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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 cm² (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.

strength gelatin syrup and white subcoating dusting powder. After tablets were completely dry, the color coating was applied. Plain coating syrup (170 g sucrose and 100 ml deionized water) and color syrup (0.300 g dye in 100 ml plain coating syrup) in the following ratios were applied. Five coats of 25 ml each in 15:1 parts, followed by 10 coats of 25 ml each in 10:1 parts, followed by 10 coats of 27 ml each in 5:1 parts, and finally 12 coats of 27 ml each in 2:1 parts of plain syrup and color syrup, respectively.

Application of Sunscreening Agents—Since the sunscreening agents used were insoluble in water, the following three coating methods were developed: alcohol film, modified sugar, and film. The coating was performed on the thoroughly dried color-coated tablets in batches of 500 g. One coat of 2 ml and four coats of 1.5 ml coating solution were applied in each case. After drying thoroughly, tablets were polished, where mentioned, with carnauba wax pieces in a canvas-lined pan. In each case, a set of control tablets was coated using the same solutions without the sunscreening agent.

Alcohol Film Coating—The formula of 5% sunscreening agent and ethanol (95%) *q.s.* was used for all sunscreening agents except benzocaine, which was applied in 0.5% concentration. In earlier experiments, it was found that 5% benzocaine caused mottled tablets.

Tablets coated with glyceryl *p*-aminobenzoate had a "wet" feeling even after drying for 24 hr at ambient temperature. Tablets coated with 2-ethoxyethyl *p*-methoxycinnamate and *m*-homomenthyl salicylate were shiny even before they were polished. A portion of the tablets coated with *m*-homomenthyl salicylate was left unpolished to compare the difference between polished and unpolished tablets.

Modified Sugar Coating—The coating solution consisted of one part of alcohol film-coating solution and 10 parts of diluted color syrups [color syrup-plain syrup (1:2)]. The resulting coating solutions were turbid with the exception of those containing glyceryl *p*-aminobenzoate and benzocaine, which were clear solutions.

Film Coating—The coating solution consisted of equal parts of Solutions A and B. Solution A consisted of 10% cellulose acetate phthalate, 4% polyethylene glycol 4000, and acetone *q.s.* Solution B consisted of 10% sunscreening agent and ethanol (95%) *q.s.*

The finished coat was uniform, hard, smooth, and glossy. However, tablets coated with salicylates had a mottled appearance after 24 hr of drying at ambient temperature. The mottled appearance was due to cracking of the film coating. A reported formula (12) for film coating was tried but did not appear satisfactory for these sunscreening agents.

Equipment—The following were used: a light cabinet used by Vaidya (12), similar to that described by Lachman *et al.* (14); a light meter[6] (range 0–5000 foot-candles); a spectrophotometer[7] with reflectance attachment (12, 14) with magnesium carbonate blocks; and a micrometer caliper[8].

Exposure to Light—Adequate samples of each set of color-coated tablets were placed in flat, white, paper trays in the light cabinet. The lower surfaces of samples were marked so as to distinguish the surface exposed to incident light. The intensity of light was maintained at a constant level of 1000 foot-candles while the temperature remained at 26 ± 2°. Regular checks were made of light intensity and temperature. Heat build-up was prevented by a constantly operating fan.

Measurement of Color Change—Samples were withdrawn from the light cabinet at designated time intervals, and the reflectance of the tablets was measured using the transmittance scale. Measurements were made between 450 and 575 nm for each sample at appropriate wavelength intervals and at the maximum for the dye (535 nm). The color of tablet samples was also evaluated by visual observation at various time intervals. This procedure is in keeping with a previous report (15) which described the importance of visual observation as a method for following color change.

Determination of Sunscreening Agents per Tablet—One hundred tablets were extracted with 150 ml ether. The ethereal layer was washed with 3 × 100 ml of deionized water to remove traces of color and water-soluble compounds. The clear ethereal layer was separated and evaporated to dryness. The residue was dissolved in alcohol, dilutions were made, and the agent was determined quantitatively at 295 nm for glyceryl *p*-aminobenzoate, at 292.5 nm for benzocaine, at 311 nm for 2-ethoxyethyl *p*-methoxycinnamate, at 305 nm for *m*-homomenthyl salicylate, and at 306 nm for *n*-octyl salicylate and amyl salicylate.

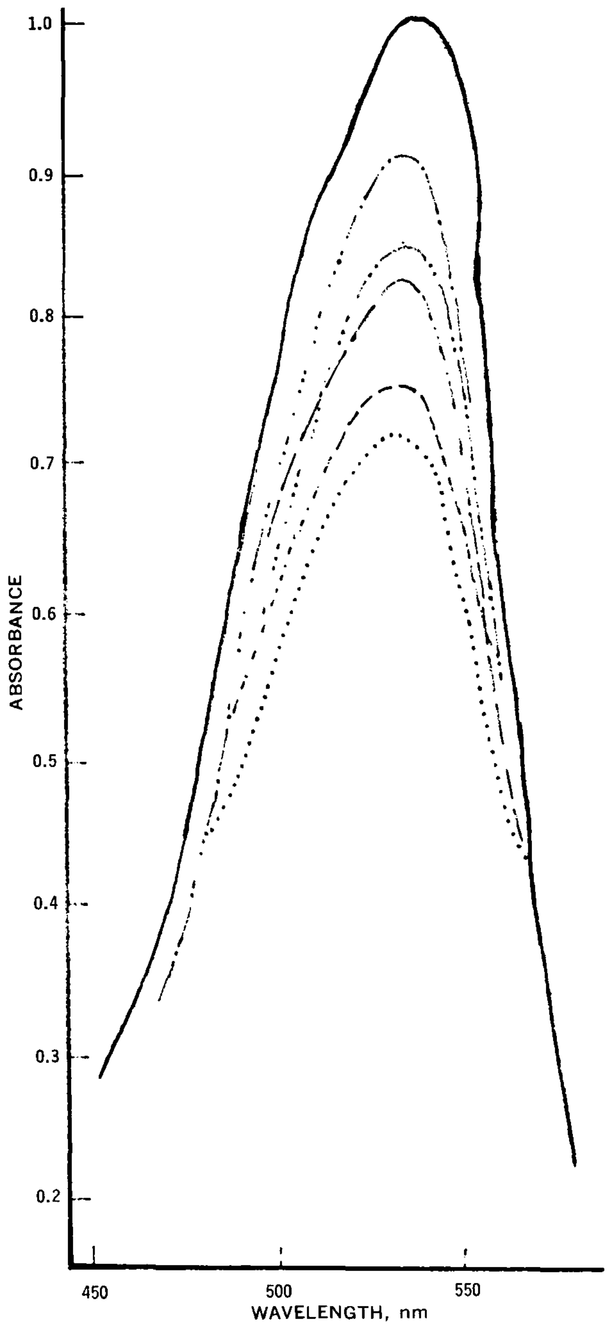

Figure 1—*Visible absorption spectra of control tablets color coated with FD&C Red No. 3 by alcohol film coating, after intervals of storage under 1000 foot-candles of illumination. Key:* ——, *initial;* —·—, *after 5 days;* —··—, *after 10 days;* — — —, *after 20 days;* - - -, *after 30 days; and* ..., *after 40 days.*

RESULTS AND DISCUSSION

The range[9] of thickness of five coatings of sunscreening agent applied by the alcohol film-coating method was 15–20 μm; by the modified sugar-coating method it was 300–400 μm, and by the film-coating method it was 30–40 μm. The greater thickness and

[6] General Electric, type 213.
[7] Beckman DU.
[8] Starrett model 436.

[9] Range of 25 readings on individual tablets.

Table I—Rate Constants for Fading of Color-Coated Tablets with FD&C Red No. 3 and Approximate Shelflife to Objectionable Fading at 50 Foot-Candles

Sunscreening Agent[a]	Alcohol Film Coating		Modified Sugar Coating		Film Coating	
	$k \times 10^5$, (foot-candle day)$^{-1}$	Shelflife, days $\times 10^{-2}$	$k \times 10^5$, (foot-candle day)$^{-1}$	Shelflife, days $\times 10^{-2}$	$k \times 10^5$, (foot-candle day)$^{-1}$	Shelflife, days $\times 10^{-2}$
Control	5.1	2.4	6.1	3.8	3.0	2.4
Glyceryl *p*-aminobenzoate	3.5	0.6	6.6	2.9	2.2	0
Benzocaine	1.9	6.7	4.2	2.9	5.8	2.0
2-Ethoxyethyl *p*-methoxycinnamate	3.1	3.4	2.7	6.0	2.5	8.0
m-Homomenthyl salicylate (n.p.)	3.0	6.0	—[b]	—[b]	—[b]	—[b]
m-Homomenthyl salicylate	2.1	6.1	2.0	6.6	2.7	0
n-Octyl salicylate	1.4	3.6	1.9	6.8	2.7	0
Amyl salicylate	6.3	2.0	3.8	5.0	3.2	0

[a] n.p. = not polished; all others were polished. [b] Not studied.

range with the modified sugar-coating method are due to the presence of sugar.

Amount of Sunscreening Agent Applied on Tablets as a Coating—The theoretical yield for tablets coated by the alcohol film-coating method was 400 μg/tablet, except for tablets coated with benzocaine where it was 40 μg/tablet. The theoretical yield for tablets coated by the modified sugar-coating method was 40 μg/tablet; for tablets coated by the film-coating method, it was 400 μg/tablet.

The average (of three assays) amount of sunscreening agent found was approximately two-thirds of the theoretical amount. The remaining unaccounted for sunscreening agent was probably "lost" in the coating procedure by adhering to the inside of the coating pan, hand, *etc.* The only exceptions were:

1. Tablets coated with glyceryl *p*-aminobenzoate. *Alcohol film method*—The amount present was only 40–50 μg/tablet, and it appears that a definite chemical reaction occurred which resulted in a change of hue. *Modified sugar-coating method*—No hue change was observed apparently because the amount present was very little (8–10 μg/tablet). *Film-coating method*—the hue change was marked, and the amount found ranged from 300 to 310 μg/tablet. In no case was any attempt made to isolate degradation product(s) of the dye or the sunscreening agent.
2. Tablets coated with salicylates using film-coating method. It was not possible to recover more than 10–20 μg/tablet.

Influence of Sunscreening Agents—The reflectance curves of tablets were recorded, and a typical curve is shown in Fig. 1. To evaluate the effect of sunscreening agents on FD&C Red No. 3, the Kubelka-Munk equation (Eq. 1) was used:

$$\ln \theta_t = -ktI + \ln \theta_t' \qquad \text{(Eq. 1)}$$

where $\theta_t = (1 - R)^2/2R$ in which R is the reflectance at the absorbance maximum at time t, I is the intensity in foot-candles, and k is an apparent first-order rate constant; θ_t' is θ_t at $t = 0$. The theoretical concepts of the Kubelka-Munk equation and its wide use were described elsewhere (8, 9).

Figure 2 shows typical plots of θ_t *versus* product of time and intensity. The fading of FD&C Red No. 3 fits a first-order rate equation in the presence and absence of sunscreening agents. The first-order rate constants were calculated (Table I), and the rate constant for this dye is different than those reported previously (3, 8). The difference is due to the differences in the overall composition of the coating plus the background material. Previous investigators included the dye and UV absorber within the granulation, while in this study they were applied to the tablet as coatings.

Visual observations were made on all tablets (Table II). A scale value of 1, 2, or 3 (fading less than, similar to, or greater than the control, respectively) was arbitrarily assigned. The time at which objectionable fading or appearance was seen, in the opinion of the author, was also noted. To determine the shelflife of coated tablets, the light intensity in a well-illuminated room was taken as 50 foot-candles. By substituting $I = 50$ in Eq. 1, the approximate shelflife in days was calculated for the minimum acceptable value of θ_t (Table I).

When compared with values for control tablets (Table I), it is apparent that the rate constant decreases to almost half when

Table II—Visual Observations of Tablets Coated with FD&C Red No. 3 Exposed to an Intensity of 1000 Foot-Candles of Light over 40 Days

Sunscreening Agent	Coating Type[a] Alcohol Film	Modified Sugar	Film
Control	Noticeable fading becoming objectionable within 20–30 days		
Glyceryl *p*-aminobenzoate	1A	3	1A
Benzocaine	1	2–3	3
2-Ethoxyethyl *p*-methoxycinnamate	2	1	1
m-Homomenthyl salicylate (not polished)	1	Not studied	Not studied
m-Homomenthyl salicylate	1	1	2A
n-Octyl salicylate	2	1	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, and 3 = fading greater than control. All polished except as noted.

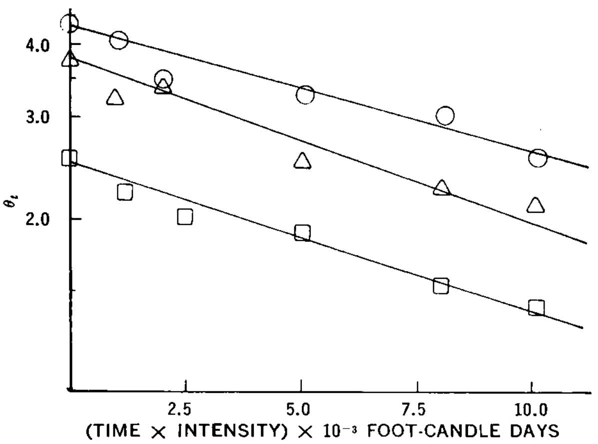

Figure 2—*Plots of* θ_t versus *the product of time and intensity for tablets color coated with FD&C Red No. 3. Key:* ○, *control, alcohol film coating;* △, *glyceryl* p*-aminobenzoate, modified sugar coating; and* □, *benzocaine, film coating.*

Table III—Relative Protective Action of Sunscreening Agents for FD&C Red No. 3

Sunscreening Agent	Type of Coating	Days $\times$ 10^{-2}
2-Ethoxyethyl *p*-methoxycinnamate	Film	8.0
n-Octyl salicylate	Modified sugar	6.8
Benzocaine	Alcohol film	6.7
m-Homomenthyl salicylate	Modified sugar	6.6
None (control)	Average of three methods	2.9

film coating is applied. However, a decrease in the rate constant does not necessarily indicate an increase in shelflife.

Glyceryl p-*Aminobenzoate*—When tablets were coated by either alcohol film coating or film coating, a distinct change of hue was noticed. The hue change was not observed with the modified sugar method, perhaps because of the small amount of glyceryl *p*-aminobenzoate found in the tablets coated with the modified sugar coating or perhaps because the combination with sugar had some influence on the rate of hue change. The rate constant is not much different from the control except for tablets coated with the alcohol film coating where it is considerably smaller. The hue change is the reason for the decrease in shelflife to as much as a fourth. The shelflife is zero for tablets coated by the film-coating method since the color change is immediately noticed following the application of the sunscreening agent.

Benzocaine—For FD&C Red No. 3 protected with benzocaine, the rate constant varied considerably from one method to another. It is lowest for the alcohol film-coating method which reduced color change to about half of that found for the control tablets.

2-Ethoxyethyl p-*Methoxycinnamate*—This compound appears to have a distinct protective action on FD&C Red No. 3 when applied as a tablet coating by either the modified sugar-coating or the film-coating method. The longest shelflife of 800 days was calculated for tablets coated by the film-coating method. A brilliant shine was also noticed.

m-*Homomenthyl Salicylate*—Tablets coated with FD&C Red No. 3 appear to be most effectively protected with *m*-homomenthyl salicylate when it is applied by the alcohol film-coating or the modified sugar-coating method.

Polished tablets had a smaller rate constant than unpolished tablets. This may be due to the fact that polished tablets can "reflect" light whereas unpolished tablets "absorb" light. Thus, polished tablets should have a longer shelflife. However, based on visual observation, there did not seem to be any significant difference.

Tablets coated by the film-coating method for all salicylates appeared mottled after 24 hr of drying, due to cracking of the film.

n-*Octyl Salicylate*—FD&C Red No. 3 is best protected by *n*-octyl salicylate when applied by the modified sugar-coating method. Although the rate constant is not much different from that for the alcohol film method, a longer shelflife (almost double) for tablets was found where the coating had been applied by the modified sugar-coating method. The rate constant obtained for the alcohol film-coating method was lower than that obtained for any other sunscreening agent by any other method.

Amyl Salicylate—When applied by the alcohol film method, it yielded the highest rate constant among all sunscreening agents. The shelflife is even lower than that of the control. When coated by the modified sugar-coating method, the shelflife is about a third better than the control.

SUMMARY AND CONCLUSION

The photostabilizing effect of six sunscreening agents (glyceryl *p*-aminobenzoate, benzocaine, 2-ethoxyethyl *p*-methoxycinnamate, *m*-homomethyl salicylate, *n*-octyl salicylate, and amyl salicylate) on FD&C Red No. 3 was evaluated by exposing tablets to intense measured light. Three processes were developed for application of these agents on color-coated tablets: alcohol film-coating, modified sugar-coating, and film-coating methods. The film-coating method was not satisfactory for glyceryl *p*-aminobenzoate and all of the salicylates used.

The Kubelka-Munk equation was used to study the kinetics of fading. FD&C Red No. 3 followed a first-order rate of fading. The approximate shelflives for color-coated tablets with and without sunscreening agents were calculated.

The relative protective action of sunscreening agents for FD&C Red No. 3 in terms of shelflife is listed in Table III.

It is quite difficult to correlate rate constants obtained from plots of θ_t *versus* time-intensity units with shelflives obtained from data based on visual observation. It was not uncommon to observe that the rate constant was essentially the same for two sets of tablets whose shelflife varied from zero days to several hundred days. Visual observation together with scientifically sound constants or units is an invaluable aid to the pharmaceutical formulator.

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