where C_t, C_B, and C_f represent the concentrations of total, bound, and free drug, respectively. The concentration of bound drug can be written as shown in Eq. 1. Differentiation of Eq. 1 yields:

$$\frac{d(C_B)}{dt} = \left[\frac{n_1 K_{a_1} P}{(1 + K_{a_1} C_f)^2} + \frac{n_2 K_{a_2} P}{(1 + K_{a_2} C_f)^2}\right] \frac{d(C_f)}{dt} \qquad \text{(Eq. A3)}$$

Substitution of Eqs. A3 and A2 into Eq. 5 yields Eq. 6.

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Stabilization of Sulfisomidine Tablets by Use of Film Coating Containing UV Absorber: Protection of Coloration and Photolytic Degradation from Exaggerated Light

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Abstract □ The effect of model polymer coating films of vinyl acetate, containing oxybenzone as a UV absorber, on the coloration and photolytic degradation of simple sulfisomidine tablets was examined to attempt stabilization of photosensitive solid dosage forms. Coloration of the tablet surface was followed by the tristimulus colorimetric method in the fading tester equipped with a mercury vapor lamp. Photolytic degradation in the UV region was investigated by a new method for measuring the absorption spectra of a crystal sample in the gas phase, *i.e.*, the semi-integral *attenuance spectra*. Two parameters of a film, thickness and concentration of the UV absorber, were varied at every exposure. These physical and chemical changes are discussed in relation to light transmission properties of films.

Keyphrases □ Sulfisomidine tablets—effect of film coating containing UV absorber on coloration and photolytic degradation □ Film coating—containing UV absorber, effect on coloration and photolytic degradation of sulfisomidine tablets □ UV absorber—contained in film coating, effect on coloration and photolytic degradation of sulfisomidine tablets □ Coloration—sulfisomidine tablets, effect of film coating containing UV absorber □ Photolytic degradation—sulfisomidine tablets, effect of film coating containing UV absorber □ Degradation, photolytic—sulfisomidine tablets, effect of film coating containing UV absorber □ Tablets—sulfisomidine, coloration and photolytic degradation, effect of film coating containing UV absorber

Many solid pharmaceutical medicaments exhibit physical or chemical changes because of the radiant energy of light. Light irradiation can cause color development or color fading. From pharmaceutical and therapeutic standpoints, physical changes can be as serious as chemical instability of the active ingredient. Therefore, protection of solid dosage forms under storage from the deleterious effects of light is one problem in quality control.

Pharmaceutical products can be adequately protected by the use of special glass containers, *i.e.*, light-resistant containers specified in pharmacopeias. The protective effect of colored glass on the fading of tablets containing colorants (1, 2) and on the coloration and photolytic degradation of photolabile sulfisomidine tablets (3) has been investigated.

Coating tablets with a polymer film containing UV absorbers may be another method for protection from light. Along with the use of light-resistant containers, this approach should increase the protective effect since the coating is applied to individual tablets. The effect of the protective coating on the photostability of colorants used in the tablet coating also was studied (4–6), but no report dealt with organic active ingredients. One interesting point in such studies of solid-state stability is the relationship shown to exist (3) between the apparent and chemical changes.

The purpose of the present work was to investigate the

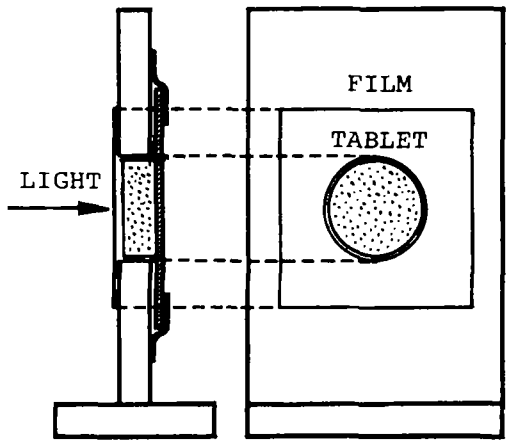

Figure 1—*Sample holder for exposure test.*

possibility of protection of dosage forms from physical and chemical changes by applying films containing a commercially available UV absorber. The solution of this problem may indicate ways to improve photolabile solid dosage forms. In examining solid-state stability, it is desirable to follow the change of samples in the solid rather than liquid state since they may exhibit different behavior in solution due to the effect of a solvent. To satisfy this requirement, a new method for measuring the absorption spectra of a crystal in the gas phase was employed, and solid-state stability was quantitated.

EXPERIMENTAL

Preparation of Tablets—One gram of sulfisomidine JP, <100 mesh in size, was filled into a single set of flat-faced punches and die, which was equipped with a compression–tension testing machine[1]. Tablets of 15-mm diameter and 4.5-mm thickness were prepared. To unify the surface condition of each tablet, a constant compression force of 2000 kg was used. Each tablet was adhered to a glass plate with an epoxide resin. Samples were stored over silica gel in a desiccator in the dark until the exposure test.

Preparation and Application of Polymer Films—Films containing a UV absorber were prepared according to the following formula: vinyl acetate (50% polymer), 10–25 g; 1,1,1-trichloroethane, 47.8–39.4 g; ethanol, 37.2–30.6 g; 2-ethoxyethanol, 5 g; and oxybenzone, *q.s.* for a total of 100 g.

Five grams of 2-ethoxyethanol, a given amount of vinyl acetate of a film base, and oxybenzone[2] (2-hydroxy-4-methoxybenzophenone) as a UV absorber were added to a mixed solvent of 1,1,1-trichloroethane and ethanol in the ratio of 54:42 (w/w) and then thoroughly dispersed and dissolved with a homogenizer. Each 5 ml of these solutions was spread over a flat horizontal glass plate and dried for 7 days at room temperature. Then the completely polymerized and transparent films were peeled, and sample films of 3 × 3 cm were prepared.

The thickness of films was varied from 18 to 110 μm by changing the amount of vinyl acetate and mixed solvent; it was obtained as a mean of the measured values at the four fixed points on a film using an electromagnetic thickness meter[3]. The concentrations of oxybenzone added were 0.5–10% of the weight of the dried film. These films were fixed on the front side of the holders for sample tablets as a case model of film-coated dosage forms.

Exposure Test—The sample holders (Fig. 1) were placed in the rack of a fading tester[4] with a 400-w mercury vapor lamp[5], as reported previously (2), and exposed to UV rays. The spectral energy distribution of this lamp included 13 line spectra with a high proportion of radiation (highest intensity at 365 and 577 nm) and a continuous spectrum with low intensity within the range of 280–720 nm. The distance between the light source and the sample was 30 cm.

The irradiation energy (300–400 nm) and illumination at the surface of a sample tablet were 3.47×10^3 μw/cm^2 and 1.74×10^4 lx, as measured with a UV intensity meter[6] and an illumination meter[7], respectively. Samples were withdrawn from the fading tester at designated time intervals for colorimetry. Elevation of temperature in the fading tester was prevented by a constantly operating fan; the temperature was maintained below 27°.

Colorimetric Measurements—To obtain a quantitative color measurement related to human color perception, the surface color of the tablets in the *Lab* system was measured with an integrating sphere-type color and color difference meter[8] equipped with a halogen lamp as the light source. A barium sulfate plate was used as the reflectance standard. The Hunter color difference formula employed to evaluate the degree of coloration is expressed by (7):

$$\Delta E(Lab) = [(\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2]^{1/2} \qquad \text{(Eq. 1)}$$

where $\Delta E(Lab)$ is the color difference in National Bureau of Standards (NBS) units in the *Lab* system, and ΔL, Δa, and Δb are the differences between two lightness values, L, and those between chromaticity coordinates a and b in the *Lab* system.

Fluctuations in the values of L, a, and b of one sample fell within 0.1 NBS unit. After the measurement, samples were returned into the fading tester, and exposure was continued.

Absorption Measurements—To follow changes in the absorption spectra of sample powders in the gas phase, a drop of acetone solution of pure sulfisomidine was placed on a quartz glass plate. The sample particles (particle size of 2–5 μm) were allowed to recrystallize on it by evaporating the solvent thoroughly and were exposed to light in the same manner as the tablets. At every exposure, they were placed in the attachment unit for semitransparent samples of a multipurpose recording spectrophotometer[9]; the absorption spectra (more precisely, the semi-integral attenuance spectra) were measured in the UV region with air as the absorption control. The semi-integral attenuance, ${}_pE_t$, is defined by (8):

$${}_pE_t = \log(I_o/I_t) \qquad \text{(Eq. 2)}$$

where $I_o = I_t + I_a + I_r$; $I_t = I_p + I_d$; $I_r = I_{sr} + I_{dr}$; I_o, I_t, and I_r are the energies of incident, transmitted, and reflected light, respectively; and the subscripts a, p, d, sr, and dr indicate absorbed, parallel transmitted, diffusely transmitted, specularly reflected, and diffusely reflected light, respectively. The transmission spectra of films were also measured, using the same spectrophotometer.

RESULTS AND DISCUSSION

Effects of Film Thickness and Concentration of Oxybenzone on Coloration—The previous study (3) with glass color filters, which have a variety of light transmission properties, showed that the photostability of sulfisomidine tablets was significantly affected by the amount of UV rays and that their coloration best fit an apparent second-order degradation equation with respect to colorimetric values.

Figure 2 gives the color changes of tablet surfaces protected with films containing oxybenzone. The result where the chromaticity coordinates, a and b, are close to zero and lightness L is nearly 100 before exposure demonstrates that the surface color of a tablet is nearly white. Characteristic changes in the values of L, a, and b were observed in the earlier stage of exposure, as in the previous work. After these marked changes, the color development followed a definite trend which was a function of time. The trajectory of the point (a_t, b_t), where t is exposure time, on the chromaticity diagram (not presented in this paper) showed that the surface color became gradually yellow tan as the exposure time proceeded.

Changes in these colorimetric values were affected by thickness of the film; the thicker the film, the more effective was its protection from coloration. The fact that the protective effect was remarkable, especially in both L and b, suggests that the yellowness of tablets was controlled by film coating.

The plots of the reciprocal of colorimetric values against time in Fig. 3 gave a good linear relation except in the early stage. It was confirmed

[1] Autograph model IS-5000, Shimadzu Co., Kyoto, Japan.
[2] Uvinul-M40, Ogawa Perfume Co., Tokyo, Japan.
[3] Permascope type ES-8, Helmut Fischer GMBH & Co., Maichingen, West Germany.
[4] Model MH-1, Mitsubishi Electric Co., Tokyo, Japan.
[5] JIS C 7604, high-pressure mercury lamps for color fading.
[6] Model UVR-365, Tokyo Optical Instruments Co., Tokyo, Japan.
[7] Model SPI-5, Tokyo Optical Instruments Co., Tokyo, Japan.
[8] Model ND-101, Nippon Denshoku Co., Tokyo, Japan.
[9] Model MPS-50L, Shimadzu Co., Kyoto, Japan.

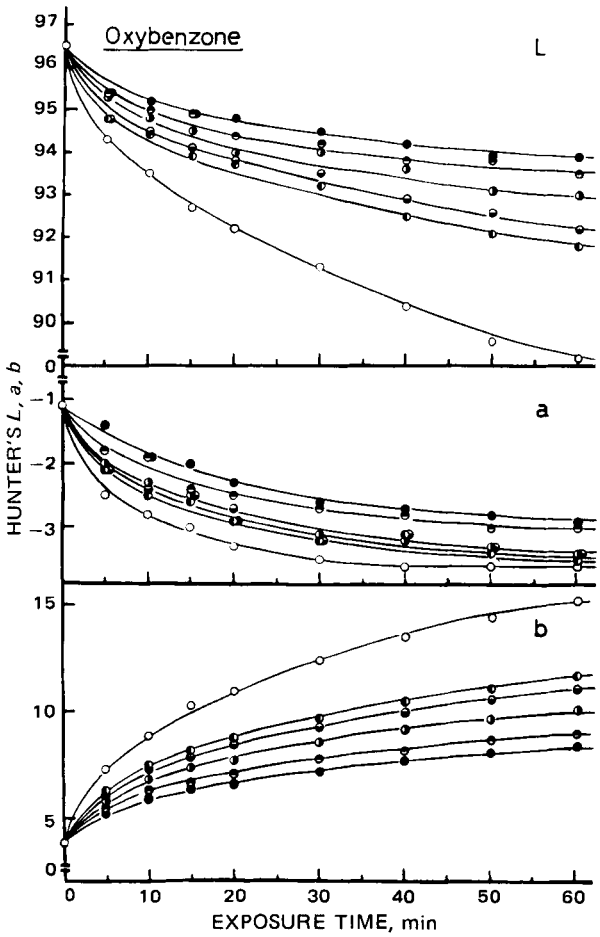

Figure 2—*Effect of exposure time and film thickness on Hunter's colorimetric values. Key:* ○, *control;* ◐, *20 μm;* ◒, *30 μm;* ◑, *50 μm;* ◓, *67 μm; and* ●, *85 μm.*

that the coloration kinetics were apparent second order also in the presence of the UV absorber, and the following equations may be applied:

$$1/L = k_L t + 1/L_0 \qquad \text{(Eq. 3}a\text{)}$$

$$1/a = k_a t + 1/a_0 \qquad \text{(Eq. 3}b\text{)}$$

$$1/b = -k_b t + 1/b_0 \qquad \text{(Eq. 3}c\text{)}$$

where k_L, k_a, and k_b are second-order rate constants with respect to L, a, and b, respectively; and L_0, a_0, and b_0 are values of L, a, and b extrapolated to the zero time. The values of L_0, a_0, and b_0 did not agree with those observed initially. This fact indicates that the complex coloration reaction is in progress in the early stage of exposure.

To examine the effect of film thickness in detail, the initial coloration rate and the rate of stabilization were defined for the first portion that deviated from the straight line and for the subsequent straight portion in Fig. 3, respectively.

The colorimetric values, L, a, and b, are scalars in themselves; however, if they are given as point A (L, a, b) in three-dimensional color space, the movement of point A should be expressed as a vector quantity. When the magnitude and direction of vector **A** vary continuously, accompanying the change of a variable, t (time), **A** should be a continuous function of t. Therefore, Eq. 4, the differential coefficient at $t = 0$ of the vector **A**, may be given as the initial coloration rate:

$$\left|\frac{d\mathbf{A}}{dt}\right|_{t=0} = \sqrt{\left(\frac{d\mathbf{A}_L}{dt}\right)^2_{t=0} + \left(\frac{d\mathbf{A}_a}{dt}\right)^2_{t=0} + \left(\frac{d\mathbf{A}_b}{dt}\right)^2_{t=0}} \qquad \text{(Eq. 4)}$$

where $\mathbf{A}_L$, $\mathbf{A}_a$, and $\mathbf{A}_b$ are components of the vectors L, a, and b, respectively, and t is exposure time. On calculating Eq. 4, $d\mathbf{A}_L/dt$, $d\mathbf{A}_a/dt$, and $d\mathbf{A}_b/dt$ were obtained by numerical differentiation of the smoothed curves in Fig. 2.

The rate of stabilization (R.S.) was calculated using:

$$\text{R.S.} = (k_{L_0} - k_L)/k_{L_0} \times 100\ (\%) \qquad \text{(Eq. 5)}$$

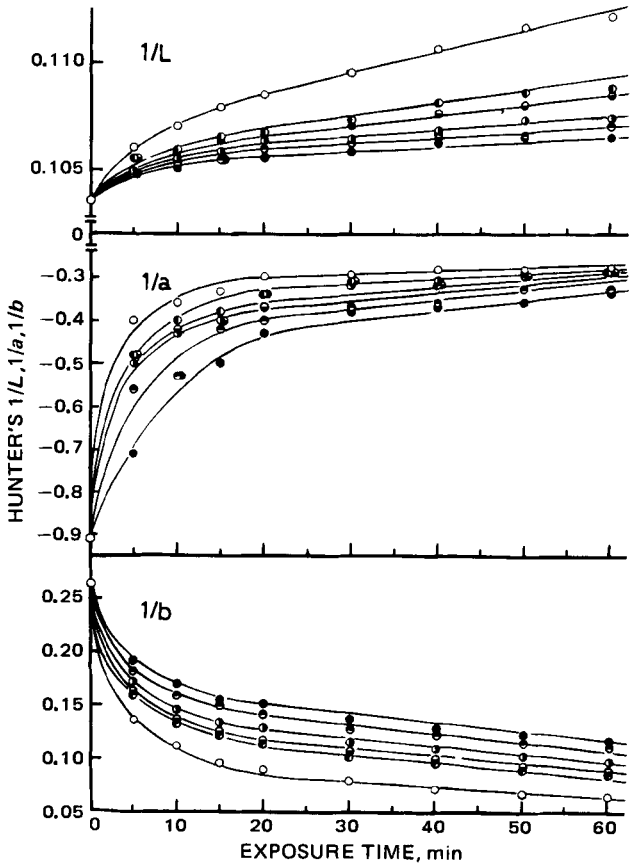

Figure 3—*Reciprocal plots of Hunter's colorimetric values in Fig. 2. Key:* ○, *control;* ◐, *20 μm;* ◒, *30 μm;* ◑, *50 μm;* ◓, *67 μm; and* ●, *85 μm.*

where k_{L_0} is the value of k_L obtained from the control without any film. Equation 5 is based on the result that, among the values of k_L, k_a, and k_b calculated from the regression lines in the portion of the second-order kinetics, the thickness of films affected mostly the k_L value but hardly affected the others.

The effects of film thickness on the initial coloration rate and on the rate of stabilization are shown in Figs. 4 and 5, respectively. The initial coloration rate was reduced significantly with increasing thickness at every concentration, and its effect increased with a decreasing concentration of oxybenzone in the range of great thickness. The values of the initial coloration rate for higher concentrations of oxybenzone were re-

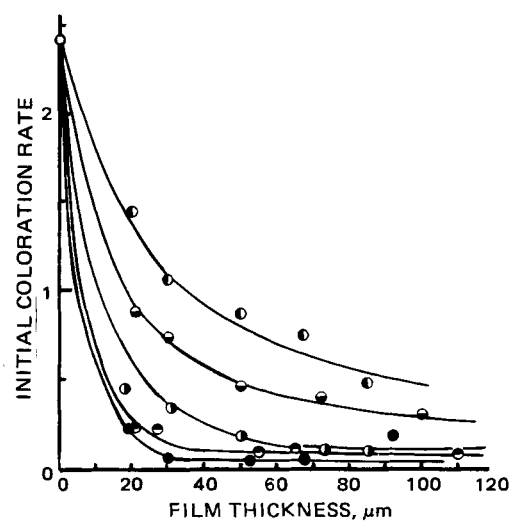

Figure 4—*Effect of film thickness and concentration of oxybenzone on initial coloration rate. Key:* ○, *control;* ◐, *0.5%;* ◒, *1%;* ◑, *2%;* ◓, *5%; and* ●, *10%.*

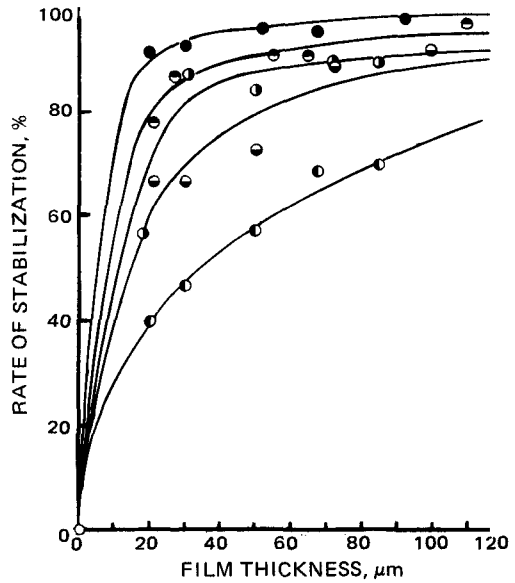

Figure 5—*Effect of film thickness and concentration of oxybenzone on rate of stabilization. Key:* ○, *control;* ◐, *0.5%;* ◒, *1%;* ◑, *2%;* ◓, *5%; and* ●, *10%.*

duced nearly to zero with a small film thickness, and the rate remained constant with additional increases in film thickness. Therefore, the protective effectiveness of a 10% addition of oxybenzone against initial coloration is almost wholly attained with about a 30-μm film thickness and is saturated in the greater thickness.

The dependency of rates of stabilization on the additive concentration of oxybenzone and film thickness in Fig. 5 showed good correspondence to that of the initial coloration rates; the rate of stabilization increased with an increase of both parameters, exhibiting a rapid initial rise and reaching values of more than 90% of stabilization above 5% addition of oxybenzone. The results illustrated in Figs. 4 and 5 indicate that if initial coloration can be protected, control of subsequent coloration also should be satisfactory.

This evidence on coloration is summarized in Fig. 6 as the color difference, ΔE, before and after 60-min exposure *versus* film thickness. At a 10% concentration of oxybenzone, ΔE remained nearly 1 NBS unit, even after such an exaggerated exposure. It was confirmed (9) that two colors less than 1 NBS unit in color difference could not be distinguished visually. Therefore, apparent coloration probably did not occur for this concentration. For a 0.5% concentration, the color difference became less than 6 NBS units for more than 80-μm film thickness. Consequently, coloration was visually "appreciable," whereas it was "very much" for the control on comparison with the relationship between visual perception and color difference (10).

Light Transmission Properties of Films—The bonding strength between atoms of photosensitive medicinal substances is usually smaller than that of ordinary organic compounds. When such substances are

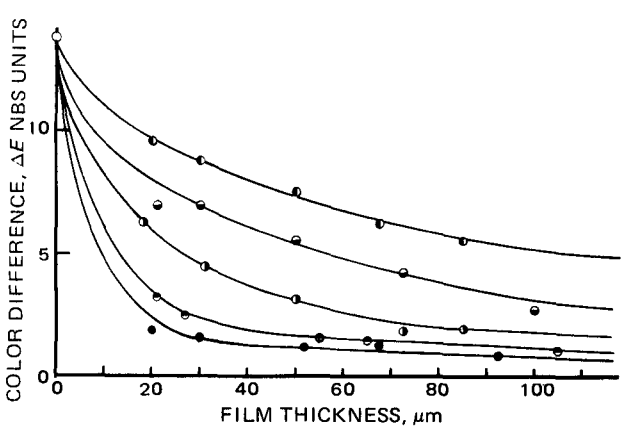

Figure 6—*Effect of film thickness and concentration of oxybenzone on coloration after a 60-min exposure. Key:* ○, *control;* ◐, *0.5%;* ◒, *1%;* ◑, *2%;* ◓, *5%; and* ●, *10%.*

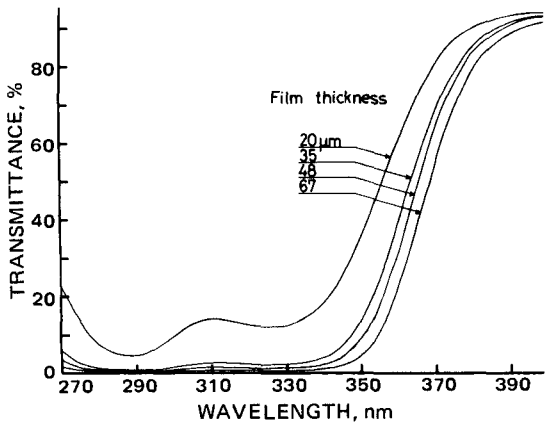

Figure 7—*Transmission curves of films containing 0.5% oxybenzone.*

exposed to light, dissociation of the bonds, *i.e.*, photolytic degradation, can occur only if the energy of light absorbed by the molecule is equal to or greater than the bonding energy. According to the quantum theory, the radiant energy of light is in inverse proportion to the wavelength. Thus, the contribution of UV rays is of prime importance in this study. Results presented previously suggest that the difference in the behavior of coloration must depend on the light transmission properties of a film.

Figure 7 shows transmission curves of films containing 0.5% oxybenzone. These films showed no change in the character of the transmission curves on 60 min of exposure to light, thus indicating that oxybenzone is photostable and will not decompose. The film without oxybenzone was virtually transparent to light above 270 nm; it did not show any absorption band, and its thickness did not affect the transmission curve in this region.

The percentage transmission of each curve in the shorter wavelength region was much lower than that in the visible region, exhibiting the maximum transmission at 310 nm and decreasing with increasing film thickness over the UV region. For more than 35-μm thickness, the shielding effect against light in the UV region was almost complete, and the films showed an excellent protective effect. Calculation of the "Sunscreen Index" according to Kumler (11) gave oxybenzone a high index of approximately 14.4. While the transmission properties in the visible region above 400 nm were little affected by film thickness, the wavelength at which the curve rose shifted to longer wavelengths and the

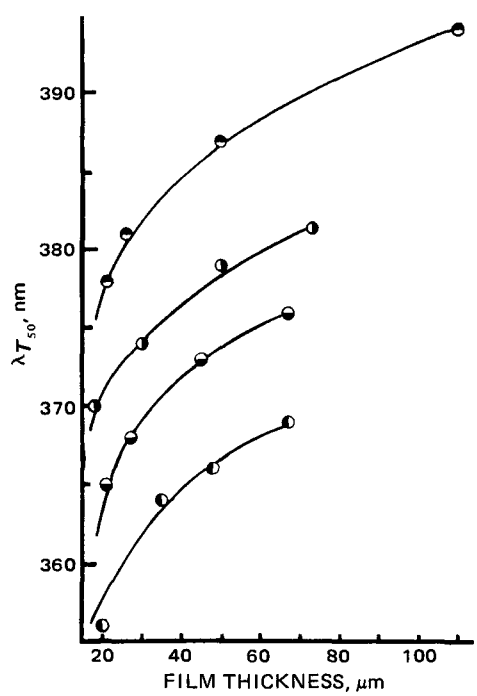

Figure 8—*Effect of film thickness and concentration of oxybenzone on* $\lambda_{T_{50}}$. *Key:* ◐, *0.5%;* ◒, *1%;* ◑, *2%; and* ◓, *5%.*

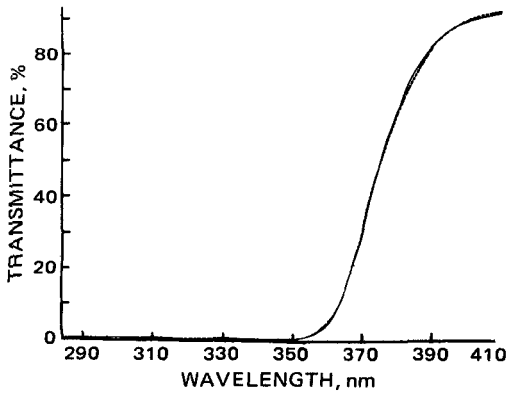

Figure 9—*Transmission properties of films having a similar* CL *value. Key* (CL *value*): —, *67.0 (1%, 67 μm); and - - -, 62.0 (2%, 31 μm).*

slope of the curve became steeper with increasing thickness. The same tendency was found when the additive concentration was varied for one thickness. From these characteristics, the film containing oxybenzone can be considered to play the role of a sharp-cut filter.

The effect of addition of oxybenzone on the cut wavelength of a film, λ_{T50}, at which the percentage transmission corresponds to 50% on the transmission curve, is shown in Fig. 8. The intensity of more than 50% of the line spectrum at 365 nm, which was the highest in the UV region, was shut out even for a 0.5% film of 50-μm thickness and most of the UV rays for a 5% film of 110 μm. It was proved from this finding and the data shown in Fig. 7 that visible light could not take part in the coloration.

According to the Lambert–Beer law, the absorbance of a solution is in proportion to the product of its concentration, C, and the length of the light path, L. Therefore, films having the same value of this product should give the same transmission curve if this law holds. The transmission curves of two films having a similar *CL* value are shown in Fig. 9; the transmission properties of both curves coincide precisely over the whole wavelength range, indicating that this law is applicable to a solid film. Consequently, a 0.5% film of 40-μm thickness, for example, would have as much protective effectiveness as a 2% film of 10 μm. The validity of this statement is supported by the fact that plots having a similar *CL* value in Figs. 4 and 5 gave approximately equal values of two parameters for coloration. In any case, the protective effectiveness of films from light should be evaluated not only by cut wavelengths but also by steepness of the transmission curve.

Photolytic Degradation—The mechanism of coloration of solid materials by light has not been fully understood because of its complex reaction system. Thus, it is not well known whether coloration has some connection with decomposition. However, photolytic degradation of materials in solid dosage forms is essentially a surface phenomenon. In such a case, to study the effect of light properly, microscopic crystal particles of sample materials should be exposed to light so that they uniformly absorb the energy of light and then should be analyzed spectrophotometrically.

Typical absorption spectra for the control and 0.5% film of 20 μm are given in Figs. 10 and 11, respectively. The spectrum of the original state before exposure gave an absorption maximum and minimum at 266 and 232 nm, respectively. As the exposure time proceeded, the absorption curve showed a flattening tendency, increasing the minimum and decreasing the maximum. The isosbestic points were confirmed at 219, 253, and 317 nm; for a 0.5% film, however, these points were not obtained and

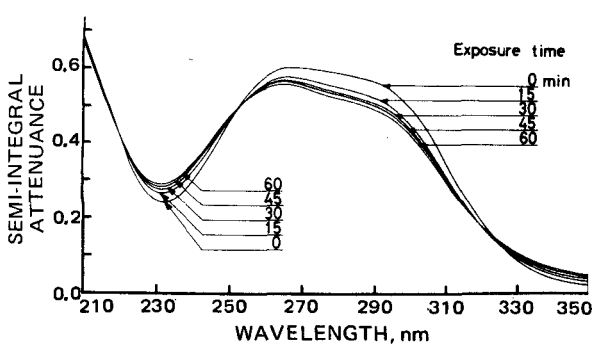

Figure 10—*Effect of exposure time on absorption spectrum for control.*

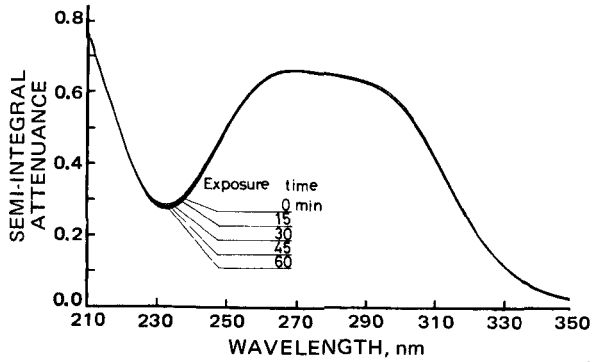

Figure 11—*Effect of exposure time on absorption spectrum for 0.5% film of 20 μm.*

the absorption curve gradually decreased without intersecting the original curve in any wavelength region. The photolytic degradation was not apparently observed for films with more than 1% addition. The presence and absence of isosbestic points may suggest induction of a photooxidation reaction on the crystal surface, which has a selectivity with respect to wavelength.

The changes in the nondimensionalized absorbance at 266 nm, E_t/E_0, with time (3) indicated that the degradation followed apparent zero-order kinetics, accompanying an induction period, and that the kinetic equation might be applied as follows:

$$d(E_t/E_0)/dt = -k \qquad \text{(Eq. 6}a\text{)}$$

or:

$$E_t/E_0 = 1 - kt \qquad \text{(Eq. 6}b\text{)}$$

where k is the apparent zero-order rate constant and the subscripts t and 0 are exposure time and initial time, respectively. From these degradation kinetics, it was confirmed that even a 0.5% film of 20-μm thickness, which permitted the transmission of UV rays the most among the films used, was less than 2% degraded after the 60-min exposure whereas the control was 8% degraded. This fact demonstrates that a lower concentration of addition gives sufficient protection from degradation.

It was stated (12) that the color change not indicative of significant degradation might be visually unacceptable. However, the result illustrated in Fig. 6 suggests that an evident correlation does not always exist between coloration and photolytic degradation. For films with more than 1% addition, sulfisomidine tablets under ordinary storage conditions will be sufficiently stable and remain unchanged; the tablets were hardly changed in spite of their coloration, even under intense UV irradiation. These films are expected to have a better protective effectiveness for degradation than for coloration.

SUMMARY AND CONCLUSIONS

The photolabile sulfisomidine tablets protected by a polymer film containing oxybenzone were exposed to exaggerated UV rays in a fading tester. Coloration of these tablet surfaces was significantly controlled by a film coating, and the coloration kinetics were apparent second order, accompanying an induction period with respect to colorimetric values. Two variables to evaluate the protective effectiveness of the film, the initial coloration rate and the rate of stabilization, showed a good correspondence and were improved with increasing film thickness or concentration of oxybenzone. The visible light apparently could not be responsible for these coloration processes.

From the light transmission properties of the films, they could be considered as sharp-cut filters. The cut wavelength, which permitted the transmission of 50% of the light, shifted to longer wavelengths with increasing film thickness, indicating improvement of the shielding effect of UV energy.

Photolytic degradation, examined by a spectrophotometric method, followed apparent zero-order kinetics, accompanying a similar induction period as the coloration, presumably due to photooxidation on the surface of crystal particles. However, photolytic degradation was not observed with higher concentrations of oxybenzone. Results obtained from coloration and photolytic degradation suggested that an evident correlation did not necessarily exist between them.

In conclusion, a UV absorber, if nonpoisonous for the additive amount in the ordinary dosage administration, is expected to be an excellent additive for the protection of photolabile solid dosage forms.

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Electron-Capture Detector GLC Technique for Estimating Tocainide in Biological Fluids

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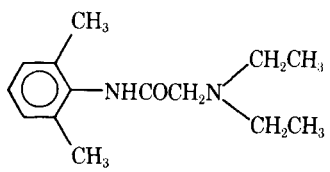
Abstract □ A sensitive and specific electron-capture detector GLC method capable of detecting picogram quantities of tocainide, a lidocaine analog, in biological fluids was developed. This method consists of extracting the compound into methylene chloride and derivatizing with heptafluorobutyric anhydride to form the monoheptafluorobutyryl derivative. The derivative formation was confirmed by GLC–mass spectrometry. Quantitative estimation was performed using 1-bromonaphthalene as an internal standard. The minimum detectable level by the electron-capture method was approximately 30 pg/injection as opposed to approximately 3 ng/injection with a flame-ionization detector. Linear response was observed in the range from 50 pg to 3 ng using an electron-capture detector. No interference from endogenous substances was observed.

Keyphrases □ Tocainide—electron-capture GLC analysis in biological fluids □ GLC, electron capture—analysis, tocainide in biological fluids □ Cardiac depressants—tocainide, electron-capture GLC analysis in biological fluids

Lidocaine (I), a commonly used drug in acute coronary care for the treatment of acute myocardial infarction (1), has a prompt onset of action and elicits minimal hemodynamic disturbances (2). In spite of these advantages over other commonly used antiarrhythmic agents such as propranolol, procainamide, and quinidine (3), lidocaine is not an ideal antiarrhythmic agent. Its undesirable features include a short biological half-life ($t_{1/2}$ = 90 min) (4), inactivation by first-pass metabolism (5), and formation of toxic metabolites (6).

Tocainide[1,2], 2-amino-*N*-(2,6-dimethylphenyl)propanamide (II) hydrochloride, a primary amine analog of lidocaine, has antiarrhythmic activity without the disadvantages of lidocaine therapy. Tocainide exhibits a biological half-life of approximately 11 hr in normal healthy volunteers (7), oral effectiveness (8), and total availability after oral administration (9).



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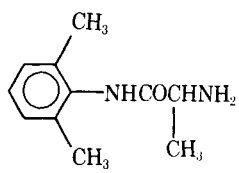

II

A flame-ionization detector GLC assay method was developed for the separation and quantitation of this compound in biological fluids[3]. Flame-ionization detectors are inherently less sensitive than electron-capture or nitrogen-specific detectors and, as a consequence, relatively large volumes of biological samples (1–5 ml of blood) are required for quantitation of compounds. Unfortunately, the sample volume required for the flame-ionization detector method is greater than what can be routinely obtained from small animals when serial samples are taken.

The limitations of the flame-ionization detector assay technique necessitated the development of a more sensitive assay method for the quantitative analysis of II. It was desirable to convert II to a suitable derivative that is highly electronegative and amenable to electron-capture detection. Several derivatizing agents have been used in the quantitative analysis of primary amines (10). In the present study, heptafluorobutyric anhydride satisfied the requirements.

EXPERIMENTAL

Materials—The hydrochloride salt of II was used. The solvents, methylene chloride[4], hexane[4], and benzene[4], were either pesticide grade[5] or distilled in glass.

[1] Astra Pharmaceutical Products, Framingham, Mass.

[2] Previous publications referred to this compound as W36095-HCL.

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[4] Caledon, Georgetown, Ontario, Canada.

[5] Nanograde, Mallinckrodt Chemical Works, St. Louis, Mo.