloth-covered pan with intermittent gentle tumbling during the final sugar coating operation. We first established the conditions necessary for reproducing the whitening. Then, we sought additives that would retard the recrystallization-rate of sucrose by lowering the critical relative humidity (CRH) [1-5] of the sugar layer including below the ambient humidity (approximately 60% RH, 25°C). Hydrophilic water-soluble polymers were also expected to retard the recrystallization-rate. Hydrophilic, synthesized or natural polymers were also examined in anticipation of rapid moisture absorption that will prevent the dissolution of the sugar. The effectiveness of wetting agents, water-soluble wax, and packaging forms were also studied.

I. EXPERIMENTAL

1. Materials

Alginic acid, sodium alginate, polyvinylalcohol, ethylene glycol, cellulose acetate phthalate were purchased from Wako Pure Chemical, alpha starch from Nippon Starch Chemical Co., and Pluronic F68 from Asahi Denka Co. These additives were of reagent grade. Red No. 2 (amaranth) and its aluminum lake met Japanese Standards of Food Additives. All other materials used were of JP grade.

2. Preparation of tablets

Lactose tablets (diameter 9 mm, thickness 4.3 mm, radius of convex 7.5 mm, weight 240 mg) consisting of lactose, corn starch, hydroxypropyl cellulose and magnesium stearate were prepared by a wet granulation. Tablets were given with subcoating layer (135 mg) and smoothing layer (50 mg) as reported previously [6]. Red No. 2 (0.1% w/v) was added as the coloring agent to the binder suspension for each layer. The three thousand tablets with smoothing layer were coated with syrup containing Red No. 2 (0.1% w/w) and additives (none, or 5% [others]), and then polished with a mixture of carnauba wax, beeswax, and wetting agents (none, 1%) in a conventional small sugarcoating pan (diameter 30.5 cm; Kikusui Seisakusho Ltd., Kyoto, Japan) (sugar layer: 30 mg). The coloring agent and each additive except wetting agents were dissolved or dispersed in a small amount of water and added to the syrup. Before polishing with wax, the final sugar coating operation was performed by applying the colored syrup over the surface of the sugar-coated tablets, which had been cooled to room temperature by rotating the pan. The rotation was then stopped and the pan was covered with a piece of thin cloth to prevent rapid drying of the syrup solution and tumbling intermittently and gently to prevent the tablets from sticking to each other, until the sugar surface became dried. For polishing, the petroleum benzin solution of carnauba wax and beeswax, with or without wetting agents were applied onto sugar-coated tablets. Macrogol 6000 was also used as water-soluble wax in place of carnauba wax and bee wax.

A 10-mg film coat named Warf Coat (prepared from a mixture of macrogol 6000 [60 parts], cellulose acetate phthalate [40 parts], Red No.2 aluminum lake [0.5 part] and titanium dioxide [10 parts]) was also used as an alternative final coat.

Each coated tablet which was prepared for this every experiment was kept under 30% RH at 25°C for 2 days for controlling the relative humidity of the sugar-coated tablets.

3. Packaging form

Press-through packaging and strip packaging systems consisting of aluminum (thickness:10 μm) lining and PVC sheets (thickness: 150 μm) were evaluated as alternatives to glass.

4. Humidity control conditions

Taking the CRH of sucrose (85% [4]) into consideration, we chose three conditions (*Figure 1*) for humidifying and drying the sugar layer of tablets without additives in order to evaluate the whitening (*Figure 2b*). Condition I: the tablets were exposed to humidity below the CRH of sucrose and then exposed to the rapid drying conditions. Condition II: the tablets were exposed to humidity above the CRH of sucrose and then exposed to the rapid drying conditions. Condition III: the tablets were exposed to humidity above the CRH of sucrose and then exposed to the slow drying condition, to simulate a final sugar coating process. Twenty tablets were placed in a Petri dish and exposed to each condition.

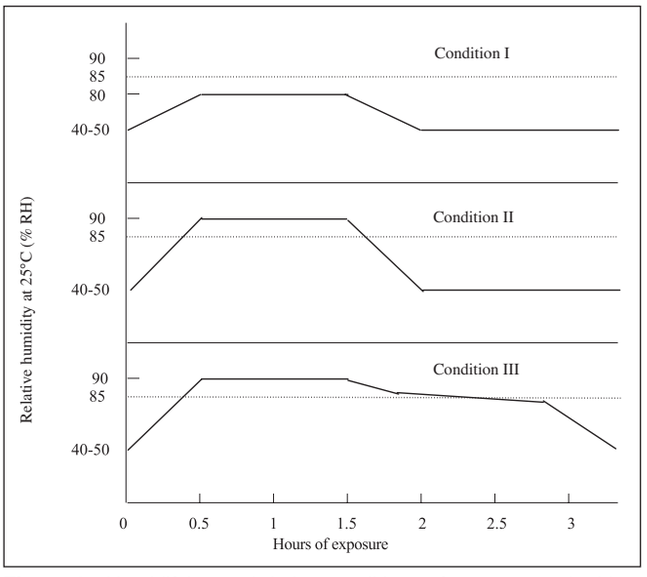

Figure 1 - Humidifying and drying conditions of sugar-coated tablets (CRH of sugar: 85% RH at 25°C).

Tablets with additives were also tested in Condition II. Ten packaged tablets were exposed to modified Condition II (the humidifying and drying processes were extended to 12 h, respectively, which were enough for moisture to penetrate the film packaging). We used Climate Lab (Aminco, USA) that can control the wetting and drying conditions of the tablets and record the temperature and humidity.

As another method, two tablets with or without additives were taken with wet fingers (dampened with a damp towel) out of a glass bottle (30 ml) containing 50 dry untouched tablets, and then returned to the same bottle at an ambient temperature. The extent of the whitening was also assessed visually for each case.

5. Concentration of coloring agent in the whitened part

The whitened and non-whitened parts were carefully scrabbled from the surface of additive-free tablets with a knife, and then each concentration of water-soluble coloring agent was determined by ultraviolet visual spectrometry (JP).

6. Observation of whitened tablet surface

Scanning electron microscope (Hitachi Co. Model S-2300, 20 kv) was used, in a conventional way, to determine the difference between the surfaces of a final sugar layer, a wax-coated, and a whitened tablet.

II. RESULTS AND DISCUSSION

1. Effects of humidity conditions on appearance of tablets without additives

A shown in *Table I*, the examination of the relation between the whitening and humidity conditions revealed that the whitening occurred when the colored tablets without additives were exposed to Condition II (rapid drying after sucrose dissolved); the whitening did not occur under Condition I (which did not dissolve sucrose) and III (slow during after sucrose dissolved). The tablets also whitened when handled with wet fingers as described above. As a representative example, untouched and whitened tablets are shown in *Figure 2*.

Table I - Tablets stored under each humidifying and drying conditions.

Condition	Result
I. Humidity < CRH + rapid drying	not whitened
II. Humidity > CRH + rapid drying	whitened
III. Humidity > CRH + slow drying	not whitened
wet fingers	whitened

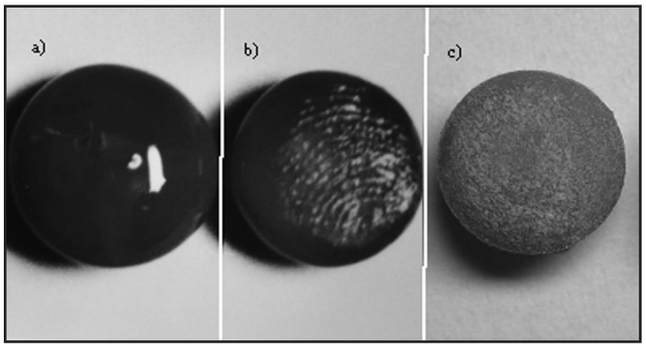

Figure 2 - The surface of a) an intact tablet, and whitened tablets b) after taken out with damp fingers and then returned to other dry tablets and c) exposed to condition II.

2. Concentration of coloring agent in the whitened part

The concentrations of the water-soluble coloring agent in the whitened and non-whitened parts of tablets did not significantly differ (dry base: 0.095 % and 0.093%, respectively). It is well known that diffused light reflection from powdery material gives it a white appearance regardless of its original color. The observation with a electron microscope (*Figure 3*) of the whitened part revealed that its surface was covered with loosely packed sugar crystals suitable structure for diffused light reflection. We concluded that the whitening was caused by the same diffused light reflection as that in powdery material.

3. Observation of tablet surfaces

The electron microscopic examination revealed that the surface of a final sugar-coated tablet without wax layer was densely covered with rigid cubic or rectangular crystals as shown in *Figure 3A*. The wax layer over the final sugar-coated tablet is considered effective to evenly fill the surface roughness and gives the gloss through multi-reflection (*Figure 3B*). On the other hand, the surface of a whitened tablet (*Figure 3C*) was covered with irregularly and loosely packed recrystallized sugar disturbing the wax layer. Smoothing rough surface with wax or oil often removes whitishness to intensify the color and gloss of the surface by multi-reflection as seen in wax-coating a whitish surface of colored car-bonnet with fine net-like cracks. Therefore loss of multi-reflection in the wax layer due to the destruction of the layer was also considered to result in the whitening, but the fact that

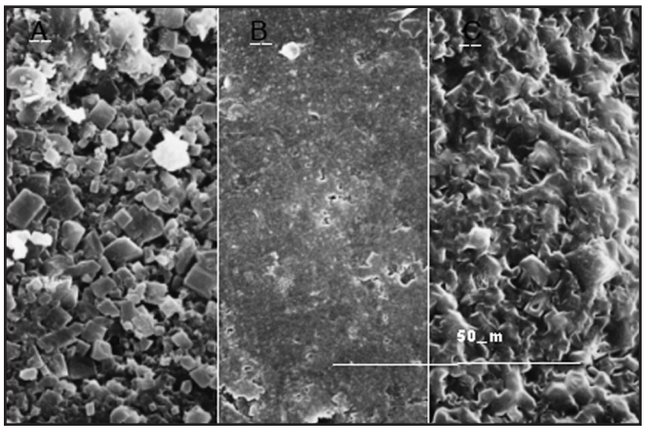

Figure 3 - The electronic scanning microscopic photograph showing surface of a) a final sugar-coated, b) a wax-coated, and c) a whitened tablet, from left to right, respectively.