Stability of Certified Dyes in Tablets I

Fading of FD&C Red No. 3 in Tablets as a Function of Concentration, Time, and Light Intensity

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The effect of concentration, time, and light intensity on the rate of fading of FD&C Red No. 3 in tablets has been examined. By modification of the Nolan and Foote equation relating the Kubelka-Munk function, θ, to dye concentration, a linear relation between the concentration of dye in the tablet and the θ calculated from the reflectance was found. A first-order rate equation for fading is given. This equation allows the fading which occurs under normal light intensity to be calculated from the fading which occurs at high light intensity.

ONE OF the recurrent pharmaceutical problems is the instability of certified dyes in tablet formulations. The problem has historically been solved by selecting dyes which exhibit good stability in similar formulations. Within the last few years, several investigators have undertaken studies to determine the color stability by measuring the reflectance properties of the formulation.

Reflectance measurements of creams, powders, granulations, and coated tablets were made by McKeehan and Christian (1) using a modified Beckman DU spectrophotometer. This type of study was made quantitative by Lachman, et al. (2–5), who observed the changes in reflectance of tablets with time when exposed to visible radiation. In this latter case, the fading of the dyes was accelerated by using a high intensity light cabinet (6, 7). A plot of log (−log reflectance) vs. time demonstrated the fading rates of the dyes to be apparent first order.

It is necessary, however, to develop equations for relating dye fading as a function of time and light intensity so that more fundamental aspects of color degradation can be studied. Qualitative studies in our laboratory have shown that certain drug-dye incompatibilities alter fading and that, furthermore, tablet diluents, binders, lubricants, and processing methods may also do the same. Whether these factors are significant has not been determined. The dye concentration is also an important factor since apparent increased stability can sometimes be gained by increasing concentration. Therefore, we have conducted a series of experiments to determine the effect of dye concentration on the stability of FD&C Red No. 3[1] in tablets, and have discovered certain time-intensity relationships which are of significant importance to the research pharmacist.

EXPERIMENTAL

Materials.—Lactose U.S.P., acacia U.S.P., magnesium stearate U.S.P., and FD&C Red No. 3.

Equipment.—Light sources were a bank of G.E. F40CW fluorescent tubes, an incandescent lamp of 25 watts, and a light cabinet similar to that previously described (6, 7). The cabinet was equipped with a G.E. No. 6G1020-150 watts ballast and No. F40CW-3 fluorescent tubes. The tubes were 1.5 in. in diameter and 48 in. long, slant line cool white. They were G.E. rated at 3250 lumens per each 40 watt tube.

The temperature of the tablets was about 22 to 24°, except for the tablets stored in the light cabinet. The temperature of the tablets in the light cabinet was 2 to 3° higher than room temperature.

A Bausch and Lomb Spectronic 505 spectrophotometer with a reflectance attachment was used to obtain tablet reflectances. Magnesium carbonate was used as a white standard. A Gossen Tri-Lux foot-candle meter employing a microgalvanometer connected to the photoelectric cell by a 3-ft. extension cord was utilized to determine incident flux.

Preparation of Tablets.—Tablets were prepared according to the following three formulas

	L	M	N
Lactose U.S.P., %	93.940	93.970	93.985
Acacia U.S.P., %	5.000	5.000	5.000
Magnesium stearate U.S.P., %	1.000	1.000	1.000
FD&C Red No. 3, %	0.060	0.030	0.015
Distilled water, ml.	50	50	50

Lactose and acacia were mixed together and pulverized. The dye, dissolved in 50 ml. of distilled water, was poured onto the powder mixture while mixing. The wet powder was dried at 75° F. and 40% relative humidity for 16 hours, and then in an oven at 100° F. for 2 hours. The dyed powder was pulverized and the magnesium stearate added and

[1] Disodium salt of 9-o-carboxyphenyl-6-hydroxy-2,4,5,7-tetraiodo-3-isoxanthone (erythrosine).

blended with the powder. Uniformly colored, flat-faced pink slugs were produced on the Stokes F-4 tablet press using 1-in. punches and die. The tablets were run at uniform weights and pressures in order to produce tablets having consistent surface properties. The free moisture content of the tablets was about 1%.

Preparation of Tablet Samples.—Tablets were glued on large, black rubber stoppers.[2] The stoppers were marked so that the geometry could be reproduced when returning the sample to the reflectance sample holder.

Storage of Tablets.—Prepared tablet samples were exposed under the following conditions: (a) in the light stability cabinet at a flux of 655 foot-candles, (b) under a bank of fluorescent lights at 80 foot-candles, (c) under fluorescent lights and amber glass (0.120 in.) at 11 foot-candles, and (d) under incandescent light at 50 foot-candles.

DISCUSSION AND RESULTS

Previous workers have plotted the logarithm of the function log $1/R$ vs. time, where R is the fraction of the light reflected at a specified wavelength. They interpreted the results in terms of apparent first-order reactions (3). Although they did not explicitly state that log $1/R$ is a linear function of dye concentration, just as log transmission is a linear function of concentration in transmission work, this is inferred because they interpret their results in kinetic terms (8). However, when this assumption was tested at different dye concentrations, a new "kinetic" constant, k, was found for the rate equation at each concentration, although the results for any one concentration were linear and reproducible. Since k is different for each concentration, the reaction is either not first order or an incorrect rate equation was used. In the present work, doubling the dye concentration resulted in a 20% change in k when plots of log R vs. time were made. Similar results were obtained by using R vs. time, that is, zero-order plots. Since the reflectance value is not proportional to concentration, an expression relating these two quantities is needed.

From theoretical consideration Kubelka and Munk (9, 10) derived a series of differential equations describing the behavior of light when it strikes a diffusing surface. These equations can be combined and integrated to give one simple equation if certain assumptions are met

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

Where θ is the ratio of absorbed light to scattered light at a given wavelength. The most important assumptions are that the material is homogeneous, that it has sufficient thickness to be opaque, and that the reflectance is diffuse. These assumptions are easily met by using uniformly dyed tablets with a dull surface.

Nolan (11) and Foote (12), in working with the Kubelka-Munk function, found that if the scattering coefficient is assumed to be very small, zero, or constant, θ is proportional to concentration. The scattering coefficient is the fraction of incident light

lost due to scattering. If this is assumed, then

$$\theta_d = AC \qquad \text{(Eq. 2)}$$

where θ_d is the Kubelka-Munk function for the dye, A is a constant of proportionality, and C is the concentration of dye in weight per cent. The observed reflectance, however, is due to the dye and the inert, background materials in the formulation. Nolan showed that the Kubelka-Munk function of a mixture is the sum of the individual Kubelka-Munk functions. Therefore

$$\theta_t = \theta_d + \theta_b \qquad \text{(Eq. 3)}$$

where θ_t is the Kubelka-Munk function of the tablet and θ_b of the background. Substituting Eqs. 1 and 2 into 3 gives

$$\theta_t = (1 - R_t)^2/2 R_t = AC + \theta_b \quad \text{(Eq. 4)}$$

where R_t is the measured reflectance of the tablet at the minimum in the reflectance-wavelength curve, 543 mμ.

Since the concentration of inert material, mostly lactose, is essentially constant, θ_b is a constant. Therefore, a plot of θ_t vs. C, Eq. 4, should be a straight line. By using the smoothed values of θ_t at zero time from Fig. 1, a straight line is obtained. The value of A is 8.2 and θ_o is 0.146, within 2%. This shows that θ_t is linearly related to the concentration and suitable for use in kinetic plots.

Previous attempts to correlate the fading of tablets at different intensities of the incident light have not been satisfactory. Each intensity was considered a separate case and different kinetic constants were calculated for each intensity (3, 4). However, since fading is proportional to the product of time, t, and intensity, I (13), plots of θ_t vs. the product of time and intensity were made. The plots are shown in Fig. 1. The consistency of the k value at the three different concentrations shows that the decomposition of the dye is indeed first order. By using the product of time and intensity, each intensity condition was found to lie on the same straight line for any given concentration.

The general first-order rate equation is

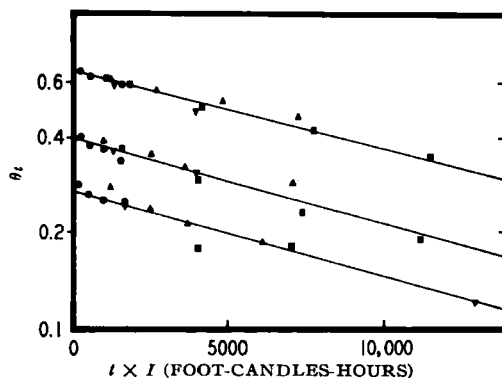$$\ln \theta_t = -ktI + \ln \theta_t' \qquad \text{(Eq. 5)}$$

Fig. 1.—Plots of θ_t vs. the product of time and intensity. ●, 11 foot-candles; △, 50 foot-candles; □, 80 foot-candles; ▽, 655 foot-candles. Top line, 0.06% dye; middle line, 0.03% dye; bottom line, 0.015% dye.
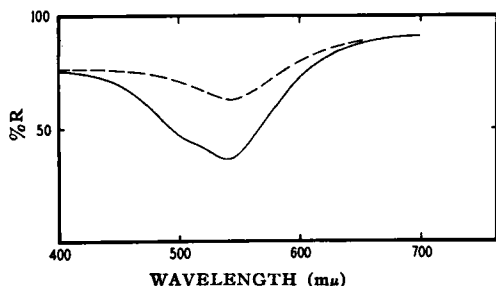

Fig. 2.—Reflectance curves for 0.06% dye. Solid line, initial; dashed line, after 140 hours at 80 foot-candles.

where θ_t is the θ calculated at time t, θ_t' is the θ_t at $t = 0$, and the other symbols have the meanings explained above. The rate constant was calculated to be $6.1 \pm 0.3 \times 10^{-5}$ hr.$^{-1}$ foot-candles^{-1}.

Figure 2 shows the 543 mμ absorbance peak and the shape of the reflectance curve before and after fading. Since the rate of fading is the same for incandescent and fluorescent illumination, as well as for samples protected by amber glass, the decomposition must be due largely to absorption at wavelengths greater than 500 mμ.

The times at which objectionable fading under high light intensity occurred for this dye, in the opinion of the authors, at all three concentrations are shown in Table I. From these time-intensity values, the time for objectionable fading at lower intensities was calculated using Eq. 5. The advantage of using high intensity lighting conditions is obvious from this table.

TABLE I.—TIME REQUIRED FOR OBJECTIONABLE FADING AT LOW LIGHT INTENSITIES AS CALCULATED FROM ACCELERATED LIGHT CONDITIONS

Concentration of Dye, % w/w	Hours at 540 f.-c.	Calcd. Hours at 50 f.-c.	Calcd. Hours at 10 f.-c.
0.060	17	180	920
0.030	7	75	380
0.015	2	20	110

Examination of the cross section of the tablets showed that fading proceeds to a given depth into the tablet and a fairly sharp demarcation can be seen between the white faded portion and the unchanged dye. The fading occurs first at the surface and gradually progresses into the tablet. When the tablet is viewed from above, the pink color seems to fade uniformly, indicating that the lower layers of dye are responsible for some of the surface color.

When the fading had penetrated to about 0.3 mm. into the tablet, the tablet surface appeared white and no further increase in the thickness of the white layer occurred.

The faded top layer did not interfere with the measurements of the reflectance until about 15,000 foot-candle-hours. After that, the fading rate slowed, probably because the upper layers of faded dye were thick enough to offer some protection to the lower, visible layers. The lower fading rate was obtained only in the light cabinet and is not shown in Fig. 1.

This work will be continued by measuring rate constants for other dyes using the equations developed above. It is hoped that when enough experience is obtained, it will be possible to predict the rate of fading for various combinations of dyes in the same tablet or tablets of different composition. By use of the present data, it is now possible to predict the amount of fading of FD&C Red No. 3 in the formulation studied at any specified time under any light intensity.

REFERENCES

(1) McKeehan, C. W., and Christian, J. E., THIS JOURNAL, **46**, 631(1957).
(2) Urbanyi, T., Swartz, C. J., and Lachman, L., *ibid.*, **49**, 163(1960).
(3) Lachman, L., Swartz, C. J., Urbanyi, T., and Cooper, J., *ibid.*, **49**, 165(1960).
(4) Lachman, L., Weinstein, S., Swartz, C. J., and Cooper, J., *ibid.*, **50**, 141(1961).
(5) Swartz, C. J., Lachman, L., Urbanyi, T., and Cooper, J., *ibid.*, **50**, 145(1961).
(6) Lachman, L., and Cooper, J., *ibid.*, **48**, 226(1959).
(7) Lachman, L., Swartz, C. J., and Cooper, J., *ibid.*, **49**, 213(1960).
(8) Frost A. A., and Pearson, R. G., "Kinetics and Mechanism," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1961, pp. 9, 10.
(9) Kubelka, P., and Munk, F., *Z. Tech. Physik*, **12**, 593 (1931).
(10) Kubelka, P., *J. Opt. Soc. Am.*, **38**, 448(1948).
(11) Nolan, P., *Paper Trade J.*, **105**, 42(1937).
(12) Foote, W. J., *ibid.*, **109**, 31(1939).
(13) Morton, T. H., *J. Soc. Dyers Colourists*, **65**, 597(1949).