Quantitative Assessment of Surface Mottling of Colored Tablets

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Abstract □ A photographic technique was developed to measure the degree of mottling of calcium phosphate tablets colored with FD&C Blue No. 1 dye. Optimization of the photographic process is described, and mottling values calculated by this method are shown to correlate well with the visual appearance of the tablets. Although the technique was developed primarily with a view to investigating factors that affect mottling, it could form the basis of a quality control procedure for use with colored tablets where mottling may be a cause for concern.

Keyphrases □ Surface mottling of colored tablets—measurement, photographic technique and equipment □ Mottling, surface of colored tablets—measurement, photographic technique and equipment □ Tablets with colored surfaces—measurement of mottling, photographic technique and equipment

Colorants are widely used in the manufacture of compressed tablets for elegance and ease of identification. In the case of tablets prepared by a wet granulation process, however, it is difficult to attain a reproducible, uniform surface coloration. The wet mass generally is uniformly colored before granulation, but during drying the colorants migrate with the granulating fluid and accumulate at the drying surface. Compression of these nonuniformly colored granules results in mottled tablets.

To quantify some factors which influence tablet mottling, it was necessary to develop a reproducible technique for assessing the uniformity of color dispersion exhibited by a tablet. Currently used methods (1, 2) for the measurement of overall tablet color are based on the Kubelka–Munk equation, which can only be applied to light reflected from a uniformly colored surface; therefore, these methods are unsuitable for the evaluation of mottled tablets. For this evaluation, one requires an apparatus capable of measuring variations in light reflectance along a predetermined path across a tablet surface. Two apparatus appeared to be suitable. One of these[1] utilizes the reflectance of an intense beam of light from the tablet surface. Although convenient, it had to be abandoned since the light beam caused fading of the dye. The second apparatus[2] measures the absorbance of a photographic negative image of the tablet.

This report describes a method using the second apparatus which provides reproducible measurement of tablet mottling and includes the development of a standardized photographic process to eliminate artifacts caused during the production of a photographic negative.

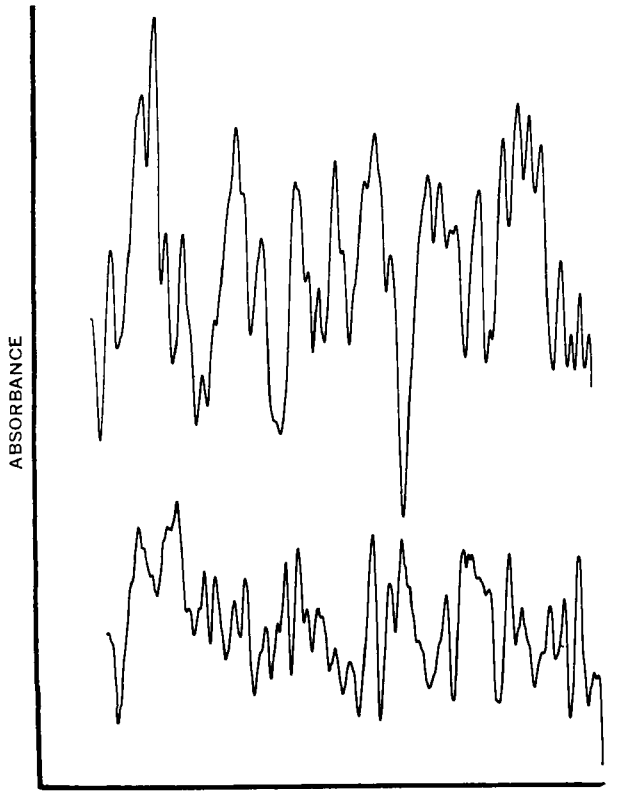

Figure 1—*Microdensitometer traces of mottling across the surface of (bottom) a slightly mottled (8.5 units) tablet and (top) a more severely mottled (24.5 units) tablet of calcium phosphate colored with FD&C Blue No. 1 dye.*

EXPERIMENTAL

Tablet Preparation—Dibasic calcium phosphate NF was colored with 0.0333% (w/w) FD&C Blue No. 1 dye (92% dye content)[3] dissolved in water (100 ml). The colored powder was granulated with polyvinylpyrrolidone[4] (15% w/w in water) and sieved through a 2.8-mm mesh screen using an oscillating granulator[5]. A portion of the wet granulate was dried for 20 min in a fluid-bed drier[6] (air inlet temperature 60°). The remaining material was spread to a depth of 1 cm and dried in a tray drier[7] for 8 hr at 60°.

The cake of tray-dried granules was broken down by an oscillating granulator fitted with a 1.70-mm mesh screen, but the fluid-bed dried granules were not comminuted further. Sieve fractions of each granulation were collected by shaking for 20 min on a vibratory sieve shaker fitted with British standard sieves[8]. Each fraction was lubricated with magnesium stearate BP (1%) colored with the same dye (0.0333%) and compressed into tablets by a single-stroke tablet machine[9] fitted with 12.5-mm diameter flat-faced punches. Each tablet weighed 660 mg and had a thickness of 4.00 mm.

[1]Vitatron densitometer, Fisons Scientific Apparatus Ltd., Loughborough, United Kingdom.

[2]Joyce Loebl microdensitometer Mark III CS, Joyce Loebl and Co. Ltd., Team Valley, Gateshead, United Kingdom.

[3]D. F. Anstead Ltd., Billericay, United Kingdom.

[4]Plasdone-25, Badische Anilin and Soda-Fabrik A. G., Ludwigshafen am Rhein, West Germany.

[5]Type 143A, Apex Construction Co., London, United Kingdom.

[6]Type SSE65, Apex Construction Co., London, United Kingdom.

[7]Model VA, L. A. Mitchell Ltd., Manchester, United Kingdom.

[8]Pascall Engineering Co. Ltd., Crawley, United Kingdom.

[9]Model E2, Manesty Machines Ltd., Liverpool, United Kingdom.

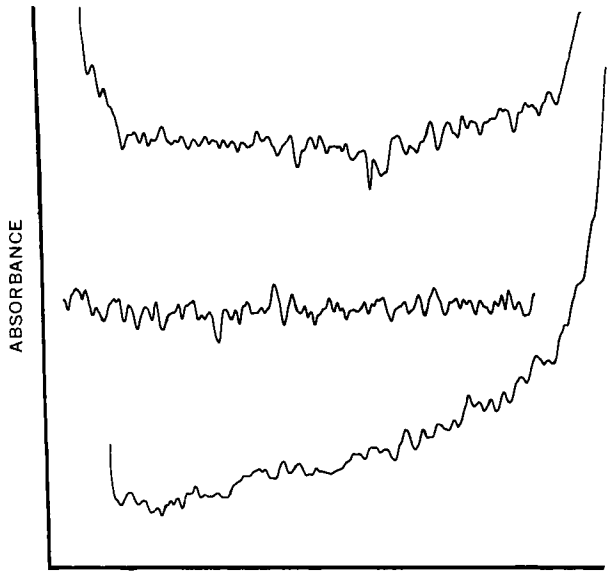

Figure 2—*Effect of developer type and agitation during development on the uniformity of density exhibited by negatives of a uniformly illuminated gray card. Key: top, a fast developer with agitation; middle, a slow developer with agitation; and bottom, a slow developer without agitation.*

Preparation of Photographic Negatives by a Standardized Method—A standard camera unit[10], consisting of a camera with a 127-mm lens, camera stand, baseboard, and lamp supports, was illuminated by four floodlights (150 w, 240–250 v), one mounted at each corner of the baseboard. A tablet set in a circular orifice cut in a gray neutral test card[11] was mounted at the center of the baseboard. Photographs were taken using 35-mm fine grain roll-film[12], with optimum exposure (4.0 sec). Contrast was enhanced by the use of a red gelatin filter[13]. After exposure, the film was placed in a daylight development tank[14] containing developer[15] (760 ml). The tank was inverted 15.0 sec after the film had been placed in the developer solution and then inverted (0.5 sec) at 5.0-sec intervals throughout the development process (10.00 min). The temperature of the developer solution was maintained at 20.0° by partially submerging the tank in a water bath. Agitation of the developer solution was ceased 10.0 sec before the end of the development period and the film was fixed[16], washed, and dried.

Method of Assessing Mottling—The microdensitometer[2] is designed to produce a graphic record of the changes in absorbance along a predetermined path across a transparent specimen such as a photographic negative. Absorbance (A) is defined as $A = \log P_0/P_t$, where P_0 and P_t are, respectively, the incident and radiant flux of a measured area of specimen.

A photographic negative image (14.30 mm diameter) developed by the standard method was scanned by the microdensitometer along paths (1.166 mm wide) across four diameters orientated at 45° to each other. The dimensions of the rectangular scanning beam were 1.166 × 0.136 mm. Typical traces obtained from a severely mottled tablet and a more uniformly colored specimen are shown in Fig. 1. An arbitrary baseline was drawn on each graph, and the ordinate of the trace was measured at equidistant intervals along this abscissa, giving some 45 values per graph. (Each interval was equivalent to about 0.25 mm on the actual tablet surface.) A numerical assessment of mottling was made by calculating the standard deviation of these values around a mean, the standard deviation being independent of the position of the baseline. Finally, the average was calculated from the four standard deviation values obtained from each tablet.

[10]Polaroid MP-3.
[11]Kodak Ltd., Kingsway, London, United Kingdom.
[12]Ilford Pan F, Ilford Ltd., Ilford, United Kingdom.
[13]No. 25 Wratten, Kodak Ltd., London, United Kingdom.
[14]Johnsons of Hendon Ltd., London, United Kingdom.
[15]Ilford ID11, Ilford Ltd., Ilford, United Kingdom.
[16]Ilford Hypam fixing solution, Ilford Ltd., Ilford, United Kingdom.

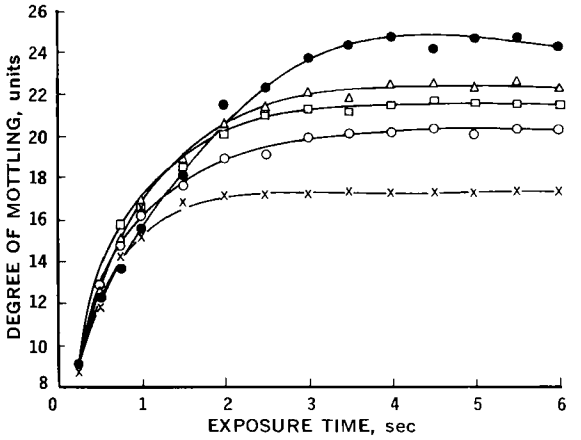

Figure 3—*Effect of development time on the numerical values obtained for the mottling on the surface of a tablet. Key (development time): ×, 8 min; ○, 9 min; □, 10 min; △, 11 min; and ●, 12 min.*

Effect of Developer Type and Agitation on Development Uniformity—Three sets of photographic negatives of a uniformly illuminated neutral test card were prepared. One set was developed by the standard method using a slow acting developer[15]. Another set was prepared by a similar process, but the tank was not inverted during development. The third set was developed for 2.00 min in a fast developer[17] by the agitation process described in the standardized method.

Effect of Exposure and Development Time on the Mottling Value—Negatives of a mottled tablet were prepared at a range of exposure levels by the standard method. Other negatives of this subject were prepared by the same process but were developed for different periods.

Negatives of other mottled tablets exhibiting different levels of color saturation were prepared at a range of exposure levels by the standard method.

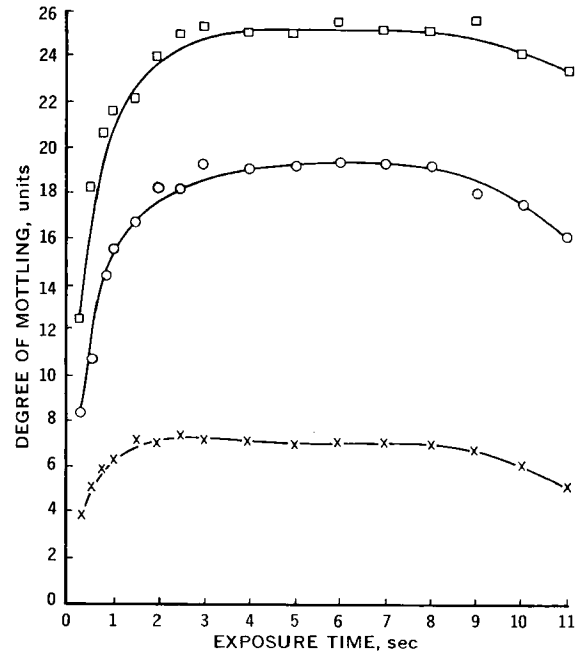

Figure 4—*Effect of exposure time on the numerical values obtained for the mottling on the surface of tablets exhibiting different levels of color saturation and mottling. Key: □, dark-blue, severely mottled tablet; ○, blue, mottled tablet; and ×, pale-blue, relatively uniformly colored tablet.*

[17]Ilford Contrast FF.

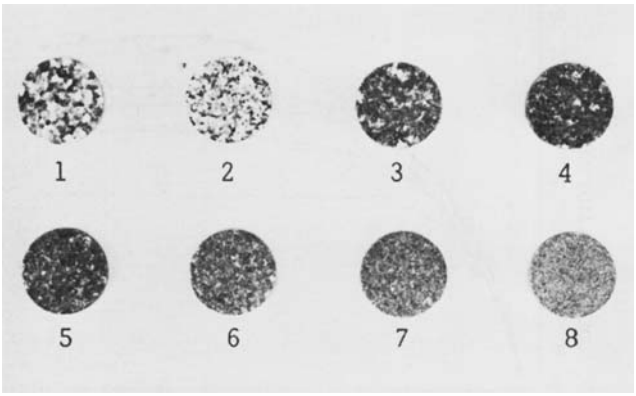

Figure 5—*Effect of drying method and granule size on the mottling shown by calcium phosphate tablets colored with FD&C Blue No. 1 dye (numbers refer to Table I).*

RESULTS AND DISCUSSION

The irregular traces (Fig. 1) representing the changes in absorbance across tablet images were evaluated by the method utilized by Bricout (3) to quantify similar traces representing the random distribution of silver grains in a photographic negative. The traces in that study were obtained with a high power microdensitometer. Mottling, being a random distribution of color over a tablet surface, was not constant and the standard deviation value for each path across a tablet was different. However, reproducible results could be obtained by evaluating four diametrical paths per tablet.

Since this method depends on changes in absorbance across a photographic negative, it is essential to minimize variations in density due to insufficient agitation of the developer (Fig. 2). This problem is well recognized in photography, and many elaborate methods have been devised to ensure reproducible vigorous agitation during the development process (4). The inversion technique used in this investigation is based on that described by the British Standards Institution (5) and gave adequate turbulence using a slow acting developer[15] (Fig. 2). The negatives of a uniformly illuminated test card had a mottling value of 1.9; this figure, representing background mottling due to silver grains and development artifacts, was subtracted from all subsequent mottling determinations. The background value was constant for each of the 36 negatives of a roll-film and reproducible from batch to batch. The inversion technique could not, however, be used to produce sufficient agitation (Fig. 2) for a faster developer[17].

It has been shown that there is a linear relationship between the logarithm of the exposure time and the density exhibited by a uniformly exposed negative (6), unless a film is underexposed or overexposed. Since density is also affected by the development time, both development and exposure time affect the contrast of a negative and, consequently, the numerical value for mottling assigned to the negative image of a tablet. Prolongation of development (Fig. 3) increased density and, hence, negative contrast and mottling values, but development times greater than 11 min caused excessive granularity of the negatives through agglomeration of silver particles. These negatives could not detect fine detail, and values for mottling were not constant. There was less variation between the values for mottling obtained with negatives developed for 8 min, but the mean value was less reproducible. This was due to slight variations in the time required to transfer the film to and from the developer solution. A development time of 10.00 min was found to be satisfactory and was selected as standard.

Reproducible results could only be obtained when the film had been adequately exposed, and the time required to attain an adequate level of exposure varied according to the depth of color of the tablet. Light-colored tablets, which reflect more light, required a shorter exposure time before reaching the region of linearity than those of greater color saturation (Fig. 4). Tablets of dibasic calcium phosphate colored with FD&C Blue No. 1 were prepared from fluid-bed dried granules of closely defined size. Visual examination showed that the tablets prepared from coarse material were a darker color and more mottled than those prepared from smaller granules. The minimum exposure level suitable for very severely mottled dark-blue tablets was 4.0 sec (Fig. 4). This level was insufficient to produce a decrease in values for mottling of paler, less mottled tablets due to overexposure (longer than 8.0 sec).

The high degree of mottling exhibited by tablets prepared from coarse granules is thought to be due to their relatively low surface area–volume ratio. On drying, dye migration to the periphery of the granule produced a layer with a high concentration of colorant. On fracture, there was a marked contrast between the color of the periphery of a large granule and its color-deficient interior; therefore, the tablets were severely mottled. Figure 5 is a photograph of this range of tablets, and Table I shows the corresponding values for mottling.

The correlation between experimentally determined mottling values and the visual appearance of those tablets will not necessarily apply to tablets incorporating a dye of a different color. This is because the human eye is not equally sensitive to light from all regions of the spectrum (7) but is most sensitive to yellow (wavelength 570 nm) and least sensitive to blue (400 nm) and red (700 nm) light. Blue and red objects, therefore, appear to reflect less light than those colored yellow. Sumner (8) showed that differences in light reflectance have a much greater influence on the legibility of print than have differences in color. Consequently, yellow and white mottled tablets appear to the eye to be more uniformly colored than those prepared with blue or red colorants. A photographic film, however, is equally sensitive to light of all visible wavelengths and a photographic negative would show all nonuniformly colored tablets to be mottled, irrespective of their actual color.

Although the foregoing technique was primarily developed to facilitate investigation of the factors affecting mottling, it could form the basis of a quality control procedure for colored tablets where mottling is a problem. For a specific product, it is possible that a range of tablets could be produced showing quantified degrees of mottling and these could be used as reference standards.

Table I—Effect of Drying Method and Granule Size on Mottling Shown by Calcium Phosphate Tablets Colored with FD&C Blue No. 1 Dye[a]

Tablet Number	Method of Drying	Granule Size Range, μm	Mottling Value
1	Tray dried	710–1000	38.8
2	Tray dried	355–600	23.1
3	Fluid bed dried	1400–1680	21.1
4	Fluid bed dried	1000–1400	19.8
5	Fluid bed dried	710–1000	17.3
6	Fluid bed dried	600–710	14.0
7	Fluid bed dried	355–600	7.0
8	Fluid bed dried	250–355	5.5

[a] Photographs of these tablets are shown in Fig. 5.

REFERENCES

(1) M. E. Everhard and F. W. Goodhart, *J. Pharm. Sci.*, **52**, 281(1963).

(2) M. E. Everhard, D. A. Dickcius, and F. W. Goodhart, *ibid.*, **53**, 173(1964).

(3) P. Bricout, *C. R. Acad. Sci.*, **197**, 1202(1933).

(4) J. A. Smibert and M. O'Bern, in "Science and Applications of Photography," R. S. Schultze, Ed., Royal Photographic Society, London, England, 1955, p. 471.

(5) British Standards Institution Technical Committee (PHC/1), *Photog. J.*, **80**, 341(1940).

(6) F. Hurter and W. C. Driffield, *J. Soc. Chem. Ind. (London)*, **9**, 455(1890).

(7) N. I. Pinegin, *Dokl. Akad. Nauk SSSR*, **30**, 206(1941).

(8) F. C. Sumner, *J. Appl. Psychol.*, **16**, 201(1932).

ACKNOWLEDGMENTS AND ADDRESSES

Received February 26, 1973, from the *Welsh School of Pharma-*

cy, University of Wales Institute of Science and Technology, Cardiff, United Kingdom.

Accepted for publication July 31, 1973.

The award to G. A. March of a research scholarship by the Pharmaceutical Society of Great Britain and the help of Merck Sharp & Dohme Research Laboratories are gratefully acknowledged.

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Influence of Sunscreening Agents on Color Stability of Tablets Coated with Certified Dyes I: FD&C Red No. 3

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Abstract □ The influence of a protective coating of certain sunscreening agents upon the photostability of FD&C Red No. 3 used to color coat tablets was studied. The sunscreening agents used were glyceryl *p*-aminobenzoate, 2-ethoxyethyl *p*-methoxycinnamate, benzocaine, *m*-homomenthyl salicylate, *n*-octyl salicylate, and amyl salicylate. Alcohol film-, modified sugar-, and film-coating methods were developed and used to apply the sunscreening agents. Tablet samples were exposed to intensified artificial light of a measured intensity. At certain intervals, the change in reflectance of the surface of the colored tablets was measured using a reflectance instrument. Visual observations were also made. Kinetic studies were performed, and approximate shelflives of the various colored tablets were calculated using the Kubelka-Munk equation. The greatest protection against fading was observed with 2-ethoxyethyl *p*-methoxycinnamate as the protective agent.

Keyphrases □ Sunscreening agents—effect on color stability (shelflife) of tablets coated with FD&C Red No. 3 □ Tablets—three methods for coating with sunscreening agents, effect of agents on color stability (shelflife) of FD&C Red No. 3 □ Dyes, color stability of coated tablets—effect of sunscreening agents on FD&C Red No. 3

The stability of certified dyes used in pharmaceuticals has been of continued interest to the pharmaceutical formulator. Within the last decade, reflectance measurements have been used to determine the stability of various dyes. The effect of light on creams, powders, granules, and coated tablets was studied (1). Lachman and coworkers (2–7) carried out extensive quantitative studies on color-coated tablets. The fading of dyes was observed to follow an apparent first-order reaction, but their work did not take into account the sensitivity of the human eye.

Several other studies were made to quantitate the dye-fading phenomenon. These studies utilized various equations such as the Kubelka-Munk equation (8, 9) based on kinetic principles or the Adams-Nickerson or McAdam equations (10) based on color differences and chromaticity coordinates. Recently, a fadeometer was employed for the rapid determination of color stability (11). Some attempts were made to stabilize dye fading in tablets, using derivatives of benzophenones (6, 12, 13), resorcinol (12), and sulfonic and acrylic acids (13). Sunscreening agents, *e.g.*, salicylates, benzoates, and cinnamates, are mainly used for protection from sunburn, to control the degree of tanning, and for protection of colors in textiles and plastics. These agents could provide protection against color fading if applied as a coating on tablets coated with certified dyes.

The purposes of this study were to: (*a*) develop a procedure for the application of these sunscreening agents to tablets coated with certified dyes; (*b*) determine the thickness of the coating of the sunscreening agents on the tablets; (*c*) determine the amount of sunscreening agent applied on tablets in the form of a coating; (*d*) evaluate the influence of sunscreening agents of the salicylate, benzoate, and cinnamate types on tablets coated with the FD&C Red No. 3; and (*e*) predict the color shelflife of tablets.

EXPERIMENTAL

Materials—Six sunscreening agents were selected: glyceryl *p*-aminobenzoate[1], benzocaine, 2-ethoxyethyl *p*-methoxycinnamate[2], *m*-homomenthyl salicylate, *n*-octyl salicylate, and amyl salicylate[3]. The dye used was FD&C Red No. 3. All compounds were used as received without further purification.

Tablet Preparation—Tablets were prepared according to the following formula:

calcium phosphate, dibasic	99.4%
magnesium stearate	0.5%
talc	0.1%
acacia solution, 25%	*q.s.*

The granules were prepared according to commonly employed tableting techniques, using 25% acacia solution as the granulating agent. Tablets weighing 365 mg, with a thickness of 3.45 mm and a hardness[4] of approximately 13 kg/6.45 cm^2 (1 in.^{2}), were compressed using a 1.06-cm (0.42-in.) deep concave punch[5].

Coating Procedure—Ten subcoats and 25 smoothing coats were applied to core tablets, in lots of 6 kg, using medium

[1] Escalol 106, Van Dyk & Co.
[2] Giv-Tan-F, Sindar Corp.
[3] Amyl Salicylate Extra, Fristsche Brothers, Inc.
[4] Pfizer hardness tester, Chas. Pfizer Co.
[5] Stokes model B-2 rotary machine.