Stability of Certified Dyes in Tablets II. Fading of FD&C Red No. 3 and FD&C Red No. 3 Aluminum Lake in Three Tablet Formulas

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The fading rates of FD&C Red No. 3 and its aluminum lake were determined in three tablet formulas which differed only in the excipient employed. In tablets of calcium sulfate the dye faded at about twice the rate of the same dye in either dicalcium phosphate or lactose tablets. However, the use of the corresponding lake in the calcium sulfate formulation reduced the fading rate significantly. No significant differences in fading rates were demonstrated between the dye and the lake in tablets of dicalcium phosphate or lactose. The method of size reduction of the dyed powder did not significantly affect the fading rate.

IN A PREVIOUS COMMUNICATION (1), a method was described by which the approximate color shelf life of a tablet formulation can be predicted on the basis of high intensity fading. This study demonstrated that FD&C Red No. 3 possessed a fading rate independent of the dye concentration in the tablet. The first-order rate equation which described the fading was

$$\ln\theta_t = -kIt + \ln\theta_{t_o} \qquad \text{(Eq. 1)}$$

where $\theta_t = \left(\frac{1 - R_t}{2R_t}\right)^2 = AC$, in which R_t is the reflectance at 543 mμ (the absorption peak) at time t, A is a constant, C is the concentration of dye in weight per cent, k is the first-order rate constant, I is the intensity of light, and t_o is time zero.

The present work was concerned with three variables. The first of these was the nature of the colorant, dye or lake. Enhanced stability to ultraviolet radiation was indicated for several lakes (2), but quantitative data comparing fading rates for FD&C Red No. 3 and its lake were not reported. The influence of tablet diluents on dye stability has not been investigated; since the diluent itself is sometimes a source of incompatibility, this factor was included. Another factor investigated was the method of preparation of the dyed powder used in preparing the tablets. While the affinity of the dye for different diluents varies, this property alone did not determine the color uniformity. Some formulas appeared to be uniformly dyed, but an unusual degree of mottling was noted when pressed into tablets. Therefore, three methods of size reduction were included to improve color uniformity and to determine whether this variable altered the rate of fading.

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EXPERIMENTAL

Materials.—Lactose U.S.P., calcium sulfate dihydrate, anhydrous dibasic calcium phosphate N F., acacia U.S.P., magnesium stearate U.S.P., FD&C Red No. 3, and FD&C Red No. 3 aluminum lake were employed.

Equipment.—Low intensity light was provided by a bank of G.E. F40CW fluorescent tubes; high intensity light was provided by a light cabinet previously described (3, 4). Reflectance measurement, light intensity measurement, and preparation of the tablets were the same as described in our first study (1), except that some formulas were reduced by comminuting or ball milling rather than micropulverizing. Comminuting was carried out on the Fitzpatrick model D comminutor and micropulverizing on the Pulverizing Machine Co. micro-sample mill.

Storage of Tablets.—Prepared tablet samples were placed in a light cabinet under a flux of 518 f.-c. and under a bank of fluorescent light at 195, 74, 50, and 11 f.-c. Samples were withdrawn periodically for reflectance measurement.

RESULTS AND DISCUSSION

Results.—A summary of the first-order rate

TABLE I.—RATE CONSTANTS FOR THE FADING OF FD&C RED NO. 3

Diluent	Nature of Colorant	Dye Dispersion Method	$k \times 10^5$ (f.-c. hr.)$^{-1}$
$CaSO_4 \cdot 2H_2O$	Dye	Comminuted[a]	11.3 ± 1.1
$CaSO_4 \cdot 2H_2O$	Dye	Micropulverized[a]	11.4 ± 0.8
$CaSO_4 \cdot 2H_2O$	Lake	Comminuted or ball milled[b]	7.4 ± 0.8
$CaHPO_4$	Dye	Micropulverized[a]	6.7 ± 0.6
$CaHPO_4$	Lake	Comminuted or ball milled[b]	7.8 ± 0.3
Lactose	Dye	Micropulverized[a]	6.1 ± 0.3
Lactose	Lake	Micropulverized[b]	4.6 ± 0.9

[a] Average of three slopes, each a different dye concentration. [b] Average of two slopes, each the same dye concentration.

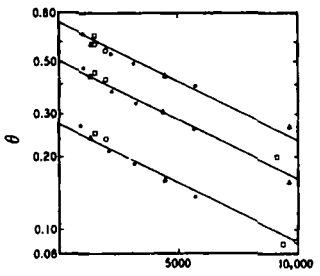

Fig. 1.—Plots of θ_t *vs.* the product of time x intensity for the dye on $CaSO_4 \cdot 2H_2O$. Key: ●, 518 f-c.; △, 195 f.-c.; ○, 74 f.-c.; □, 50 f.-c.; and ×, 11 f.-c. Upper line, 0.060% w/w dye; middle line, 0.030% w/w dye; lower line, 0.015% w/w dye. Method of size reduction was micropulverization.

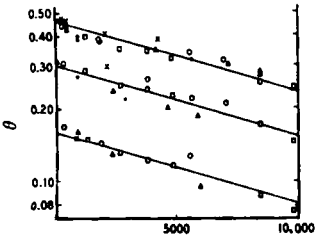

Fig. 2.—Plots of θ_t *vs.* the product of time x intensity for the dye on $CaHPO_4$. Key: ●, 518 f.-c.; △, 195 f.-c.; ○, 74 f.-c.; □, 50 f.-c.; and ×, 11 f.-c. Upper line, 0.060% w/w dye; middle line, 0.030% w/w dye; lower line, 0.015% w/w dye. Method of size reduction was micropulverization.

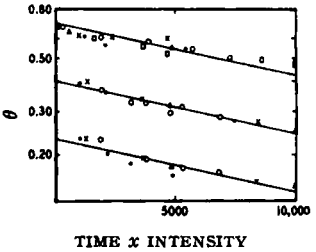

Fig. 4.—Plots of θ_t *vs.* the product of time x intensity for the lake on lactose. ●, 518 f.-c.; △, 195 f.-c.; ○, 74 f.-c.; □, 50 f.-c.; and ×, 11 f.-c. Upper line, 0.060% w/w dye; middle line, 0.030% w/w dye; lower line, 0.015% w/w dye. Method of size reduction was micropulverization.

TABLE II.—EFFECT OF CALCIUM ION ON FADING OF FD&C RED NO. 3 AT 25° AND 900 F.-C.

Soln.	Initial mM of Calcium Ion	mg./ml. of Dye Initial[c]	Initial pH	Final pH	% Dye Remaining After 17 Hr. Exposure
Control	None	0.78	6.8	4.9	85
$CaSO_4 \cdot 2H_2O$	0.12	0.71	7.1	5.5	85
$CaHPO_4$[a]	0.15	0.76	7.8	6.4	82
$CaCl_2$	0.90	0.76	6.9	5.0	67
$CaSO_4 \cdot 2H_2O$[b]	1.5	0.40	7.1	5.3	55
$CaCl_2$	9.0	0.14	7.3	4.3	46

[a] Saturated solution of calcium phosphate at 23°C. [b] Saturated solution of calcium sulfate at 23°C. [c] All solutions were prepared to contain 0.78 mg./ml. of dye. Precipitation of calcium salt of dye is responsible for reduction of initial dye concentration in all experiments except the control.

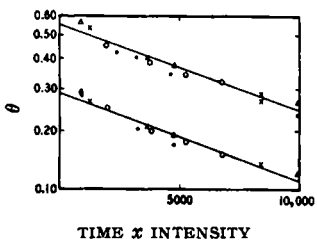

Fig. 3.—Plots of θ_t *vs.* the product of time x intensity for the lake on $CaSO_4 \cdot 2H_2O$ and $CaHPO_4$. Upper line, $CaSO_4 \cdot 2H_2O$, 0.060% w/w dye; lower line, $CaHPO_4$, 0.060% w/w dye. Key: ●, 518 f.-c.; △, 195 f.-c.; ○, 74 f.-c.; □, 50 f.-c.; X, 11 f.-c. Method of preparation was micropulverization.

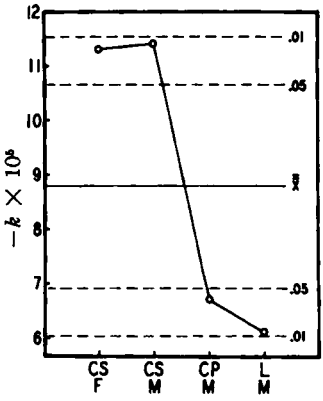

Fig. 5.—Statistical analysis of means illustrating significant differences of rate constants for the dye in tablets of calcium sulfate dihydrate, dibasic calcium phosphate, and lactose. $\bar{X}$ is overall average of 12 rate constants and dotted lines give 95 and 99% limits. Key: CS, calcium sulfate dihydrate; CP, dicalcium phosphate; L, lactose; F, comminuted; and M, micropulverized.

constants, k, calculated by Eq. 1, along with their average deviations is given in Table I for all systems studied.

The rate constants listed in Table I were determined by fitting the best straight line using regression analysis. Correlation coefficients ranged from 0.90 to 0.99. The standard deviation of the rate constant was also calculated to determine whether any rate constants were statistically different from others at 95% confidence limits.

Effects of Size Reduction.—While the dye seems to have an affinity for all three diluents employed, the calcium sulfate tablets were noticeably more mottled than those made with either dicalcium phosphate or lactose. Dispersion by comminuting rather than micropulverization did not decrease this effect. As seen in Table I the rate constants for dye in calcium sulfate were the same regardless of the kind of size reduction employed. Figure 1 illustrates the fading of the dye on calcium sulfate tablets prepared by micropulverization.

Marked speckling occurred with both calcium salts when the lake was employed. Therefore, these blends were subjected to ball milling to produce a uniform color. Although the fading rate was slightly lower for the tablets prepared by ball milling compared to comminuting, the difference between the rates was not statistically significant at the 95% level. An average value is therefore reported in Table I.

Effect of Diluent on the Fading Rate of the Dye.—Figures 1 and 2 show the fading of the dye on calcium sulfate and calcium phosphate, respectively. As seen in Table I, the rate constant for calcium sulfate was nearly double that found for either calcium phosphate or lactose. A statistical treatment of the rates (5) is shown in Fig. 5. The significant differences demonstrate an incompatibility of the dye with calcium sulfate.

To substantiate that calcium was the cause of the faster fading, a series of dye solutions was prepared and exposed to high intensity fluorescent light (900 f.-c.) for 17 hours. The results of the experiment

are shown in Table II. As the concentration of calcium increases, the dye deteriorates more rapidly. It is apparent that no correlation exists between degree of fading and the initial or final pH. Therefore, it can be concluded that the higher solubility of calcium sulfate dihydrate (0.2 Gm./100 ml. at 25°) is the cause for the more rapid fading. The solubility of dicalcium phosphate is about 0.05 Gm./100 ml. at 25°, an amount apparently insufficient to cause a significant increase in the fading rate.

Effect of Colorant Nature.—No significant differences in the fading rates existed between the dye and the lake on either dicalcium phosphate or lactose. However, in the case of calcium sulfate a marked reduction in the rate was afforded by use of the lake over the dye as seen in Table I and Figs. 1 and 3. The reason for increased stability with the lake can be attributed to the adsorption of the dye to its substrate. In this form the dye is not free to react freely with available calcium ion.

SUMMARY AND CONCLUSIONS

The usefulness of semilogarithmic plots of the Kubelka-Munk function and the product of time x intensity has been shown applicable to tablet systems other than those originally employed. The rate constants for tablets of calcium sulfate dihydrate lake, dibasic calcium phosphate-dye or lake, and lactose-dye or lake are not statistically different. However, tablets of calcium sulfate dihydrate and dye show a fading rate significantly higher than other tablet formulas studied. The method of size reduction did not significantly alter the fading rate in those tablets that were mottled or speckled when prepared by micropulverization.

It is believed that better control of pressure and the selection of more closely matched tablets will reduce experimental error due to tablet-to-tablet variation. This factor along with the use of color differences calculated from tristimulus values will no doubt lead to new interpretations of color fading.

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In Vitro Evaluation of Sustained-Release Tablets by Dual Channel Scintillation Counting

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A rapid procedure was developed for the study of the *in vitro* release characteristics of two radiolabeled drugs in a tertiary drug system. The use of dual channel scintillation spectroscopy allowed for simultaneous determinations of per cent release of each labeled drug from the single sustained-action core tablet.

RADIOISOTOPES have been used extensively in the testing of various pharmaceutical dosage forms (1). The literature contains several reports of evaluative methodology regarding *in vivo* and *in vitro* uses of radioisotopes with the sustained-release dosage form (2–5). This report will be restricted to the determination of the release characteristics of Cl-36 labeled phenylephrine hydrochloride and C-14 labeled aspirin in the presence of chlorpheniramine hydrochloride *in vitro* from the single sustained-release core tablet. The method employed was that of dual channel scintillation spectroscopy which permitted the simultaneous determination of the percentage released of the individual radiolabeled drugs.

EXPERIMENTAL

Preparation of Labeled Compounds.—Chlorine-36 labeled phenylephrine hydrochloride was prepared by dissolving 3 Gm. of compound in distilled water and crystallizing out the free base from the solution rendered alkaline with ammonia. The base was filtered, washed, and dried. Fifty microcuries of chlorine-36 labeled hydrochloric acid was then added to a mixture of 1.23 Gm. of the base and 4 ml. of distilled water. One drop of methyl red T.S. was added; the solution was neutralized with dilute hydrochloric acid. This solution was later added to the mass during the preparation of the tablet cores. Carbon-14 labeled aspirin was synthesized using 50 μc. of carbon-14 labeled acetic anhydride and salicylic acid A.R. using routine procedures (6). The labeled aspirin was then blended with about 25 Gm. aspirin C.P. by dissolving both in an ether–petroleum ether mixture. The blend was then crystallized and dried. The specific activities for the respective compounds were 15 μc./Gm. for phenylephrine hydrochloride and 45 μc./Gm. for aspirin prior to dilution.

Preparation of Tablets.—A batch of 100 core tablets, each made to weigh 405 mg., was prepared by using a single punch tablet press fitted with a $^{11}/_{32}$-in. die and standard concave punches. Each tablet contained 180 mg. of labeled aspirin, 1.3 mg. of labeled phenylephrine hydrochloride, and 8.3 mg. of chlorpheniramine hydrochloride after preparation by the methods of Nash and Jeffries (7, 8). The cores were not compression coated. An immediate release portion—additional quantities of drugs in lactose—would lend nothing to the evaluation of the sustained-action formula and, therefore, was not used.

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