SUMMARY

1. The photostabilizing effect of the ultraviolet absorber 2,4-dihydroxybenzophenone for tablets colored with three certified dyes was evaluated. These studies were performed under light sources simulating the spectral energy distribution of sunlight and normal and exaggerated room illumination.

2. The relative protective effect of this ultraviolet absorber for the three colors studied was as follows: FD&C Yellow No. 5 > FD&C Blue No. 1 > FD&C Red No. 3.

3. The complete absorption characteristics of the color must be studied when determining the factors responsible for the photostabilizing effects of the ultraviolet absorber.

4. The ultraviolet absorber was most effective against color fading for tablets exposed to simulated sunlight. However, it must be remembered that drugs are rarely exposed to direct or indirect sunlight.

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Color Stability of Tablet Formulations VI

Preliminary Study of Temperature Dependency of Colorant Loss in Tablets at Various pH Levels

By C. J. SWARTZ, L. LACHMAN, T. URBANYI, S. WEINSTEIN, and J. COOPER

The influence of temperature and pH on the surface color and total dye content of tablets colored with selected dyes was studied. The representative dyes included were FD&C Red No. 4, Blue No. 1, and Yellow No. 5. Samples of tablets colored with these dyes and buffered at several pH levels were stored at elevated temperatures and tested for both residual dye concentration and fading at their surface. FD&C Red No. 4 was found to be the most stable of the three dyes tested. However, from the results of this study there appears to be no correlation between the fading at the surface of the tablets and the loss in colorant concentration at elevated temperatures.

THE USE of accelerated stability tests for predicting the extended shelf life of pharmaceutical dosage forms has gained considerable acceptance in recent years. Through the application of chemical kinetic principles to elevated temperature storage data, it has been possible to predict accurately the stability of active ingredients at ambient temperatures.

In the past several years a number of reports have appeared in the literature relative to the thermal stability of certified colorants in liquid preparations (1–3). However, little information on the thermal stability of colorants in tablets has been reported. Since tablets constitute the major dosage form in most pharmaceutical companies, a study of color degradation in tablets was essential. Consequently, this study was initiated to evaluate the influence of thermal radiations on dyes when used in tablets.

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EXPERIMENTAL

Materials Used.—FD&C Blue No. 1, FD&C Yellow No. 5, and FD&C Red No. 4, H. Kohnstamm and Co. 0.2 *M* Tartrate buffer at pH 3. 0.2 *M* Phosphate-citrate buffer at pH 5. 0.2 *M* Phosphate-tartrate buffer at pH 7.

Equipment.—Precision and Hotpack ovens. Comprex tablet press. Beckman spectrophotometer model DU with reflectance attachment (4). Cary

recording spectrophotometer model 11. Beckman Zeromatic pH meter. Fitzpatrick Homoloid mill. Beckman Aquameter.

Preparation of Tablets.—Tablets containing the water-soluble dyes were prepared unbuffered and at the three pH levels: 3, 5, 7. The tablet formulations prepared for this study were as follows

	Unbuffered, %	pH 3, %	pH 5, %	pH 7, %
Calcium sulfate $\cdot 2H_2O$	96.90	93.42	91.98	89.17
Tragacanth U.S.P.	2.00	2.00	2.00	2.00
Magnesium stearate U.S.P.	1.00	1.00	1.00	1.00
Dye	0.10	0.10	0.10	0.10
Tartaric acid	...	0.75	...	...
Sodium tartrate $\cdot 2H_2O$	...	2.73	...	2.73
Sodium phosphate, primary	...	...	1.58	...
Sodium citrate	...	...	3.34	...
Sodium phosphate, dibasic $\cdot 7H_2O$	...	...	...	5.00
Purified water	*q.s.*	*q.s.*	*q.s.*	*q.s.*

The granulations were made by dissolving the buffer salts in 150 ml. of water at 80° and the dye in 50 ml. of water at 40°. The dye solution was added first to the mixed powders, followed by the buffer solution. The separate addition of the dye and buffer solutions was necessary in order to prevent precipitation of the dye by the buffer salts. All granulations were terminally milled through a Fitzpatrick Homoloid mill using a 050 screen to insure uniform color distribution in the finished tablet. The tablets were compressed on a Comprex tablet press using flat faced $^{8}/_{32}$ inch punches to a hardness of 7 Kg./in.^{2} with a weight of 100 mg. The moisture content of the dried granulations was maintained below 0.5%. The use of the dyes at the 0.1% concentration level was necessary so that sufficient dye would be available to permit accurate extractions for quantitative determination.

Storage of Samples.—Tablets colored with FD&C Red No. 4, Blue No. 1, and Yellow No. 5 were studied in such a manner that light or moisture-induced effects on the color degradation would be kept to a minimum. Indicating Drierite, 100 Gm., was placed into 8-oz. wide-mouth amber bottles which had been previously covered with opaque masking tape. The Drierite was covered with glass wool and 1,000 tablets were added to each bottle and the bottles capped. Sample bottles were stored at 25, 60, and 80 ± 1°. Test samples were withdrawn at designated time intervals for chemical assay and reflectance measurements.

Measurement of Tablet Reflectance.—The techniques and equipment employed to follow changes in the reflectance at the surface of the tablets were described in a previous publication (4). Reflectance measurements were made on the colored tablets at 630 mμ for FD&C Blue No. 1, at 505 mμ for FD&C Red No. 4, and at 430 mμ for FD&C Yellow No. 5.

Spectrophotometric Analysis for Dye Content of Tablets.—The changes in dye concentration with storage were determined in accordance with the following procedure: An adequate number of tablets were ground in a mortar from which a 1.0-Gm. aliquot was accurately weighed and transferred into a glass-stoppered 40-ml. centrifuge tube. The sample was extracted with two 25-ml. portions of methanol followed by two 20-ml. portions of water. Prior to the first aqueous extraction, 5 Gm. of sodium chloride was added to each centrifuge tube. Each extract was filtered through a medium porosity sintered-glass filter into a 100-ml. volumetric flask containing an additional 5 Gm. of sodium chloride. The sodium chloride was employed to coagulate the colloidal tragacanth present in the extract. Following thorough agitation, the solution was brought to 100 ml. with water. A quantity of this solution was passed through a medium sintered-glass filter and complete absorption curves in the visible spectrum were run on the Cary spectrophotometer. As a result of the intense absorption of FD&C Blue No. 1, only 0.5-Gm. samples of tablets containing this dye were used.

Determination of Tablet pH.—Ten tablets were crushed in a mortar and triturated with 10 ml. of purified water. The material was then transferred to a 20-ml. beaker and stirred for 5 minutes. The pH of the suspension was determined, using the Beckman Zeromatic pH meter. The results are recorded in Table I.

TABLE I.—APPARENT pH OF SUSPENSIONS OF CRUSHED TABLETS IN WATER

pH	FD&C Red No. 4	FD&C Yellow No. 5	FD&C Blue No. 1
Unbuffered	6.4	5.9	6.5
3	3.0	3.1	3.0
5	4.9	5.1	5.2
7	6.8	6.6	6.5

RESULTS AND DISCUSSION

The influence of temperature and pH on the thermal stability of colorants in tablets has been investigated. In addition to studying the changes that take place in dye concentration, observations of fading at the tablet surface were made.

A representative plot showing the decrease in the concentration of FD&C Yellow No. 5 stored at 80° for 60 days is shown in Fig. 1. It is evident from this figure that the absorption decreases with storage. The complete curves, however, maintain their characteristics at all the temperature and pH levels tested. The tablets buffered to pH 7 showed the greatest loss of colorant. The curves for the unbuffered and pH 3 tablets have not been presented here, as no breakdown was observed under these conditions.

The per cent total loss of colorants after storage for 60 days at 25, 60, and 80° is summarized in Table II. It is apparent from this data that the tablets colored with FD&C Red No. 4 have exhibited the greatest stability under the conditions of study. Only the tablets buffered at pH 5 showed any loss of

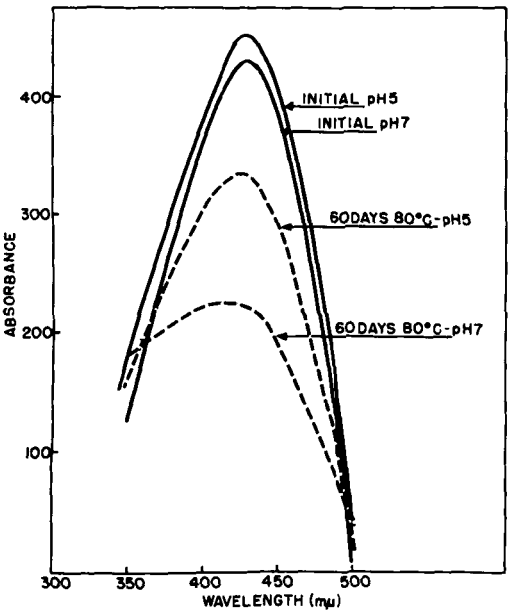

Fig. 1.—The effect of temperature, 80°, on the visible absorption spectra of FD&C Yellow No. 5 dye extracted from tablets.

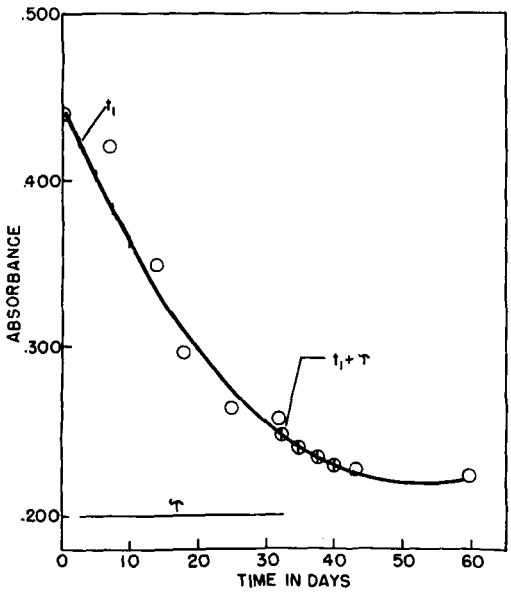

Fig. 2.—Plot of change of absorbance of FD&C Yellow No. 5 at 80°, pH 7, with time.

dye content. In the case of tablets colored with FD&C Yellow No. 5, poor stability is noted in the tablets buffered to a pH of 5 and 7, with the tablets at pH 7 showing approximately twice the loss of those at pH 5. This may be attributed to the action of the buffer salts and/or pH environment created by them. The data for the tablets colored with FD&C Blue No. 1 indicate that loss of dye concentration is essentially pH independent. The per cent loss in dye concentration both at 60 and 80° are of a similar magnitude. It should be noted that at 25° no change in dye concentration resulted for the tablets colored with the three dyes and at the several pH levels.

A representative plot for the change in absorbance with time for the tablets colored with FD&C Yellow No. 5 is shown in Fig. 2. It is evident from this curve that the reaction proceeds to an infinity value. In order to obtain an accurate estimate of the rate of loss of color from the tablets, the loss data was treated according to the method of Guggenheim (5). By employing this technique it is unnecessary to know the value at infinity time. The method is applicable where a property other than concentration is being followed. If t_1, t_2, t_3, and t_4 and $t_1 + \tau$, $t_2 + \tau$, $t_3 + \tau$, and $t_4 + \tau$, are selected where τ is a constant increment, the differential equation for a first-order reaction takes the form

$$\ln (P_t - P_{t+\tau}) + kt = \text{constant}$$

By plotting $\log (P_t - P_{t+\tau})$ *vs.* t, the slope of the line will be equivalent to $-k/2.3$. Therefore, by measuring the slope of this line, one is able to obtain the first-order rate constant for the reaction ($k = -\text{slope} \times 2.3$). The interval τ should be at least two or three times as great as the half-life period of the reaction in order to obtain maximum accuracy.

By the application of the Guggenheim method, the rate constants (k) for loss in colorant concentration were obtained for tablets colored with FD&C Yellow No. 5 at pH 5 and 7 stored at 60 and 80°.

At pH 5: 60° = 5.6×10^{-2} days $^{-1}$; 80° = 12.7×10^{-2} days^{-1}. At pH 7: 60° = 1.43×10^{-2} days^{-1}; 80° = 4.1×10^{-2} days^{-1}.

It is interesting to note that although the samples buffered at pH 5 are degrading at a faster rate, these tablets show only about one-half the loss in total dye concentration when compared with the tablets buffered to pH 7 (Table II). This is due to the fact that the loss curve has a higher infinity value for the tablets buffered to a pH 5 than those at pH 7, thus a lower net rate results. But the rate at which the loss in color reaches the infinity value at pH 5 is faster than that at pH 7 and, according to chemical kinetic principles, the rates obtained here must be used.

In Table III a summary is presented of the surface fading of tablets colored with FD&C Yellow No. 5 and Blue No. 1 and at several pH levels. Uncolored tablets were used as a control and reflectance readings obtained from the surface of these tablets, after storage, were subtracted from the reflectance values obtained with the colored tablets after similar storage. These results show that the fading from the surface of the tablets colored with FD&C Blue No. 1 was small and in the same range for all pH levels. However, for the tablets colored with FD&C Yellow No. 5, a significant surface color change was observed in all the buffered samples. Although there appears to be considerable surface fading for the tablets at pH 3, the color concentration loss obtained at this pH was not of the same order.

As a result of irregularities in the surface hue of tablets colored with FD&C Red No. 4, reflectance data for these tablets have been omitted. It is apparent from the information presented in Tables II and III that there appears to be no correlation between the fading at the surface of the tablets and the loss in colorant concentration. A possible

TABLE II.—PER CENT LOSS OF DYE IN BUFFERED TABLETS AFTER 60 DAYS STORAGE AT VARIOUS TEMPERATURES

Temperature, °C.	FD&C Red No. 4				FD&C Yellow No. 5				FD&C Blue No. 1			
	Unbuffered	pH 3	pH 5	pH 7	Unbuffered	pH 3	pH 5	pH 7	Unbuffered	pH 3	pH 5	pH 7
25	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	15	29	11	11	13	8
80	0	0	6	0	0	0	25	48	13	11	19	12

TABLE III.—REFLECTANCE CHANGES AT THE SURFACE OF TABLETS FOLLOWING STORAGE

	FD&C Blue No. 1				FD&C Yellow No. 5			
	Unbuffered	pH 3	pH 5	pH 7	Unbuffered	pH 3	pH 5	pH 7
Initial	1.200	1.120	1.045	1.080	0.825	0.768	0.785	0.770
25°, 60 days	1.175	1.110	1.020	1.030	0.825	0.760	0.760	0.750
80°, 60 days	1.000	0.884	0.851	0.885	0.715	0.500	0.515	0.475

explanation for this is the high concentration of dye used for the tablets.

The pH of the colored and uncolored tablets showed similar variations relative to maintenance of initial pH with storage. A slight decrease in pH was noticed in all cases except for the tablets buffered at pH 3 where essentially no change took place. Initially, it was intended to utilize the same buffer salts (phosphates) for the entire pH range of this investigation; however, it soon became apparent that the buffer capacity of the phosphate salts was not adequate at all the pH levels required. Therefore, varied buffered salt combinations were used for the different pH's to give optimum buffer capacity.

This study was designed to obtain an initial insight into the thermal stability of colorants when used in tablets. Although only limited data have been obtained, further experiments are necessary to define the complex factors contributing to dye instability. As a result of this information, additional investigations are contemplated to evaluate thoroughly the thermal stability of all FD&C colorants when employed in solid dosage forms.

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Stability of Metal Complexes of Nuclear-Substituted Salicylic Acids: Correlation with Biological Effects

By WILLIAM O. FOYE and JOSEPH G. TURCOTTE

Stability constants are reported for the chelation of ferric and aluminum ions by a series of salicylic acid derivatives having amino, alkyl, chloro, and nitro groups in the ring. The sequence of complex stabilities found is in agreement with current organic theory and shows a parallelism with the ionization constants. Three of the biological effects known for salicylates, antibacterial, analgesic-antipyretic, and fungicidal, can be related to the magnitude of complex stability or ionization constant.

A NUMBER of experimental approaches have been made in the attempt to explain the biological effects of the salicylates. One explanation for these effects has implicated the metal-binding ability of the salicylates (1–4), since the *meta*- and *para*-hydroxybenzoic acids, which are incapable of binding metal ions through complexation, exert none of the classical salicylate effects (1). The literature, however, does not provide much information regarding the relative abilities of the various salicylates to bind metal ions. The measurement of stability constants should provide a much fuller knowledge of these abilities and give us a better insight as to the importance of metal-binding in salicylate actions.

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