Rapid Determination of Color Stability of Tablet Formulations

P. TURI▲, D. BRUSCO, H. V. MAULDING, R. A. TAUSENDFREUND, and A. F. MICHAELIS

Abstract □ Compressed and sugar-coated tablets containing certified dyes were exposed to light under controlled conditions. Samples were subjected to the light directly in an open Petri dish as well as in a variety of containers. The color change was measured with the aid of a recording spectrophotometer, equipped with an integrating sphere. Interpretation of the reflectance curve and quantitative measurement of the color characteristics were achieved by a computer system. Data obtained in the fadeometer in 24 hr., as well as results from exposure in the light cabinet for 28 days, facilitate the comparative evaluation of color stability.

Keyphrases □ Color stability of tablets—rapid determination, fadeometer □ Discoloration of tablets—rapid determination of color stability □ Tablets containing dyes—rapid determination of color stability □ Light stability of tablets containing dyes—rapid determination

Color fading is one problem that the industrial pharmacist almost always has to face. Exposed to sunlight or artificial light (particularly the shorter wavelength portion of the radiation), dyes approved for use in the pharmaceutical industry undergo discoloration. This phenomenon and its mechanism were investigated by several researchers, and certain aspects of reducing the light effect and decelerating the fading of tablets were reported. The color stability of soluble dyes and lakes was compared (1), the protective effect of colored glass containers was investigated (2), and the presence of UV absorbers, sugars, antioxidants, and other factors influencing color stability was studied (3, 4). Rates of degradation were determined in liquids as well as in solid dosage forms, indicating good to fair correlations with zero-order, first-order, or apparent first-order kinetics (1, 5, 6).

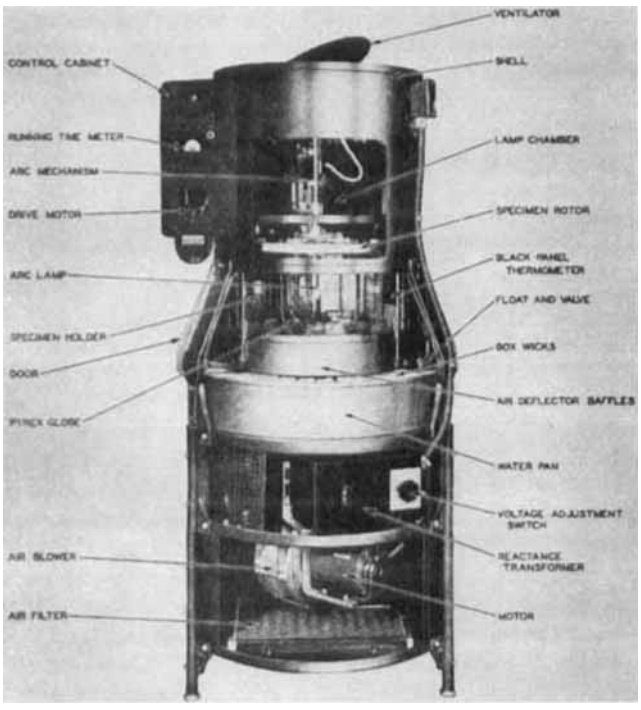


Figure 1—*Cutaway view of fadeometer.*

Table I—Composition of Tablets Studied

	Amount, mg.
Compressed Tablet	
Composition	
Lactose powder USP	56.340
Avicel	25.000
Starch USP	12.500
Polyvinylpyrrolidone	5.000
Magnesium stearate USP	1.000
FD&C Yellow No. 5, aluminum lake, (24–26%), jet-milled	0.045
FD&C Blue No. 1, aluminum lake, (11–13%), jet-milled	0.115
Alcohol, specially denatured No. 30	*q.s.*
Purified water USP	*q.s.*
	100.000
Sugar-Coated Tablet A	
Composition (of coating)	
Acacia USP	3.65
Talc USP	16.15
Titanium dioxide USP	0.6385
Sorbitol USP	0.0558
Sucrose USP	78.4192
Polyvinylpyrrolidone	0.0096
Sodium benzoate USP	0.0192
FD&C Red No. 2 aluminum lake (40%)	0.1000
FD&C Red No. 3 aluminum lake (18%)	0.6385
FD&C Red No. 5 aluminum lake (34%)	0.1596
FD&C Yellow No. 6 aluminum lake (40%)	0.1596
Total coating thickness: 0.7 mm.	100.0000
Color-containing layer thickness: 0.27 mm.	
Sugar-Coated Tablet B	
Composition (of coating)	
Acacia USP	11.5
Talc USP	57.0
Sucrose USP	190.5
Pink color composition aluminum lake[a]	6.0
Total coating thickness: 0.81 mm.	265.0
Color-containing layer thickness: 0.16 mm.	

[a] Contains 0.023 ± 0.008 mg. FD&C Red No. 3 dye.

The objective of the present study was to establish a rapid method to evaluate relative light stability of tablets containing dyes or dye mixtures.

EXPERIMENTAL

Materials—The materials used are listed in Table I.

Equipment—A light stability cabinet, equipped with 12 30-w. fluorescent tubes[1] and four 20-w. fluorescent tubes[2], was used. The

[1] Cool White, Westinghouse F30T8/CW.
[2] Cool White, General Electric F20T12/CW.

Table II—Fading Characteristics of Sugar-Coated Tablet B (Open Exposure)

Fadeometer		Light Cabinet	
Hours	$\log \frac{1}{R}$	Days	$\log \frac{1}{R}$
0	0.6000	0	0.6000
1	0.4935	1	0.5100
3	0.4400	5	0.4597
7	0.4001	7	0.4248
—	—	14	0.3535
—	—	21	0.3363
24	0.3354	28	0.3206

light was adjusted in such a manner that the illumination at the surface of the center of the shelf was 1100 ftc. as measured with a foot candle light meter[3].

The fadeometer[4] was equipped with a carbon arc, 167.4 w./sq. ft., sample distance 25.4 cm. (10 in.) (Fig. 1).

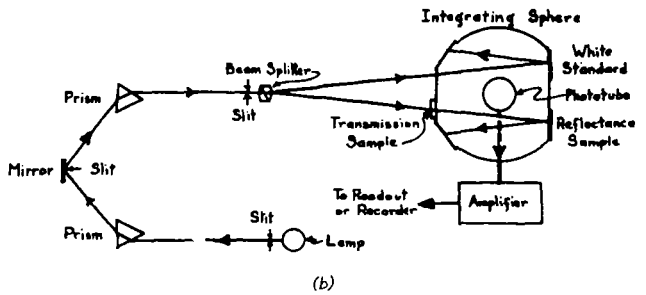
The recording spectrophotometer[5] was equipped with an automatic tristimulus integrator and with an integrating sphere coated inside with a smoked surface of magnesium oxide. Barium sulfate was used as the reference standard (Figs. 2*a* and 2*b*).

Preparation of the Tablet Samples —*Direct Exposure*—In the fadeometer: Uncoated tablets were glued onto special holders, originally designed for colored fabric or paper samples, and were attached to the holders of the fadeometer (Fig. 3). For coated tablets, a series of metal plates was made with circular holes. The tablets were taped to a selected plate having holes with a diameter approximately 2 mm. less than the diameter of the tablets. The plates were finally masked with aluminum foil cut in such a manner as to allow two tablets to be exposed at a time.

In the light cabinet: Samples were exposed in an open Petri dish at the center of the shelf.

Tablets in Containers—Tablets in amber glass or opaque high density polyethylene containers were arranged in such a manner that a set of tablets was held, with the aid of a cotton fill, against the wall of the container facing the light source, either in the fadeometer or in the light cabinet.

(a)



(b)

Figure 2—(a) *The spectrophotometer with automatic digital readout system.* (b) *Schematic diagram of recording spectrophotometer* (9).

[3] Gossen-Tri-Lux.
[4] Atlas Fade-Ometer, model FO-2428, type FDA-R.
[5] General Electric (Hardy).

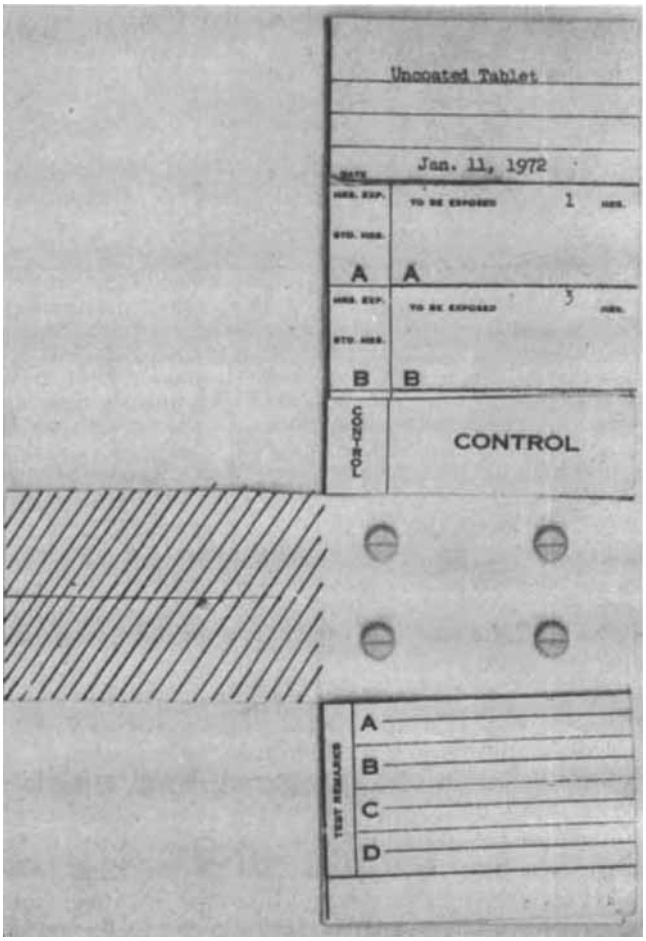


Figure 3—*Sample holder for the fadeometer (7- and 24-hr. lids are open to allow the exposure of the tablets).*

Procedure and Results—Tablets exposed either in the fadeometer or in the light cabinet were periodically withdrawn and reflectance values were determined by the recording spectrophotometer. Total exposure time was 24 hr. in the fadeometer and 21–30 days in the light cabinet. (Typical reflectance curves are shown in Figs. 4 and 5.)

Log $1/R$ values were calculated at the wavelength of the minimum reflectance, plotted against time, and rates of degradation were determined from the linear portions of the curves. (A typical example is shown in Table II and Fig. 6.)

DISCUSSION

Fadeometers as tools for predicting relative light fastness have been used extensively in the textile and paper industry. Without

Table III—Fading Rates of Colored Tablets

	Fadeometer ($hr.^{-1}$)		Light Cabinet ($days^{-1}$)	
	$K_1 \times 10^3$	$K_2 \times 10^3$	$K_1 \times 10^3$	$K_2 \times 10^3$
Coated Tablets A (open)	2.6	0.6	1.5	0.6
Coated Tablets B (open)	97.8	12.1	49.5	16.7
Compressed tablets (open)	146.3	9.1	77.2	19.1
Compressed tablets (natural high density polyethylene)	116.4	4.0	58.8	21.1
Compressed tablets (opaque high density polyethylene)	21.1	6.3	30.4	9.3
Compressed tablets (amber glass)	53.8	6.7	12.4	8.2

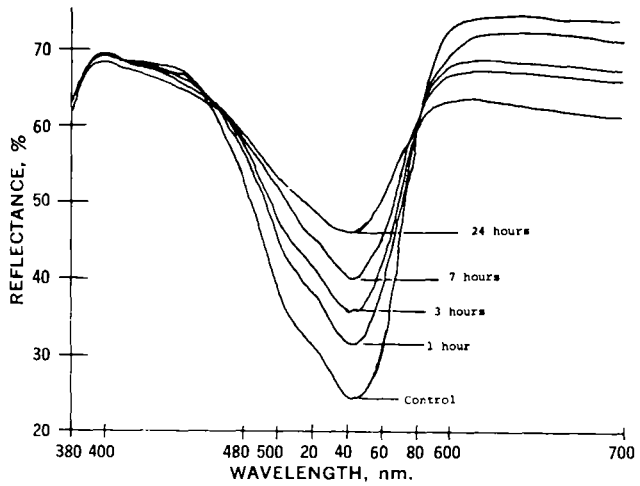


Figure 4—*Effect of time on reflectance as a function of wavelength, using sugar-coated Tablet B, the fadeometer, and direct exposure.*

claiming direct convertibility to the exposure to sunlight (which is, of course, dependent on weather conditions, geographic location, and many other factors), fadeometers were used successfully for the stated purpose. By comparing the relative energy distribution of the natural light, the carbon arc lamp used in the fadeometer, and the fluorescent lamps of commercially used light cabinets (Fig. 7), it is quite obvious that a sizable portion of the radiation of the carbon arc lamp lies in the UV region, while the other sources radiate mostly in the visible region.

Both the compressed and sugar-coated tablets show similar fading characteristics when exposed to exaggerated illumination in either the fadeometer or the light cabinet. After an initial induction period of rapid fading, represented by K_1 (usually 1–2 hr. in the fadeometer or 1–3 days in the light cabinet), the rates decrease; the obtained values indicate an apparent first-order reaction.

Earlier investigations (7, 8) proved that the Kubelka-Munk function:

$$\theta = \frac{(1 - R)^2}{2R} \qquad \text{(Eq. 1)}$$

where R is the light reflectance, applies well for determining the rates of color fading of tablets as long as the dye concentration varies. A linear relation was established when the log θ was plotted *versus* the product of the time and intensity. However, if the dye concentration is constant (as under our experimental conditions), the K

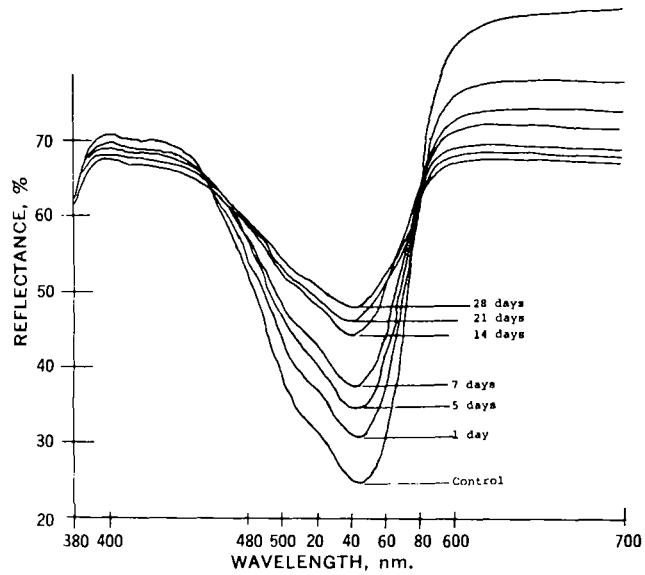


Figure 5—*Effect of time on reflectance as a function of wavelength, using sugar-coated Tablet B, the light cabinet, and direct exposure.*

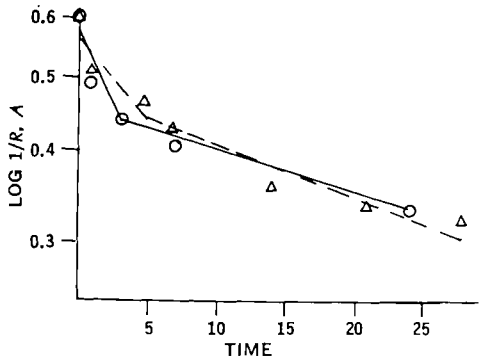


Figure 6—*Plots of log 1/*R versus *time (sugar-coated Tablet B, direct exposure). Key: - - -, days; and ——, hours.*

values fit the usual first-order rate equation:

$$K = \frac{2.303\,(\log A_1 - \log A_2)}{t_2 - t_1} \qquad \text{(Eq. 2)}$$

The fading rates are tabulated as shown in Table III.

Evaluation of Data—The relative color stability of the tablets can be well established by comparison of the data in Table III. The most significant step in the fading mechanism, which basically determines the extent of fading, occurs evidently in the early phase characterized by the K_1 values. Coated Tablet A exhibited superior color stability under the accelerated testing conditions; this was shown quantitatively by its comparatively low K_1 values (2.6×10^{-3} hr.$^{-1}$ in the fadeometer and 1.5×10^{-3} days^{-1} in the light cabinet). Coated Tablet B and the uncoated tablet faded rapidly. A comparison of the packaging materials showed that the natural high density polyethylene container was practically transparent in both the UV and visible regions of the spectrum. The opaque high density polyethylene and amber glass containers offered good protection against the damaging light effects.

Due to its higher energy level, the fadeometer experiment yielded reproducible and reliable data in 24 hr., approximately equivalent to that obtained in the light cabinet after 21–28 days storage. An addi-

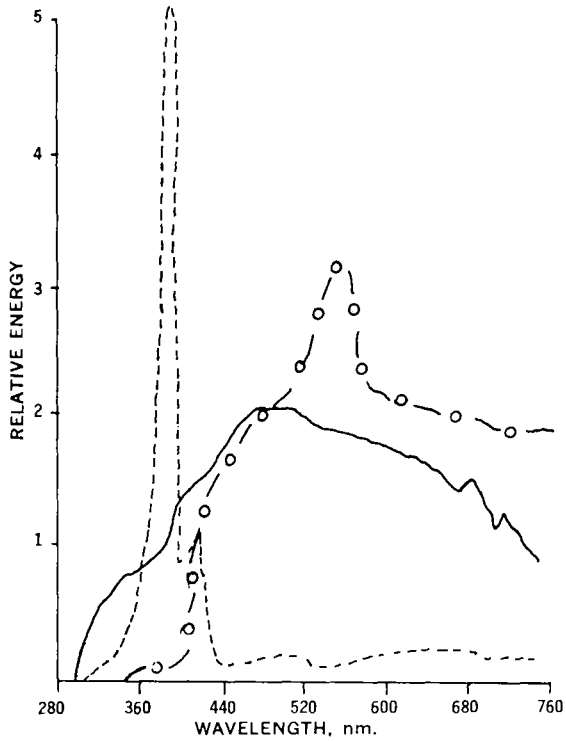


Figure 7—*Relative energy distribution of light sources. Key: · · ·, natural sunlight (noon, June); - - -, carbon arc (fadeometer); and —O O, fluorescent tubes (light cabinet).*

tional advantage is the favorable geometry of the fadeometer where the tablets are always in a fixed distance from the light source; in the light cabinet, a slight error may be involved since all tablets cannot be placed exactly in the center of the tray.

CONCLUSIONS

1. An apparent first-order rate of fading was established by earlier investigators for colored tablets in conventional light cabinets and in natural light. In this study, it was shown that a similar rate is valid for samples exposed to the carbon arc light source of a fadeometer.

2. In the initial (K_1) phase, color fading is approximately 50–100 times faster in the fadeometer than in the light cabinet. Therefore, in each experiment, a 24-hr. exposure in the fadeometer was found sufficient to compare the fading behavior of tablets and to predict color stability under environmental conditions. (Followup testing under normal conditions for 2 years demonstrated good agreement with predicted stability.)

3. The rapid fadeometer test is a valuable tool which aids the pharmaceutical formulator in the application of optimal colorants and the packaging engineer in the selection of containers most suitable for protecting colored tablets from the effects of light.

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▲ To whom inquiries should be directed.

NOTES

Purification of a Potent Antitumor Agent from a Tahitian Sea Anemone and Methods of Administration Studies with Ehrlich Ascites Tumor in Mice

TED R. NORTON▲ and MIDORI KASHIWAGI

Abstract □ An antitumor substance, stoichactin, was obtained from an aqueous alcoholic extract of the sea anemone, identified as most probably being *Stoichactis kenti*, using dialysis and gel permeation chromatography. The drug is effective at very low dosages using several different methods of administration in the control and cure of Ehrlich ascites tumor in mice.

Keyphrases □ Stoichactin—identification and pharmacological studies as an antitumor agent, mice □ Antitumor agents—purification of stoichactin from sea anemone, pharmacological testing with Ehrlich ascites tumor, mice □ *Stoichactis kenti*—isolation and purification of stoichactin, a potent antitumor agent, pharmacological testing, mice

During a rather broad study of pharmacological activity of over 1000 species of natural products from the Pacific basin, it was found that a number of extracts of coelenterates were highly effective in the control of Ehrlich ascites tumor in mice (1). One of these coelenterates was the anemone, identified as most probably being *Stoichactis kenti*[1]. Because of the very high specific activity found in a 30% ethanolic extract of this anemone, purification of the active constituent was undertaken. Partial purification results were recently reported (1). A fraction which deposited crystals on evaporation of an aqueous solution has now been obtained, and the active substance, now essentially pure, is being named "stoichactin." This drug was evaluated

[1] Collected from the reef of Arue Bay in Tahiti by Dr. Frank Tabrah. Dr. Cadet Hand, Director of the University of California Bodega Marine Laboratory, identified this sea anemone as definitely being in the genus *Stoichactis* and most probably as the species *S. kenti*.