Rapid Evaluation of Effect of Excipients on Color Fading II

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Abstract □ Model solutions of certified dyes (FD&C Blue No. 2, FD&C Yellow No. 5, and FD&C Yellow No. 6) were exposed, alone or with added selected excipients, in a fadeometer to accelerate light-induced color fading. At predetermined intervals, the solutions were tested spectrophotometrically. The method is a valuable rapid screening technique for predicting the comparative light stability of dyes used in pharmaceutical formulations.

Keyphrases □ Colorants, FD&C Blue No. 2, FD&C Yellow No. 5, and FD&C Yellow No. 6—rapid evaluation of effect of excipients on color fading □ Certified dyes—effect of excipients on color fading, method for evaluation □ Dyes, certified—effect of excipients on color fading, method for evaluation

Coloring agents have been used in medicine since ancient times to achieve a more attractive appearance. Recently, colors have become even more important in pharmaceuticals due to the necessity of rapid product identification. Natural dyes, usually obtained from the plant or animal kingdom, were gradually replaced in modern medicine by synthetic products with well-defined stability and uniformity. However, many artificial coloring agents previously permitted for foods and pharmaceuticals were recently eliminated or their use was severely restricted because of intensive research showing carcinogenesis or teratological damage in animals when massive doses of the coloring agents were used. "Martindale's Extra Pharmacopoeia" (1) lists 39 synthetic coloring agents used in food products. The size of this list, however, is sharply reduced if one selects only those approved in most industrialized countries, because the legislation regulating colorants varies widely. Only three synthetic coloring agents are almost universally accepted (2): FD&C Yellow No. 5, FD&C Yellow No. 6, and FD&C Blue No. 2. The objective of this study was to develop a rapid screening method for evaluating the compatibility of these three coloring agents with generally used excipients in pharmaceutical formulations.

Table I—Composition of Sample Solutions

Colorant		Additive	
Name	%	Name	%
FD&C Yellow No. 5	0.025	—	—
	0.025	Lactose	0.25
	0.025	Sucrose	0.25
FD&C Yellow No. 6	0.025	—	—
	0.025	Lactose	0.25
	0.025	Sucrose	0.25
FD&C Blue No. 2	0.030	—	—
	0.030	Lactose	0.75
	0.030	Sucrose	0.75
	0.030	Poloxalene	0.075
	0.030	Polyethylene glycol 6000	0.075
	0.030	Polyvinyl-pyrrolidone	0.075
	0.030	Citric acid	0.075
	0.030	Ascorbic acid	0.015

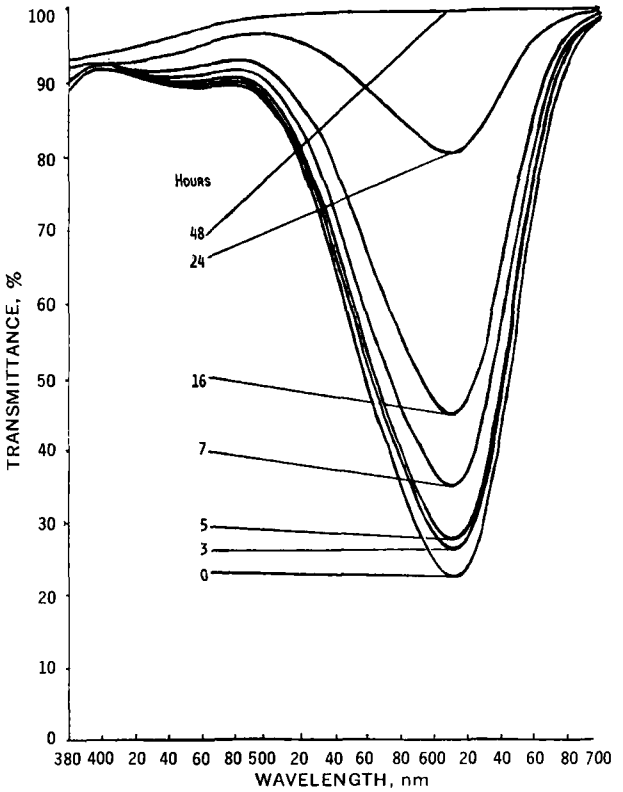

Figure 1—*Typical transmittance curves of dye solutions exposed in the fadeometer.*

It was reported earlier (3) that the fadeometer can be used successfully to predict the color stability of tablets. In the present study, the fadeometer was used also as the principal tool to obtain accelerated data on the color stability of model solutions prepared with the three selected colorants. Frequently used water-soluble excipients were added to the model solutions to study their effects on fading. These results were compared with those obtained using standard, more time-consuming techniques.

EXPERIMENTAL

Materials—The following were used: FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6 (yellow orange S), FD&C Blue No. 2 (indigo carmine), lactose USP, sucrose USP, polyvinylpyrrolidone, poloxalene [poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene)], polyethylene glycol 6000, citric acid USP, and ascorbic acid USP.

The listed materials were obtained from commercial sources in reagent or pharmaceutical grade and were used without further purification.

Equipment—A light stability cabinet, equipped with 12 30-w

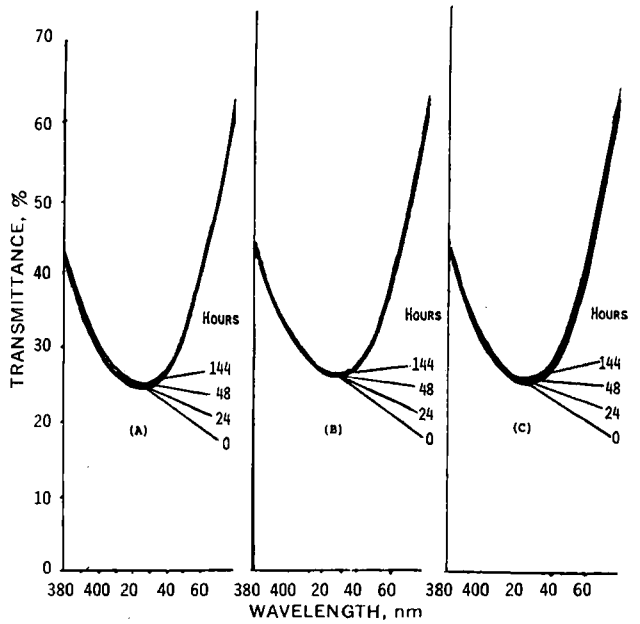

Figure 2—*Fading of FD&C Yellow No. 5 solutions. Key: (A), dye only; (B), dye plus lactose; and (C), dye plus sucrose.*

fluorescent tubes[1] and four 20-w fluorescent tubes[2], was used. The light was adjusted so that the illumination at the surface of the center of the shelf was 1100 foot candles as measured with a foot candle light meter[3].

The fadeometer[4] was equipped with a carbon arc, 167.4 w/ft^2,

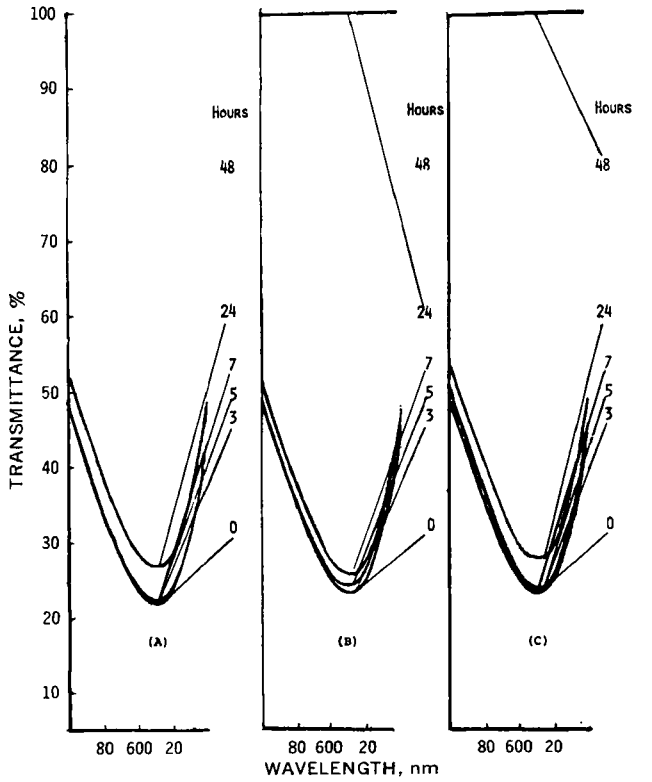

Figure 3—*Fading of FD&C Blue No. 2 solutions. Key: (A), dye only; (B), dye plus lactose; and (C), dye plus sucrose.*

[1] Cool White, Westinghouse, F30T8/CW.
[2] Cool White, General Electric F20T12/CW.
[3] Gossen Tri-Lux.
[4] Atlas Fade-Ometer, model FO-2428, Type FDA-R.

Table II—Discoloration of FD&C Blue No. 2 Solutions with Excipients Using the Fadeometer

Excipient	$t_{90\%}$, hr	Relative Order[a]
None	42.0	0
Poloxalene	30.0	1
Polyethylene glycol 6000	21.4	2
Polyvinylpyrrolidone	3.5	3
Citric acid	2.4	4
Ascorbic acid	1.5	5

[a] Relative order of initial fading velocity values.

sample distance 25.4 cm (3). Two recording spectrophotometers were utilized[5,6].

Preparation of Samples—The applied solutions are listed in Table I. Aliquots (12 ml) of the solutions were transferred into transparent glass containers and exposed in the fadeometer or the light cabinet. At predetermined intervals, the samples were withdrawn, 5.0-ml aliquots of the irradiated solutions were diluted to 100.0 ml, and transmittance (or absorbance) curves were obtained with the aid of a spectrophotometer. (A typical set of transmittance curves is shown in Fig. 1.) Total exposure time was 24–144 hr in the fadeometer and up to 12 days in the light cabinet.

RESULTS AND DISCUSSION

The earlier study using tablets showed that the intensive light source of the fadeometer caused a discoloration about 50–100 times greater than the light cabinet; therefore, a 24-hr exposure in the fadeometer was usually sufficient to judge the relative color stability of the system (3). In the first of the recent experimental series, the sample solutions were exposed in the fadeometer for 24 hr; however, the yellow solutions showed practically no fading during this time. Therefore, the experiment with the yellow solutions was continued in the fadeometer for up to 144 hr. Figure 2 shows the transmittance curves of the exposed FD&C Yellow No. 5 solutions.

Apparently, these solutions did not fade at all in 24 hr. FD&C Yellow No. 6 solutions yielded similar curves, indicating very good stability under the experimental conditions. On the other hand, the FD&C Blue No. 2 solutions faded quite signifi-

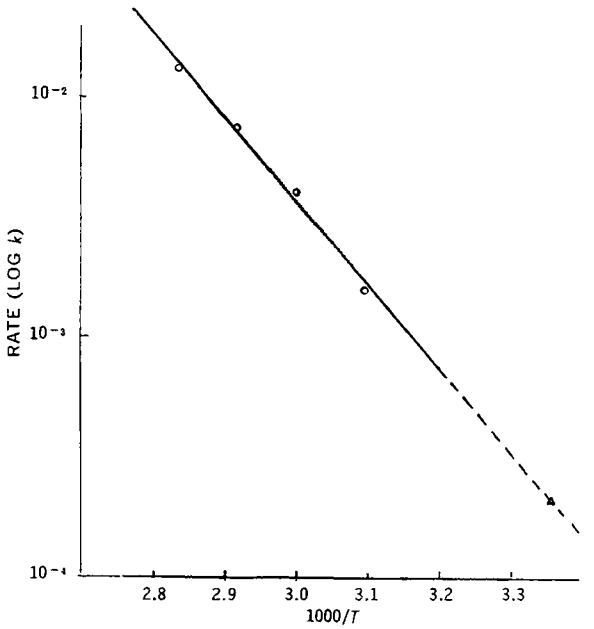

Figure 4—*Arrhenius plot for fading of 0.03% FD&C Blue No. 2 solution (pH 7).*

[5] Model "Hardy," General Electric.
[6] Cary model 14.

Table III—Discoloration of FD&C Blue No. 2 Solutions with Excipients Using the Light Cabinet

Excipient	$t_{90\%}$, days	Relative Order[a]
None	9.1	0
Poloxalene	4.3	1
Polyethylene glycol 6000	3.3	2
Polyvinylpyrrolidone	0.7	3
Citric acid	0.6	4
Ascorbic acid	0.2	5

[a] Relative order of initial fading velocity values.

cantly (Fig. 3). After 24 hr, the dye solution without additive was visibly faded and the excipients had accelerated the discoloration so rapidly as to show 100% transmittance at 610 nm in 24–48 hr. The log A values plotted *versus* time showed a rather slow initial rate (correlated to the induction period), followed later by a rapid discoloration. Since a 10% decrease in the color is observable, $t_{90\%}$ values were determined from the initial fading rates using the following equation:

$$t_{90\%} = \frac{2.303}{k} \log \frac{100}{90} \qquad \text{(Eq. 1)}$$

The data showed that the addition of the lactose accelerated the discoloration significantly, while the sucrose increased the fading at a much slower rate: $t_{90\%}$ (in hours), dye only, 42.0; dye plus lactose, 15.8; and dye plus sucrose, 36.5 (fadeometer exposure).

For the purposes of this study, the FD&C Blue No. 2 (indigo carmine) was selected as the model for further investigation. The buffered dye solution (pH 7) at room temperature fades comparatively slowly. Rate-temperature dependence curves for 0.03% FD&C Blue No. 2 solution were obtained in the usual manner by determining the absorbance maxima of the light-protected solutions kept at various temperatures. By extrapolating the log k *versus* $1/T$ plot, the half-life was found to be 234 days at 25° (Fig. 4).

The degradation of indigo carmine has been investigated (4–10). It was shown that, among others, organic acids, reducing agents, polyalcohols, and certain ions accelerate the color transition from dark blue to pale yellow. In the present study, selected pharmaceutical excipients belonging to one or more of these groups of chemicals were added to the dye solution and exposed in the fadeometer and the rates of discoloration were determined in the described manner (Table II).

For the purpose of comparison, the solutions listed in Table II were also kept in the light cabinet for up to 256 hr, exposed to 1100 foot candles illumination. Fading rates from this test series are listed in Table III.

As expected, the solutions in the light cabinet faded at a slower rate but in the same relative order of fading velocity as in the fadeometer.

It is evident that the fading of the indigo carmine solution is accelerated in the presence of the tested excipients. Other conditions being constant, the rates vary with the type of additive. In solid dosage forms, however, the interaction of these excipients and the rate of fading may be different. In a followup study, model tablets incorporating the listed excipients will be exposed to the fadeometer with the aid of a suitable holder and the rate of discoloration will be determined from the periodically obtained reflectance curves (3) to compare the actual fading of the tablets with the discoloration pattern of the dye solutions.

CONCLUSIONS

This study shows that the fadeometer method of exposing dye solutions with prospective excipients and the subsequent spectrophotometric testing for discoloration appears to be a rapid screening technique for aiding the pharmaceutical formulator in selecting the most suitable additives and eliminating those capable of accelerating the rate of fading.

In addition, the results of the experiments with FD&C Blue No. 2 corroborate earlier investigations and indicate the following:

1. Lactose accelerates the discoloration of the dye solution more than the nonreducing sucrose; however, due to its hydrolysis, even sucrose promotes the fading of the solution.

2. The poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) wetting agent and polyethylene glycol have only a moderate effect on the fading rate.

3. Polyvinylpyrrolidone and particularly the strongly reducing ascorbic acid and polycarboxylic citric acid cause a rapid fading of the indigo carmine solution.

Under the experimental conditions, solutions of FD&C Yellow No. 5 and FD&C Yellow No. 6 (alone or with added lactose or sucrose) show practically no fading when exposed to the accelerated light effect of the fadeometer.

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