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Color Stability of Tablet Formulations V

Effect of Ultraviolet Absorbers on the Photostability of Colored Tablets

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

The photostabilizing effect of the ultraviolet absorber 2,4-dihydroxybenzophenone for tablets colored with three certified dyes was evaluated. Two sources of light were employed; one approximating the spectral energy distribution of sunlight and the other simulating ordinary room illumination. The apparent rates of fading for FD&C Yellow No. 5, FD&C Blue No. 1, and FD&C Red No. 3 were determined under each light source. The relationship existing between the protective properties of the ultraviolet absorber, the absorption characteristics of the dyes, and the spectral energy distribution of the artificial light sources is discussed.

THE STATUS of certified colorants continues to be closely scrutinized by the Food and Drug Administration. With the delisting of FD&C Red No. 1, there remain 11 certified dyes available for use in foods, drugs, and cosmetics. Temporary authorization for the continued use of FD&C and D&C colorants has been given, subject to the possibility that such use may be terminated or restricted. In view of the pending restrictions inherent with the use of colorants, maximum utilization of the certified dyes has become essential. This has stimulated interest in the pharmaceutical industry for developing methods of improving the stability of the limited number of available certified dyes.

One approach for improving the photostability of dyestuffs has been the use of ultraviolet absorbing chemicals. Chemical compounds such as 3,5-dinitrobenzoic acid (1), benzoyl resorcinols (2), alkylated 2-hydroxyphenylbenzotriazole, and

derivatives of 2-hydroxybenzophenones (3) have been employed effectively as photostabilizing agents in industries such as textiles, plastics, paints, and cosmetics. These compounds are selected because they possess high absorptivity and good stability in the 300–400 $m\mu$ ultraviolet region without absorbing in the 400–800 $m\mu$ visible region. Since many FD&C colorants absorb radiation in the near ultraviolet and visible region of the spectrum, the use of an ultraviolet absorber in conjunction with these colorants should result in some stabilizing influence. This effect, however, would be governed by the spectral energy distribution of the light source used and the absorption characteristics of the colorants.

This study was initiated to determine the influence of an ultraviolet absorber, namely 2,4-dihydroxybenzophenone, on the photostability of tablets colored with three FD&C dyes representing different chemical classes. The colorants were selected so that they would exhibit absorption maxima throughout the visible spectrum (430, 540, and 640 $m\mu$). The photostability of

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these colorants in tablets with and without an ultraviolet absorber was studied upon exposure to two light sources, one approximating the spectral energy distribution of sunlight and the other ordinary artificial room illumination under normal and exaggerated light intensity.

EXPERIMENTAL

Materials.—FD&C Blue No. 1 (triphenylmethane dye), FD&C Red No. 3 (xanthene dye), and FD&C Yellow No. 5 (pyrazolone dye), H. Kohnstamm Co. 2,4-Dihydroxybenzophenone, Antara Chemical Co.

Equipment.—Gossen Tri Lux foot candle light meter, model C. Stokes model F tablet press. Beckman spectrophotometer model DU with reflectance attachment (5). Light stability cabinets exhibiting normal and exaggerated illumination. Light cabinet utilizing a General Electric type R.S. sunlamp (similar to the cabinet employed for normal illumination studies). In a previous report (4) a detailed description and discussion were presented on the light sources employed to simulate normal and exaggerated room illumination. However, a description of the light source used to simulate sunlight has not hitherto been presented. The lamp used is a self-contained unit with a 100-watt mercury discharge element and a 175-watt tungsten-filament resistance ballast incorporated into an ultraviolet transmitting reflector type bulb. The sunlamp emits energy in the ultraviolet and visible spectrum as shown in Fig. 1. It is interesting to note that its visible energy spectrum encompasses approximately the same wavelength range as does the cool white fluorescent lamp used in the normal illumination cabinet. The peak energy output for the sunlamp within this spectral range is greater than that emitted by the fluorescent lamp. The sunlamp is made with special glass which absorbs the shorter ultraviolet rays up to 280 $m\mu$, thus simulating atmospheric absorption of the shorter violet rays emitted by the sun.

Preparation of Tablets.—Tablets containing water-soluble dyes with and without ultraviolet absorbers were prepared according to the following formulas

	With Ultra- violet Absorber, %	Without Ultra- violet Absorber, %
Calcium sulfate dihydrate	94.49	96.99
Tragacanth U.S.P.	2.00	2.00
2,4-Dihydroxybenzophenone	2.50	...
Magnesium stearate U.S.P.	1.00	1.00
Dye	0.01	0.01
Ethyl alcohol 50%	<i>q.s.</i>	<i>q.s.</i>

Granulations were prepared in accordance with commonly employed tableting techniques. The colorants and the ultraviolet absorber were dissolved in 50% alcohol which was then used as the granulating solution. The granulations were dried to a moisture content below 0.5% and compressed into tablets using $\frac{3}{32}$ inch flat faced punches, uppers bisected, on a Stokes model F tablet press. The tablets were compressed to a weight of 100 mg. with a thickness of 1.5 mm. and a hardness of 8 Kg./in.²

Storage of Samples.—Samples of each of the

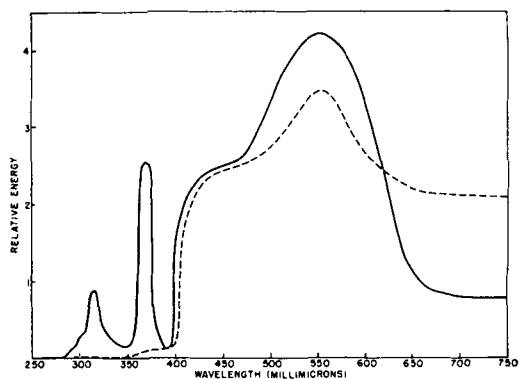


Fig. 1.—Spectral energy distribution of R.S. sunlamp and standard cool white fluorescent lamp. —, R.S. sunlamp; ---, cool white fluorescent lamp.

colored tablets, with and without ultraviolet absorber, were placed into glass Petri dishes and then stored in light cabinets simulating normal and exaggerated room illumination. Samples were also stored in a light cabinet in which a General Electric type R.S. sunlamp emitted light with a spectral energy distribution simulating sunlight. The heat radiated by the sunlamp was dissipated by an integrated blower system which maintained the temperature in the cabinet at 40°. The intensity of the light incident on the tablets in the respective cabinets was kept at a constant level through measurement with a Gossen Tri Lux meter at regular time intervals. The light intensities on the tablets in the normal and exaggerated light cabinets were 45 and 550 foot candles, respectively, with a spectral energy range from 350 to 700 $m\mu$ (Fig. 1). The intensity of light incident on the tablets in the cabinet using the sunlamp was 700 foot candles with a spectral range of 280 to 700 $m\mu$ (Fig. 1). Tablet samples were removed from the cabinets at designated time intervals for reflectance measurements.

Measurement of Tablet Reflectance.—The procedure and equipment employed to follow changes in reflectance at the surface of the tablet were described in previous reports (5, 6). Reflectance measurements were taken at 430 $m\mu$ for FD&C Yellow No. 5, 540 $m\mu$ for FD&C Red No. 3, and 640 $m\mu$ for FD&C Blue No. 1.

RESULTS AND DISCUSSION

The protection provided by 2,4-dihydroxybenzophenone on the light-induced fading of tablets colored with FD&C Blue No. 1, FD&C Red No. 3, and FD&C Yellow No. 5 was evaluated after exposure to three lighting conditions. This ultraviolet absorber was chosen because it did not impart any significant color to the tablets, exhibited good ethanol solubility, was nontoxic, and had high absorptivity throughout the ultraviolet region and into the violet-blue region of the visible spectrum. Representative curves showing the transmission characteristics of this ultraviolet absorbing chemical at 0.025% and 0.25% concentrations in methanol are presented in Fig. 2.

The plots in Figs. 3–8 show the influence of sunlamp illumination and normal and exaggerated room

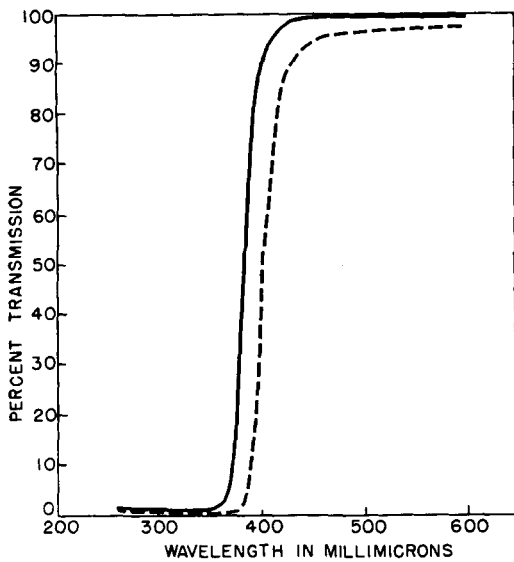


Fig. 2.—Absorption characteristics of ultraviolet absorber 2,4-dihydroxybenzophenone. —, 0.025%, 2,4-dihydroxybenzophenone 400 in methanol; ---, 0.25%, 2,4-dihydroxybenzophenone 400 in methanol.

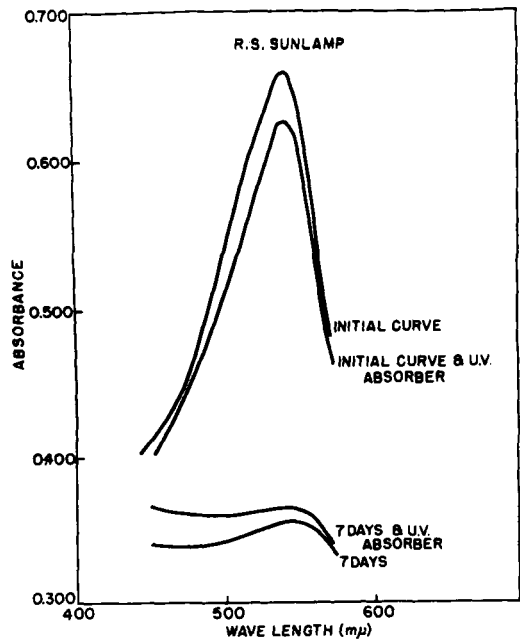


Fig. 4.—Visible absorption spectra of FD&C Red No. 3 after intervals of storage under simulated sunlight.

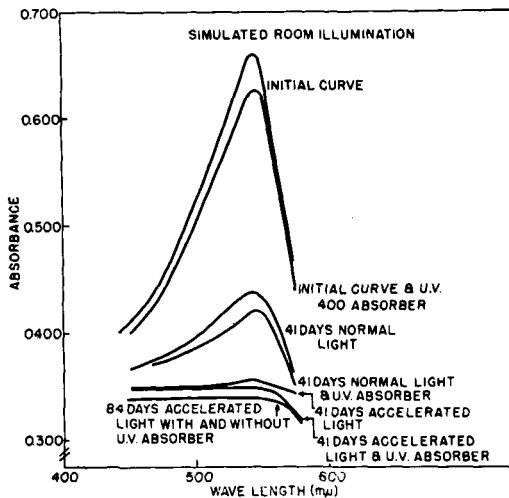


Fig. 3.—Visible absorption spectra of FD&C Red No. 3 after intervals of storage under normal and exaggerated illumination.

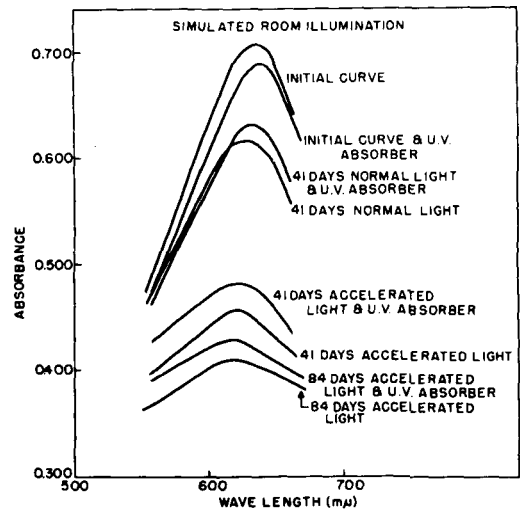


Fig. 5.—Visible absorption spectra of FD&C Blue No. 1 after intervals of storage under normal and exaggerated illumination.

lighting on the spectral absorbance at the surface of the colored tablets. It is apparent from Figs. 3 and 4 that the ultraviolet absorber does not significantly protect tablets colored with FD&C Red No. 3 when these are exposed to the three light sources. It is evident, however, that the tablets exposed to the radiations emitted from the sunlamp undergo more rapid fading than those exposed to exaggerated room lighting. This was also found to be true for the tablets colored with FD&C Blue No. 1 and FD&C Yellow No. 5.

The tablets colored with FD&C Blue No. 1 containing an ultraviolet absorber, were significantly protected from fading when exposed to each light

source. The greatest protection occurred with regard to radiations from the sunlamp, as shown in Figs. 5 and 6. In studying the curves in Fig. 5, it is difficult to explain the protective action of the ultraviolet absorber for the FD&C Blue No. 1 dye when considering its ineffectiveness with FD&C Red No. 3. In fact, the absorption maximum for FD&C Blue No. 1 is at 640 $m\mu$ which is about 100 $m\mu$ further in the visible spectrum than FD&C Red No. 3. However, by studying the complete absorption curve for FD&C Blue No. 1 as shown in Fig. 6, it becomes readily apparent that the blue color has two absorp-

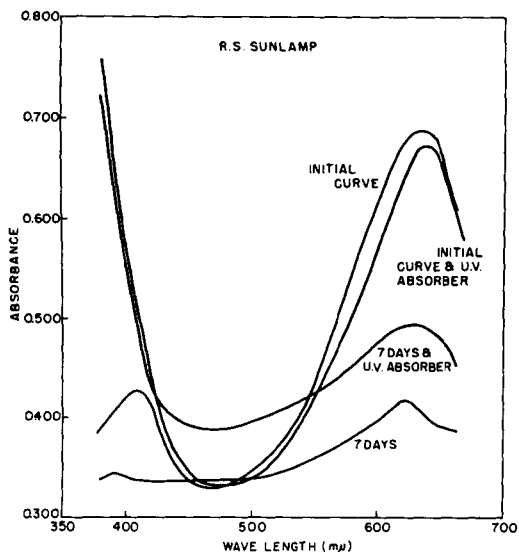


Fig. 6.—Visible absorption spectra of FD&C Blue No. 1 after intervals of storage under simulated sunlight.

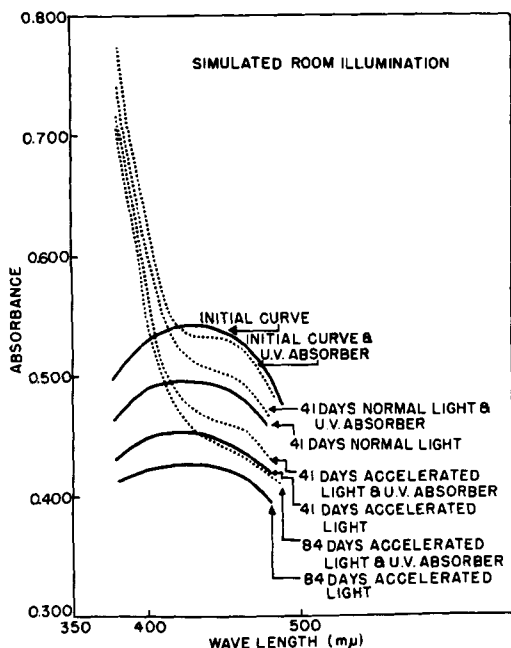


Fig. 7.—Visible absorption spectra of FD&C Yellow No. 5 after intervals of storage under normal and exaggerated illumination.

tion maxima, one at 640 $m\mu$ and another approaching the near ultraviolet 410 $m\mu$. The absorption maximum at 640 $m\mu$ is much stronger than the one at 410 $m\mu$. However, because of the strong absorbing tendencies of the ultraviolet absorber in the vicinity of 410 $m\mu$ peak of blue color, it would tend to protect this portion of the absorption curve of the dye. In turn, this would lessen the extent of fading at the absorption maximum of 640 $m\mu$. This effect is clearly shown in the absorption curves obtained for

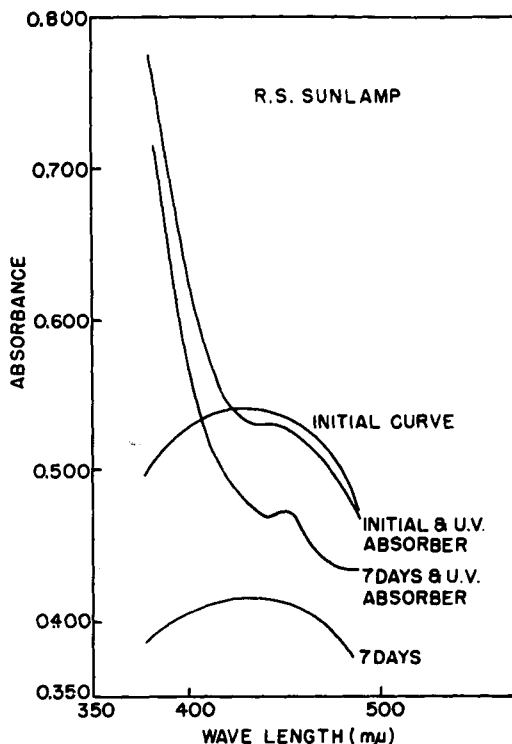


Fig. 8.—Visible absorption spectra of FD&C Yellow No. 5 after intervals of storage under simulated sunlight.

the tablets exposed to the radiations from the sunlamp (Fig. 6).

Of particular interest are the absorption curves obtained from the tablets colored with FD&C Yellow No. 5. It is evident from the curves in Figs. 7 and 8 that the absorption characteristics of the yellow color in tablets containing the ultraviolet absorber are drastically altered. This change can be ascribed to the strong absorbing properties of the 2,4-dihydroxybenzophenone in the vicinity of the absorption maximum of the yellow dye, which causes the overall spectral curve to take on the characteristics of the ultraviolet absorber.

The ultraviolet absorbing chemical exhibited its strongest stabilizing effect for the tablets colored with FD&C Yellow No. 5. This can be attributed to the close proximity of the absorption maximum of the color to that portion of the spectrum where the ultraviolet absorber exerts its strongest protective properties.

Representative plots showing the effect of the ultraviolet absorber on the rate of fading of tablets colored with FD&C Blue No. 1 and exposed to R.S. sunlamp and normal and exaggerated room illumination are presented in Figs. 9 and 10. From the linear regression of absorbance with time, it is apparent that the fading is proceeding according to apparent first-order kinetics. The plots show more than one slope and, in each instance, the initial rate of fading was greater than that obtained from the subsequent sections of the curve. Similar plots were obtained for FD&C Yellow No. 5 and FD&C Red No. 3. These results are similar to that found in our previous studies (6-8) and to those found by Baxter, *et al.*

TABLE I.—INFLUENCE OF AN ULTRAVIOLET ABSORBER ON THE RATE OF FADING OF COLORED COMPRESSED TABLETS STORED UNDER DIFFERENT LIGHT SOURCES

Color	Ordinary Room Illumination, Days $\times 10^2$		Exaggerated Room Illumination, Days $\times 10^2$		R. S. Sunlamp Illumination, Days $\times 10^4$	
	With U.V. Absorber	Without U.V. Absorber	With U.V. Absorber	Without U.V. Absorber	With U.V. Absorber	Without U.V. Absorber
FD&C Blue No. 1	3.0	4.3	14.3	16.9	64.9	252
FD&C Red No. 3	34.5	36.1	166	152	565	576
FD&C Yellow No. 5	1.8	2.3	2.4	5.8	9.4	125

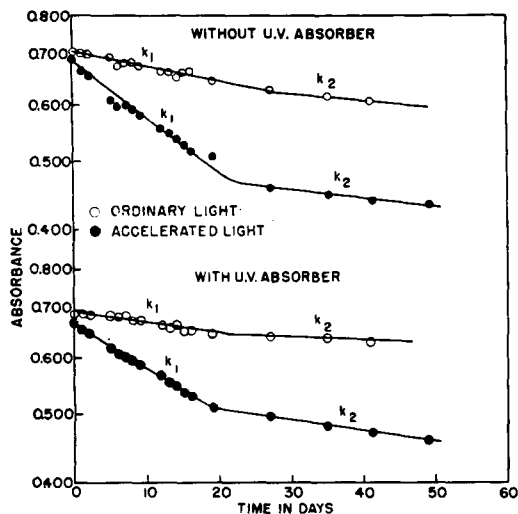


Fig. 9.—Influence of normal and exaggerated room illumination on the fading of the surface of tablets colored with FD&C Blue No. 1.

(9), in their investigations of fastness of dyes in textiles. As was indicated previously, the changes in reaction rates that are observed as the duration of irradiation is increased do not necessarily indicate that the fading mechanism consists of a series of consecutive reactions of different rates. Rather, they are generally due to several contributing factors, amongst which are: (a) alterations of the quantity of light reflected and absorbed at the surface of the tablet as fading proceeds, (b) subsequent changes in the amount of energy available to bring molecules to the excited state, (c) possible absorption of certain amounts of energy by the decomposition products, (d) porous nature of the tablets, (e) influence of substrates on the photoreaction, (f) the possibility of reaction between dye and its decomposition products, and (g) secondary reactions involving the dye and atmosphere.

Since the rate constants obtained from the first slope of the curve most accurately represent the photodegradation of the dye at the tablet surface, only the initial rate constants will be used in the subsequent discussions. The rate constants calculated from the initial slopes of the plots of log absorbance vs. time are summarized in Table I.

The data presented in this table demonstrate that the ultraviolet absorber exerted no significant protective action against fading from the surface of tablets colored with FD&C Red No. 3. However, for tablets colored with FD&C Yellow No. 5 the ultraviolet absorber reduced substantially the fading rate at the tablet surface. It is also apparent from

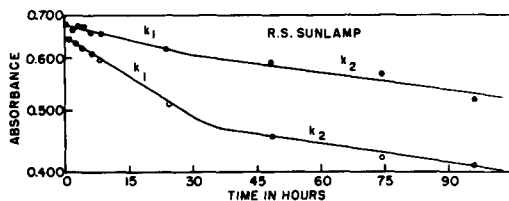


Fig. 10.—Influence of simulated sunlight on the fading of the surface of tablets colored with FD&C Blue No. 1. O, Without ultraviolet light absorber; ●, with ultraviolet light absorber.

the data in this table that the ultraviolet absorber was most effective against the light radiations from the sunlamp which was composed of significant energy in the near ultraviolet. This can be attributed to the fact that the ultraviolet absorber transmits essentially no light energy up to 400 $m\mu$. The protective action of the ultraviolet absorber against ordinary and exaggerated room illumination was minor as compared to that observed under sunlamp illumination.

The radiations from the sunlamp caused the most rapid fading for each color studied. This may be explained by the fact that the radiations in the ultraviolet spectrum emitted by the sunlamp are more active chemically than the longer visible wavelength radiations.

It is important to note that the R.S. sunlamp radiates a substantial amount of heat as well as light radiations. In order to diminish the influence of heat on the rate of fading of the colored tablets, an exhaust fan was placed into the light cabinet. This reduced the temperature to a constant level of 40°. Thus, in evaluating the data obtained under this light source, one must realize that the fading is due to both light and thermal radiations. In the studies performed under normal and exaggerated room illuminations the temperature of the tablets was maintained at approximately 25°.

From the information obtained in this investigation, it is apparent that ultraviolet absorbing chemicals exert only small, if any, stabilizing effects against fading of colored tablets exposed to normal and exaggerated artificial room illumination. On the other hand, with respect to protection against sun radiations, ultraviolet absorbers can be very beneficial. In certain instances, however, the use of ultraviolet absorbers in the presence of sun radiations may not exert any protective action, as evidenced by the data obtained for tablets colored with FD&C Red No. 3. Hardy and Coleman (10) and Gantz and Sumner (11) also found that ultraviolet absorbers do not protect all dyestuffs.

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.

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. Complex tablet press. Beckman spectrophotometer model DU with reflectance attachment (4). Cary

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