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Impact of compression pressure on tablet appearance

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Abstract

The color of model tablets deepened and tablet gloss increased with increase in compression pressure regardless of colorant type. The possible reasons for these phenomena were examined. These observations could not be explained either by polymorphic transition of the colorant or by condensation of the colorant during compression. Instead, a change in surface roughness was assumed to be the most likely reason. The increase in compression pressure made the tablet surface smoother. With the increase in the surface smoothness, diffuse reflection decreased while specular reflection increased, indicating the opposite relation between diffuse and specular reflection as a function of surface roughness. A decrease in diffuse reflection results in a deepening of color. In contrast, an increase in specular reflection causes an increase in glossiness. Thus, the surface roughness seemed to govern gloss and color. The compression pressure seems to be one of the most important factors to control tablet appearance.

Keywords: Tablet; Compression pressure; Surface roughness; Gloss; Color

1. Introduction

Appearance is an important factor for products in many areas, because it significantly affects their market value. Color and gloss are important factors when evaluating appearance (Beck et al., 1993). Color is characterized by diffuse reflection, whereas gloss is done by specular reflection (O'Brien, 1985; Stark et al., 1996; Ogawa et al., 1998; Belal et al., 2000; Salem, 2002; Sultan, 2002; Nishimura and Ishiguro, 2003; Gotardo et al., 2004; Kanda, 2004; Preston and Gate, 2005). During the clinical development of pharmaceutical products, active and placebo tablets must have a similar appearance for conducting an effective double blind study. However, controlling the color of tablets can be difficult, because their appearance is affected by slight differences in manufacturing processes and physical properties such as crystal form (Grant, 1999; He et al., 2001).

Reflections can be divided in two components, specular and diffuse reflections (Kaihara and Sato, 2000; Harima et al., 2001). The angle of the specular reflection is consistent with that of incident light, where the diffuse reflection is composed of all the reflected light in multiple directions. Specular reflection is usually described as gloss. Diffuse reflection is closely related to color impression. With the decrease in diffuse reflection, the color impression perceived by human eyes becomes deep and dark. Physiological color impression can be evaluated by the Commission International de l'Éclairage (CIE) colorimetric system, which is expressed using three parameters, L^*, a^*, and b^*. L^* serves as the psychometric correlate of perceived lightness and covers a range from white ($L^* = 100$) to black ($L^* = 0$). The values of a^* and b^* are derived from Hering's opponent color theory (McDonald, 1987). a^* represents a red/green coordinate, with $+a^*$ indicating red and $-a^*$ indicating green. b^* represents a yellow/blue coordinate, with $+b^*$ indicating yellow and $-b^*$ indicating blue. Color difference (ΔE) is calculated using the following equation:

$$\Delta E = \sqrt{(\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2}$$

where ΔL^*, Δa^*, and Δb^* are the differences in L^*, a^*, and b^* values, respectively. The widely accepted ΔE threshold that enables color discrimination by human eyes depends on purpose (Johnston and Kao, 1989; Stark et al., 1996; Guo et al., 2004; Stavridakis et al., 2004; Lee, 2005; Lee et al., 2005). For example, a value greater than 3.3 is regarded as significant in dentistry (Stavridakis et al., 2004; Lee, 2005), while 2.2 is the threshold in the pigment industry (Guo et al., 2004). In the pharmaceutical field, a ΔE value greater than 1.5 is considered a noticeable difference in color according to the U.S. National Institute of

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Standards and Technology (formerly called the National Bureau of Standards) (Stark et al., 1996; Caney and Cehreli, 2003). In this study, we manufactured tablets containing colorants at several different compression pressures. Tablets deepened in color and increased in glossiness with an increase in the compression pressure. Potential reasons for these observations are examined.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose (HPC-EXF), and magnesium stearate (MgSt) were purchased from Asahi Kasei Co. Ltd. (Tokyo, Japan), HMS (Uitgeest, the Netherlands), FMC International (Philadelphia, PA, USA), Hercules (Wilmington, DE, USA), and Mallinckrodt (St. Louis, MO, USA), respectively. Yellow ferric oxide and red ferric oxide, which were used as colorants of model tablets, were obtained from Elementis Pigments (East Saint Louis, IL, USA).

2.2. Manufacturing model tablets

Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and HPC-EXF were mixed at a weight ratio of 23.1/69.3/4.0/3.0, followed by sieving through 600 μm mesh (U.S. sieve No. 30) three times. After adding the desired amount of colorant, the mixture was ground using a mortal with the aid of 40% (w/w) purified water until the mixture became homogeneous. The mixture was dried at 50 °C for 3 h, followed by the grinding in the mortar. Lubrication was achieved by sieving the mixture with 0.5% (w/w) MgSt. Approximately 300 mg of the mixture were compressed into a tablet using a flat-faced bevel-edged stamper, Carver Press (Carver Inc., Wabash, IN, USA). Tablets with a scratched surface were prepared using a sand paper.

2.3. Gloss and color evaluations

Gloss was measured with a gloss meter GM-26 PRO (Murakami Color Research Laboratory, Tokyo, Japan) using 60° specular. A glass plate with a gloss of 92.1 units was used as a calibration reference. The specular reflectance of samples was quantified relative to the reference glass plate as 100%.

Color difference, ΔE, was measured with TC-1800 MK II (Tokyo Densyoku, Tokyo, Japan) instrument. The CIE $L^*a^*b^*$ values were calculated based on illuminant C and 10° standard observer and a white plate as a standard. The diffuse reflectance of yellow and red model tablets was determined at 470 and 520 nm, respectively.

2.4. Evaluation of surface characteristics

Tablet surfaces were observed using a digital microscope VHX-100 (Keyence, Osaka, Japan) and a scanning electron microscope (SEM) VE-7800 (Keyence, Osaka, Japan). For the SEM observations, each tablet was fixed on an aluminum sample holder using adhesive tape. The sample was exposed to 2.0 kV acceleration voltage at 10^{-3} Pa. Magnification was 100 times.

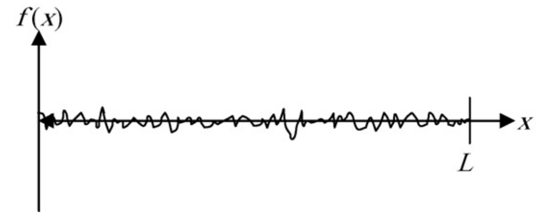

Fig. 1. Schematic representation of surface roughness profile of tablets.

To evaluate surface roughness of the tablets quantitatively, mean surface roughness, R_a, was calculated. Fig. 1 shows schematic surface roughness profiles of tablets. R_a is defined by $R_a = 1/L \int_0^L |f(x)|\, dx$, where $f(x)$ is the surface profile of tablets. Thus, the smoother the surface is, the smaller the R_a value is. The surface profile was investigated with a profile micrometer VF-7500 (Keyence, Osaka, Japan). The value for L and resolution in the $f(x)$ direction were 13 and 0.1 μm, respectively.

2.5. X-ray powder diffraction (XRPD)

XRPD measurements were performed with an X'Pert Pro-MPD powder diffraction system (PANalytical, Almelo, the Netherlands) equipped with a Cu X-ray tube (voltage: 45 kV and current: 40 mA). Approximately 50 mg of sample was loaded on an aluminum plate. Scans were performed from 5° to 45° (2θ value) at a rate of 0.04° s^{-1} with a step size of 0.02°.

To examine the effect of compression pressure on the crystal form of yellow ferric oxide, intact and compressed yellow ferric oxide were subjected to the measurement. The compressed yellow ferric oxide was ground in a mortal before the measurement.

3. Results and discussions

3.1. Effect of compression on tablet color

Table 1 shows $L^*a^*b^*$ evaluation of the model tablets containing 0.1% (w/w) yellow ferric oxide compressed at various pressures. The a^* value did not depend on the compression pressure, whereas the L^* and b^* values decreased and increased, respectively, with an increase in the pressure over the entire range investigated. The ΔE between tablets compressed at 200 and 400 MPa was 2.5. Fig. 2 shows photographs of the model tablets containing 0.1% (w/w) yellow ferric oxide compressed at 200 and 400 MPa. Color became yellow with an increase in pressure from 200 to 400 MPa. This impression was consistent with results of the color measurement in which the b^* value increased. However, ΔE between tablets compressed at 400 and 600 MPa was 0.8, which could not be perceived by human eyes.

3.2. Effect of compression on crystal form

Fig. 3 shows the X-ray diffraction patterns of intact yellow ferric oxide and the oxide compressed at 600 MPa. The diffraction patterns obtained were almost identical. Colorants

Table 1
$L^*a^*b^*$ data and ΔE of the model tablets[a] compressed at various pressures[b]

Compression pressure (MPa)	L^*	a^*	b^*	ΔE (vs. 200 MPa)
200	89.8 (0.1)	1.8 (0.0)	21.1 (0.4)	–
400	88.4 (0.1)	1.9 (0.1)	23.2 (0.3)	2.5
600	88.2 (0.1)	1.7 (0.1)	23.9 (0.5)	3.2

[a] Composition: microcrystalline cellulose 23.1%, lactose monohydrate 69.3%, croscarmelose sodium 4.0%, HPC-EXF 3.0%, MgSt 0.5%, yellow ferric oxide 0.1%.

[b] Averaged values and standard deviations (in parenthesis) of these measurements.

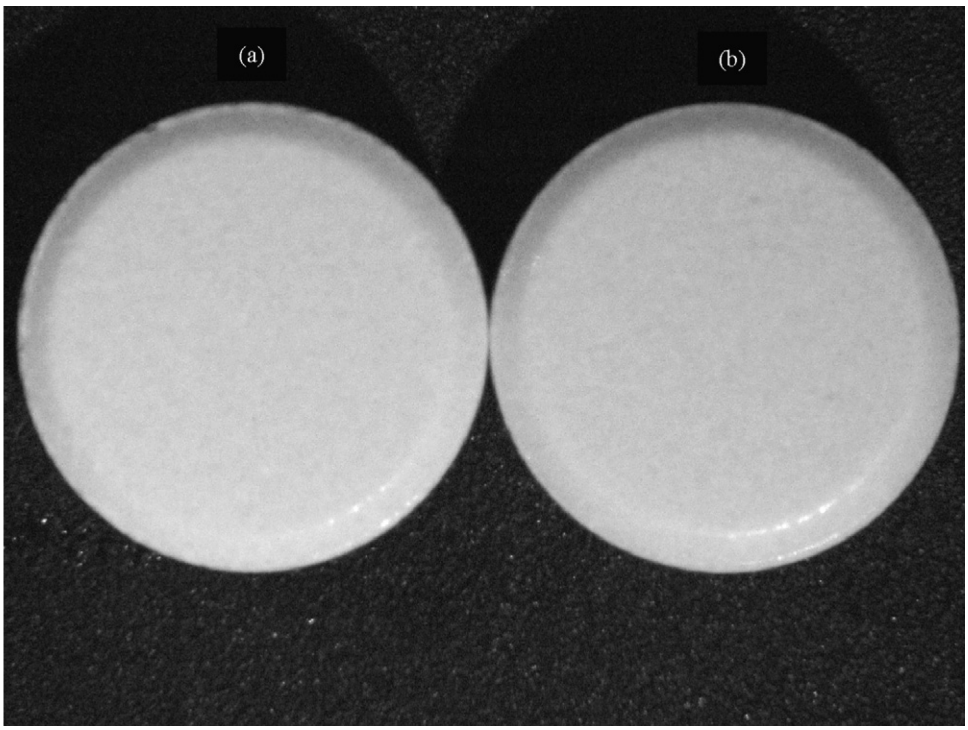

Fig. 2. Photographs of model tablets containing 0.1% (w/w) yellow ferric oxide compressed at (a) 200 MPa and (b) 400 MPa.

compressed at 200 and 400 MPa also exhibited the same diffraction pattern (data not shown). Therefore, the change in tablet appearance during compression cannot be attributed to a change in crystal form. Also, it should be noted that no other crystal forms have been identified for this colorant.

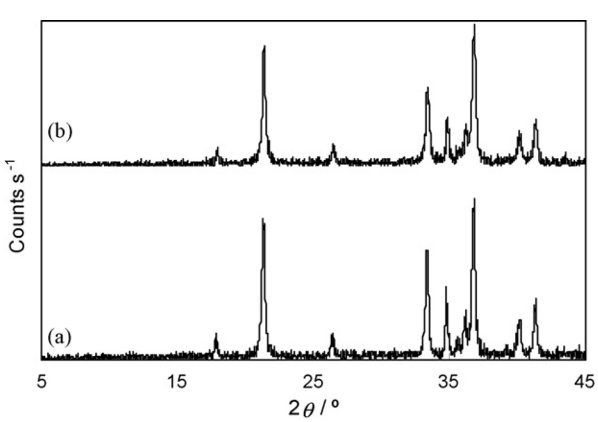

Fig. 3. X-ray diffraction patterns of yellow ferric oxide: (a) intact powder and (b) compressed at 600 MPa.

3.3. Effect of colorant density on tablet color

The thickness of tablets compressed at 200 and 600 MPa were 4.42 and 4.23 mm, respectively. Thus, the average colorant density was only minimally affected by the compression pressure. However, the colorant density at the tablet surface might be affected more by the compression (Sinka et al., 2004). Fig. 4(a) and (b) shows CIE $L^*a^*b^*$ color space profiles and its projection to the a^*–b^* plane, respectively, of the model tablet of various colorant density prepared at various compression pressures. The solid line shows the change in $L^*a^*b^*$ with an increase in colorant amount under the same compression pressure (200 MPa), while the dotted lines show color changes upon an increase in the compression pressure from 200 to 600 MPa at the same amounts of colorant. With an increase in the colorant density, the L^* and b^* values decreased and increased, respectively. Similarly, at each colorant density, an increase in the compression pressure resulted in the similar observation. However, if the color change due to the compression pressure was caused by only the change in colorant density, the direction of the dotted lines should agree with that of the solid line. Since this

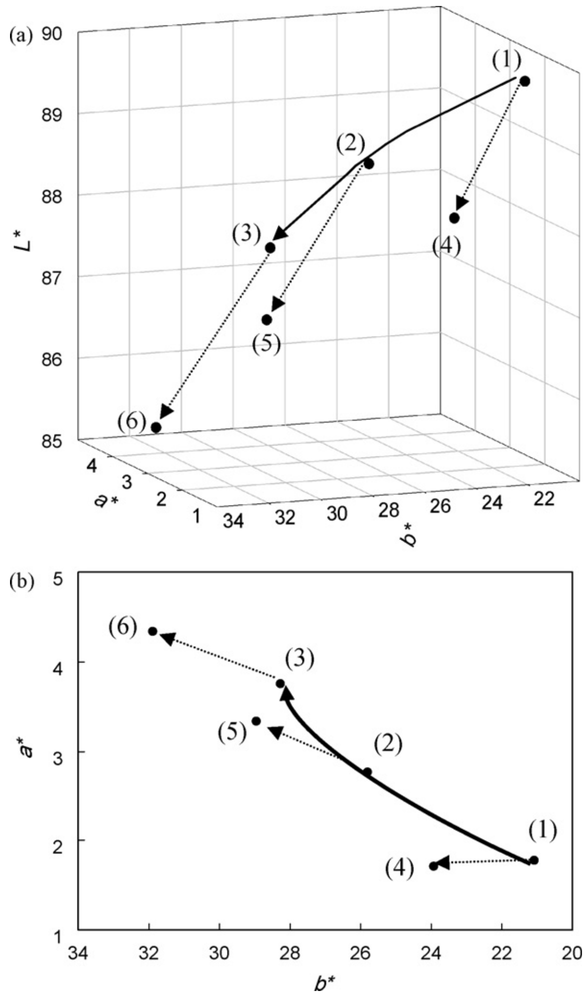

Fig. 4. (a) CIE $L^*a^*b^*$ color space profile and (b) its projection to a^*–b^* plane for yellow ferric oxide model tablets with colorant amounts of: (1, 4) 0.10% (w/w); (2, 5) 0.15% (w/w); and (3, 6) 0.20% (w/w). Compression pressure was: (1–3) 200 MPa and (4–6) 600 MPa. All measurements were done in triplicate. Error bars are omitted because of the high reproducibility.

was not the case, the change in the tablet color caused by the compression did not seem to be due to change in the colorant density.

3.4. Relation between surface roughness and reflection patterns

Fig. 5 shows SEM pictures of the surface of model tablets containing 0.1% (w/w) yellow ferric oxide compressed under various pressures. The surface of tablets compressed at 200 MPa was rough with irregular large pores. The surface became smoother with an increase in compression pressure. Fig. 6 shows R_a values for tablets containing 0.1% (w/w) yellow ferric oxide compressed under various pressures. With an increase in the compression pressure from 200 to 400 MPa, the R_a of the tablets decreased drastically, whereas R_a values were nearly constant at pressures greater than 400 MPa. This trend was consistent with the ΔE analysis, in which the difference in ΔE value was very large between 200 and 400 MPa, but was insignificant between 400 and 600 MPa.

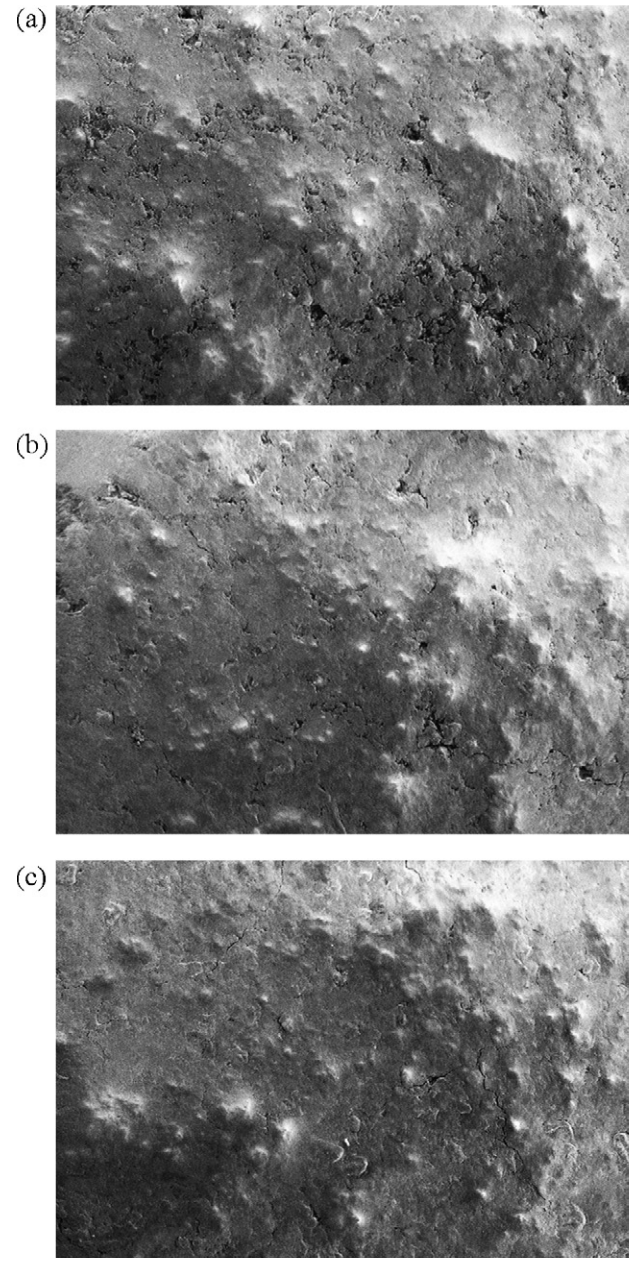

Fig. 5. SEM images of model tablets containing 0.1% (w/w) yellow ferric oxide compressed at: (a) 200 MPa; (b) 400 MPa; and (c) 600 MPa.

Surface roughness affects diffuse reflection (related to color) and specular reflection (related to gloss) (O'Brien, 1985; Nishimura and Ishiguro, 2003; Preston and Gate, 2005). Fig. 7(a) shows the diffuse reflectance and specular reflectance plotted against R_a for model tablets containing 0.1% (w/w) yellow ferric oxide. Also presented is data obtained for 'scratched' tablets. Those surface profiles were not visually distinguishable in the measurements, indicating that the scratched tablets provided good artificial model of the rough surface. Specular reflectance decreased with an increase in R_a. In contrast, diffuse reflectance increased with an increase in R_a. Thus, specular and diffuse reflectances have opposite correlations to R_a. Surface roughness likely governs the ratio of diffuse and the specular reflectances. However, deviation of the data suggests that

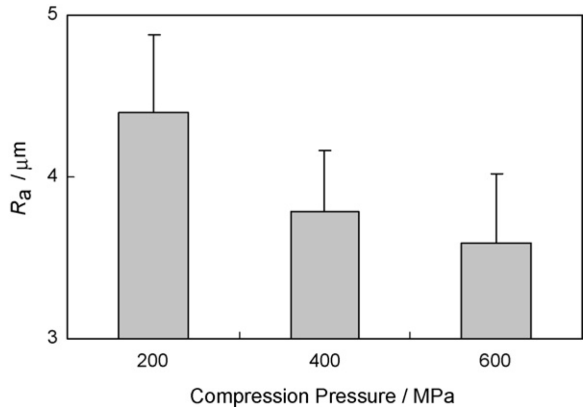

Fig. 6. R_a values as a function of compression pressure. All measurements were obtained 10 times. Error bars indicate standard deviation.

there may be other minor factors that affect the tablet appearance.

3.5. Results using another colorant

For general understanding, changes in specular and the diffuse reflectances as a function of R_a for a different model tablet was examined. Fig. 7(b) shows diffuse and specular reflectances plotted against R_a for model tablets containing 0.1% (w/w) red ferric oxide. The data for 'scratched' tablets are also shown. Results were very similar to those observed for the yellow ferric oxide tablets. Therefore, it seems to be a general conclusion that the increase in the compression pressure deepens the color and enhances the gloss. It should be noted that the overall impression of the tablet appearance becomes 'bright' because of the increase in the gloss despite the decrease in the L^* value. The surface characteristics of the both model tablets were influenced significantly in the range between 200 and 400 MPa. However, it was not significant between 400 and 600 MPa. Therefore, a higher compression pressure may be desirable to avoid unexpected color variation caused by the surface roughness.

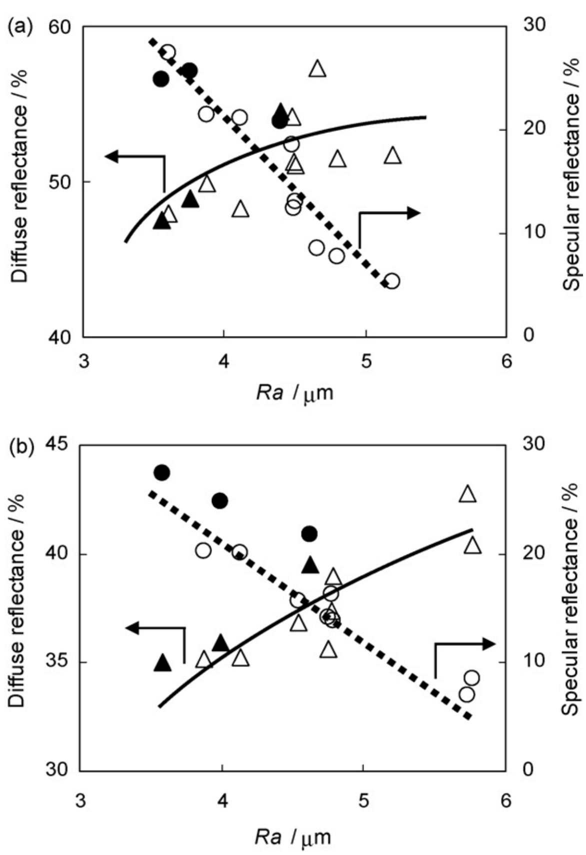

Fig. 7. Diffuse reflectance (closed triangles) and specular reflectance (closed circles) of model tablets containing: (a) 0.1% (w/w) yellow ferric oxide and (b) 0.1% (w/w) red ferric oxide as a function of R_a. Compression pressures applied for the model tablets were 200, 400, and 600 MPa (right to left). Diffuse reflectance (open triangles) and specular reflectance (open circles) of 'scratched' tablets are also shown.

4. Conclusions

Appearance of the model tablets depended significantly on the compression pressure. The color of the tablets became deep and their gloss increased upon an increase in the pressure. Investigation of possible factors revealed that the crystal form transformation of the colorant and the change in the colorant density did not explain the observation. On the other hand, variation in the surface roughness was shown to be the most likely reason. With an increase in the compression pressure, the tablet surface became smoother. Surface roughness was correlated with the diffuse and the specular reflectances, regardless of colorant type. Thus, compression pressure seems to be an important factor to be considered for controlling the tablet appearance.

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