Influence of Sunscreening Agents on Color Stability of Tablets Coated with Certified Dyes II: FD&C Blue No. 1

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Abstract □ The influence of protective coatings of six sunscreening agents (glyceryl *p*-aminobenzoate, benzocaine, 2-ethoxyethyl *p*-methoxycinnamate, *m*-homomenthyl salicylate, *n*-octyl salicylate, and amyl salicylate) upon the photostability of FD&C Blue No. 1 used to color coat tablets was studied. Alcohol film-, modified sugar-, and film-coating methods were used to apply sunscreening agents. Tablets were exposed to 1000 foot-candles of light. Visual observations as well as UV spectrophotometric determinations were made. A kinetic study, using the Kubelka–Munk equation, was made and approximate shelflives of various colored tablets were calculated. No sunscreening agent exhibited significant protective action for FD&C Blue No. 1.

Keyphrases □ Sunscreening agents—effect on color stability (shelflife) of tablets coated with FD&C Blue No. 1 □ Tablets—three methods for coating with sunscreening agents, effect of agents on color stability (shelflife) of FD&C Blue No. 1 □ Dyes, color stability of coated tablets—effect of sunscreening agents on FD&C Blue No. 1

The influence of six sunscreening agents (of salicylate, benzoate, and cinnamate types) on the color stability of tablets coated with FD&C Red No. 3 was reported previously (1). Three different methods were developed for the application of these sunscreening agents. The degree of protection was dependent not only upon the type of sunscreening agent but also upon the method by which it was applied.

In recent years, considerable attention has been directed toward the improvement and understanding of color stability. Such studies have been stimulated by the decertification of many colors. The approach commonly used to improve the light stability of a medicinal agent or to prevent color fading is to place it in a dark container. Such a solution is not always desirable, nor is it always effective.

UV absorbers (sunscreening agents) have been reported (1–5) to have a degree of effectiveness in preventing or slowing color fading under varying conditions of light exposure. Basically five types of UV absorbers have been found useful: benzoates, benzophenones, benzotriazoles, cinnamates, and salicylates. Benzoates in pharmaceuticals (1), benzophenones in textiles (6) and in pharmaceuticals (4, 5), benzotriazoles in plastics (7), and cinnamates (1) and salicylates in pharmaceuticals (1) and in plastics (7, 8) have been used for preventing color fading with some success. The toxicity of many of these UV absorbers is unknown and the reactions, if any, occurring among the dye, the UV absorber, and other "inert" or active pharmaceutical ingredients are unknown. Such reaction products may be toxic.

The purposes of this study were to evaluate the influence of selected sunscreening agents on tablets coated with FD&C Blue No. 1 and to predict the color shelflife of tablets.

EXPERIMENTAL

Materials—The six sunscreening agents used were 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 Blue No. 1. All compounds were used as received without further purification.

Procedure—The preparation of tablets, application of sunscreening agents, equipment, exposure to light, and determination of sunscreening agents per tablet were reported previously (1).

Coating Procedure—Ten subcoats and 25 smoothing coats were applied to core tablets, in lots of 6 kg, using medium strength gelatin syrup and white subcoating dusting powder. After tablets were completely dried, the color coating was applied. Plain coating syrup (170 g of sucrose and 100 ml of deionized water) and color syrup (0.300 g of dye in 100 ml of plain coating syrup) in the following ratios were applied: seven coats of 25 ml each in 40:1 parts, followed by 10 coats of 27 ml each in 30:1 parts, followed by six coats of 30 ml each in 20:1 parts, and finally 15 coats of 30 ml each in 10:1 parts of plain syrup and color syrup, respectively.

Application of Sunscreening Agents—Three coating techniques, alcohol film, modified sugar, and film, were used to apply sunscreening agents to color-coated tablets. Observations regarding the "wet" feeling of tablets coated with glyceryl *p*-aminobenzoate, turbid solutions for modified sugar-coating method, and mottled appearances in the case of tablets coated by the film-coating method with salicylates were similar to those reported (1). In earlier experiments it was noted that tablets coated with glyceryl *p*-aminobenzoate or benzocaine changed hue when exposed to light. To see whether such a hue change could be prevented, a protective coat with the following composition was applied:

cellulose acetate phthalate	5%
polyethylene glycol 4000	2%
acetone	43%
95% ethanol	*q.s.*

Five coats were applied to two sets of tablets, one containing glyceryl *p*-aminobenzoate and the other containing benzocaine.

Measurement of Color Change—Adequate samples of each set of color-coated tablets were exposed to light. Samples were withdrawn from the light cabinet, maintained at 1000 foot-candles intensity of light and 26 ± 2°, at designated time intervals. The reflectance of the tablets was measured using the transmittance scale. The spectrophotometer[4] and its reflectance attachment unit (Fig. 1) were used to measure the reflectance of individual tablets.

[1] Escalol-106, Van Dyke & Co. Inc.
[2] Giv-Tan-F, Sindar Corp.
[3] Amyl Salicylate Extra, Fritsche Brother Inc.
[4] Beckman DU.

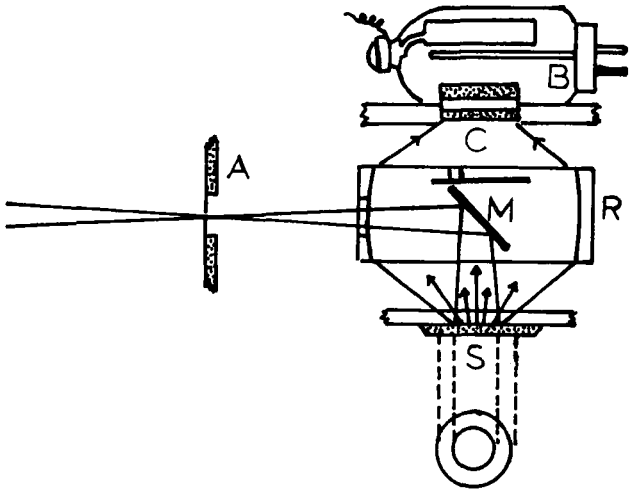

Figure 1—*Schematic diagram of the reflectance attachment for the spectrophotometer. Key: A, exit slit; B, phototube; C, diffusing plate; M, mirror; R, ellipsoidal metallic mirror ring; and S, sample.*

Two magnesium carbonate blocks [5.1 × 3.6 × 1.8 cm (2 × 1.4 × 0.7 in.)] were fitted to the compartments of the reflectance attachment. The block in the front compartment, with a concave cavity (Fig. 2), was used to hold the sample tablet while the rear compartment block was used as a reference standard. The depth of the cavity was one-half the thickness of the tablet, with a tolerance of less than 0.04 cm (0.015 in.). The cavity was centered in the magnesium carbonate block so that the tablet was always centered in front of the aperture windows of the instrument. By properly marking this position, it could be easily reproduced.

Measurements were made between 540 and 700 nm for each sample at appropriate wavelength intervals and at the maximum for the dye (640 nm) (Fig. 3). Evaluation of the color of the tablets by visual observation was carried out as previously reported (1).

RESULTS AND DISCUSSION

The color fading of FD&C Blue No. 1 followed an apparent first-order rate up to 20,000 foot-candles days. The fading followed the Kubelka–Munk equation:

$$\theta_t = \theta_t' e^{-kt I} \qquad \text{(Eq. 1)}$$

where $\theta_t = (1 - R)^2/2R$, where R is the reflectance at the absorbance maximum at time t; I is the intensity in foot-candles, k is the apparent first-order rate constant; and θ_t' is θ_t at time $t = 0$. Figure 4 shows typical plots of θ_t *versus* (time and intensity).

A hypsochromic shift of maximum from 640 to 630 nm occurred after approximately 3 days of exposure to 1000 foot-candles of light (Fig. 3). By this time, the tablets had lost most of their color (visible to naked eye). Therefore, when plotting θ_t *versus* (time × intensity), the values of time were taken only up to 4 days. The data up to 40 days show biexponential behavior and follow Eq. 2:

$$\theta_t = \theta_{t_1} e^{-k_1 t I} + \theta_{t_2} e^{-k_2 t I} \qquad \text{(Eq. 2)}$$

where $\theta_{t_1} + \theta_{t_2} = \theta_t'$.

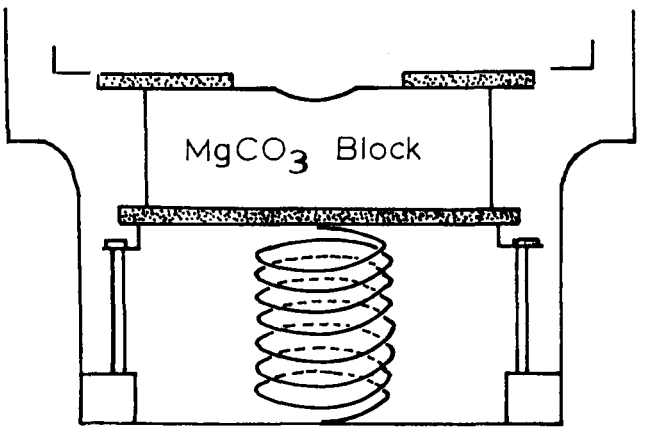

Figure 2—*Tablet arrangement with magnesium carbonate block for reflectance attachment.*

Table I—Summary of Visual Observations of Tablets Coated with FD&C Blue No. 1 Exposed to an Intensity of 1000 Foot-Candles of Light over 40 Days[a]

Sunscreening Agent	Coating Film		
	Alcohol Film	Modified Sugar	Film
Control	Noticeable fading becoming objectionable within 5 days and becoming almost colorless within 10–20 days		
Glyceryl *p*-aminobenzoate	1A, S	1	1A, S
Glyceryl *p*-aminobenzoate (p.c.)	Not studied	Not studied	1A, S
Benzocaine	2	1	1A
Benzocaine (p.c.)	Not studied	Not studied	1A
2-Ethoxyethyl *p*-methoxycinnamate	2, S	2	2, S
m-Homomenthyl salicylate (n.p.)	2, S	Not studied	Not studied
m-Homomenthyl salicylate	2, S	2	2A
n-Octyl salicylate	2	2	2A
Amyl salicylate	2	2	2A

[a] 1 = fading less than control, 1A = fading less than control with change of hue, 2 = fading similar to control, 2A = fading similar to control but with mottled appearance due to cracked film, S = brilliant shine, p.c. = contains protective coat, and n.p. = not polished (all others polished).

The units for both rate constants are foot-candles^{-1} days^{-1}. The second rate constant could represent: *(a)* changes occurring at or within the reflectance surface without any dye (9), *(b)* the possibility of reactions between the dye and its decomposition product, atmosphere, or inert ingredients of tablet (10), or *(c)* the porous nature of tablet coating. This is in general agreement with other workers (10–12). Equation 1 satisfactorily covers the color change within 4 days. After about 4 days, although a reflectance reading is obtained, the tablets appear white or "colorless" and fall past the objectionable fading period. Since the present objectives of the study were therefore met, the rate constant k_2 was not evaluated.

Visual observations were made on all tablets (Table I). The time at which objectionable fading or appearance was seen, in the opinion of the author, was also noted. The corresponding value of θ_t is obtained from plots of log θ_t *versus* (time × intensity). Thus, all values of Eq. 1 are known at $I = 1000$ foot-candles. The time at which objectionable fading occurs can then be calculated at a lower intensity. The value of $I = 50$ foot-candles as the light intensity of a well-illuminated room (1) was used for calculating approximate shelflife in days for minimum acceptable value of θ_t. Table II shows the apparent first-order rate constants and the shelflife values.

An unexplained phenomenon was observed in the reflectance curve of tablets coated with FD&C Blue No. 1 by the film-coating method (Fig. 5). When the photocell was changed at 625-nm wavelength, a hypsochromic effect was observed. This hypsochromic effect decreased upon exposure to light with time and became zero after about 20 days, but by this time the tablets had almost no visible color left. This phenomenon was observed in all FD&C Blue No. 1 tablets coated by the film-coating method, with or without sunscreening agents, but not with any other groups of tablets.

Analysis of tablets for the amount of sunscreening agent per tablet (based on average of three assays) and of thickness of coatings (based on average of 25 readings) was carried out as previously reported, and results were in excellent agreement with the values reported previously (1).

Table II—Rate Constants for Fading of Color-Coated Tablets with FD&C Blue No. 1 and Approximate Sheflife to Objectionable Fading at 50 Foot-Candles[a]

Sunscreening Agent	Alcohol Film Coating		Modified Sugar Coating		Film Coating	
	$k \times 10^4$, (foot-candles day)$^{-1}$	Shelflife, days $\times 10^{-2}$	$k \times 10^4$, (foot-candles day)$^{-1}$	Shelflife, days $\times 10^{-2}$	$k \times 10^4$, (foot-candles day)$^{-1}$	Shelflife, days $\times 10^{-2}$
Control	2.7	0.3	3.2	0.4	1.7	0.6
Glyceryl *p*-aminobenzoate	2.6	6.3	1.8	0.5	1.4	0
Glyceryl *p*-aminobenzoate (p.c.)	*a*	*a*	*a*	*a*	1.6	0
Benzocaine	3.4	0.3	2.1	0.4	1.2	0.5
Benzocaine (p.c.)	*a*	*a*	*a*	*a*	1.7	0.4
2-Ethoxyethyl *p*-methoxycinnamate	3.3	0.3	3.6	0.4	1.7	0.6
m-Homomenthyl salicylate (n.p.)	5.0	0.2	*a*	*a*	*a*	*a*
m-Homomenthyl salicylate	3.5	0.3	2.8	0.4	3.0	0
n-Octyl salicylate	3.5	0.3	2.8	0.4	3.2	0
Amyl salicylate	3.2	0.3	2.8	0.4	3.2	0

[a] p.c. = protective coat, n.p. = not polished, and *a* = not studied.

Control—The FD&C Blue No. 1 undergoes fading at nearly three times the rate of FD&C Red No. 3 (1). The fading of FD&C Blue No. 1 was shown (10) to be more stable (5–13 times, depending upon the type and intensity of light) than FD&C Red No. 3. One possible explanation for such a difference in results is the difference in overall composition of tablets, *i.e.*, the background material. Lachman *et al.* (10) included the dye and UV absorber within the granulation, while in this study they were applied to tablets as coatings. In the previous study (10) the rate constants were obtained from plots of log absorbance *versus* time whereas in this study the Kubelka–Munk equation was used. The order of fading of the two dyes reported in the present study is in agreement with a study by Vaidya (5).

Glyceryl *p*-Aminobenzoate—When tablets were coated by either alcohol film coating or film coating, a distinct change in hue (blue to green) was noticed. In both cases the tablets had a brilliant shine (prior to polishing). The protective coat does not appear to have any appreciable effect. Although the intensity of color change was slightly smaller than the one without protective coat, it was not significant. The rate constant decreased nearly by half in the case of the film-coating method but this was offset by an almost immediate change of hue. No work was carried out to determine the reaction involved or to isolate a complex if any.

Benzocaine—When the tablets were coated by the film-coating method, a distinct change of hue (blue to green) was observed after about 5 days of light exposure. The shade of hue was very different from the hue change produced by glyceryl *p*-aminobenzoate. A protective coat was applied as described before, without any apparent advantage.

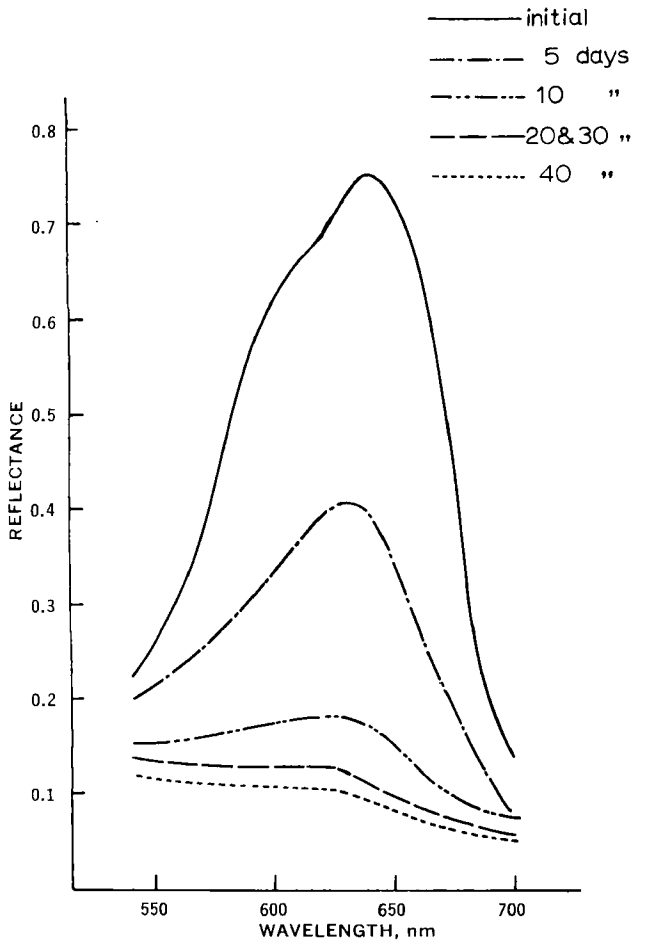

Figure 3—*Visible absorption spectra of control tablets color coated with FD&C Blue No. 1 by alcohol film coating, after intervals of storage under 1000 foot-candles of illumination.*

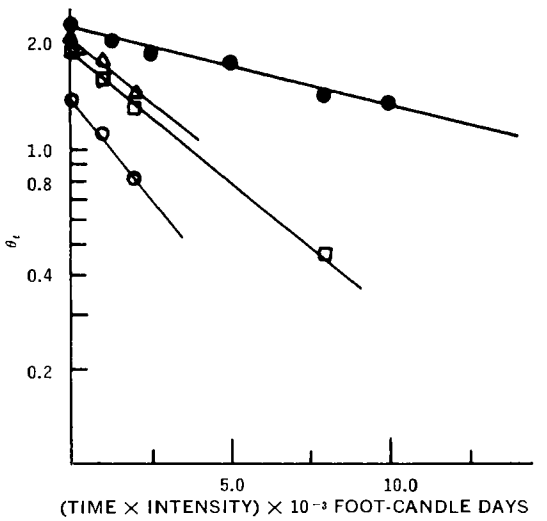

Figure 4—*Plots of* θ_t versus *the product of time and intensity for color-coated tablets. Key:* ●, *FD&C Red No.3, benzocaine, film coating;* △, *FD&C Blue No. 1, benzocaine, modified sugar coating;* □, *FD&C Blue No. 1, 2-ethoxyethyl* p*-methoxycinnamate, film coating; and* ○, *FD&C Blue No. 1, amyl salicylate, film coating.*

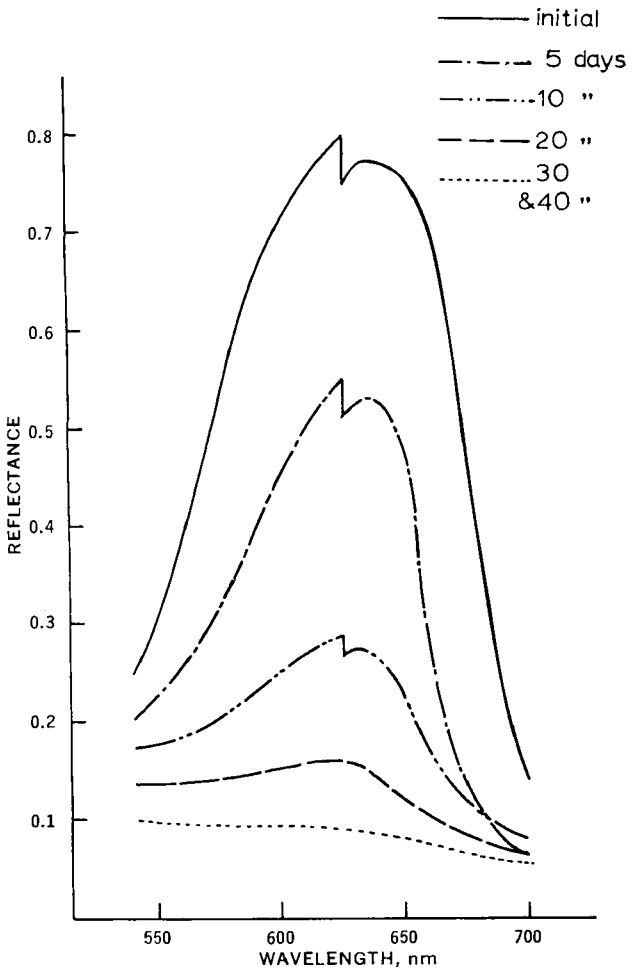

Figure 5—*Visible absorption spectra of tablets color coated with FD&C Blue No. 1 with 2-ethoxyethyl* p-*methoxycinnamate by film-coating technique, after intervals of storage under 1000 foot-candles of illumination.*

2-Ethoxyethyl *p*-Methoxycinnamate—A brilliant shine was observed when tablets were coated by the alcohol film-coating method or by the film-coating method. This did not alter the shelflife or the rate constant significantly. This compound does not appear effective as a protectant for FD&C Blue No. 1.

Salicylates—Tablets coated by the film-coating method for all salicylates appeared mottled after 24 hr of drying, due to cracking of film. When compared to control tablets, all salicylates were equally ineffective as light protectants.

None of the six sunscreening agents employed in the present study exhibited protective action for FD&C Blue No. 1 when applied in concentrations ranging from around 10 to 400 μg/tablet by the alcohol film-, modified sugar-, or film-coating method.

SUMMARY

The photostability effect of six sunscreening agents (glyceryl *p*-aminobenzoate, benzocaine, 2-ethoxyethyl *p*-methoxycinnamate, *m*-homomenthyl salicylate, *n*-octyl salicylate, and amyl salicylate) on FD&C Blue No. 1 was evaluated by exposing tablets to intense measured light.

The sunscreening agents were applied by alcohol film-, modified sugar-, and film-coating methods. The film-coating method employed was not satisfactory for glyceryl *p*-aminobenzoate (with or without protective coat), benzocaine, and all salicylates used in this study. The alcohol film-coating method was also not satisfactory for glyceryl *p*-aminobenzoate.

The rate constant for FD&C Blue No. 1 was about three times greater than for FD&C Red No. 3. Red No. 3 thus shows relatively greater fastness to light when applied in the form of a coating. None of the sunscreening agents applied by any of the three methods exhibited significant protective action for FD&C Blue No. 1.

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