[Chem. Pharm. Bull. 24(9)2229—2236(1976)]

UDC 615.453.6.011.4 : 615.014.4

Stability of Solid Dosage Forms. II.[1] Coloration and Photolytic Degradation of Sulfisomidine Tablets by Exaggerated Ultraviolet Irradiation

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(Received March 15, 1976)

The solid-state stability of sulfisomidine tablet under the irradiation of ultraviolet rays, was investigated colorimetrically and spectrophotometrically. The coloration of tablet surface was followed in the *Lab* system in the fade-o-meter. In order to examine the effect of ultraviolet intensity on the rate of coloration and photolytic degradation, a series of glass color filters which shut off the ultraviolet rays in order, were employed. The coloration was found to best fit an apparent second-order degradation equation with respect to colorimetric values.

Photolytic degradation was investigated by the semi-integral attenuance spectra in the ultraviolet region. It proceeded following the apparent zero-order kinetics which accompany an induction period. The ultraviolet intensity affected the kinetic constants as well as in the coloration. These degradation behaviors in the solid state were compared with the aqueous solution state.

Since the solid dosage medicament remains the most popular of today's commercially available and prescription drug products, there is a great need for methods of predicting their stability under various conditions of storage. However, stability of solid dosage forms is more difficult to study than that in liquid dosage forms, because the degradation mechanism of active ingredient is complex due to the inhomogeneity of the system. It has been well recognized that the important factors contributing to the degradation of pure organic compounds in the solid state are temperature, humidity, and light. Although there are a relative large number of reports concerned with the effects of temperature and humidity,[3] there is a conspicuous scarcity of reports dealing with the effect of light,[4] as far as we are aware. This may be attributed to the fact that the photochemically induced organic reactions in the crystalline or solid state, and the correspondence between the accelerated and ordinary storage conditions are not fully understood yet. Nevertheless, many pharmaceutical medicaments exhibit physical or chemical changes due to the radiant energy of light. As a result, light irradiation can cause color development or color fading. Sulfonamides, as an example, are known to be affected by light, and their stability to light[5] or heat[6] in the form of injection has been investigated.

The purpose of the present work was to investigate the physical and chemical changes of simple sulfisomidine tablets under the irradiation of ultraviolet rays, and to compare with

1) Part I: Y. Matsuda and Y. Minamida, *Yakugaku Zasshi*, **96**, 425 (1976).
2) Location: *Motoyama-Kitamachi, Higashinada, Kobe, 658, Japan.*
3) *a*) E. Garrett, *J. Am. Pharm. Assoc.*, **43**, 539 (1954); *b*) E.R. Garrett, E.L. Schumann, and M.F. Gloslic, *ibid.*, **48**, 684 (1959); *c*) L.J. Leeson and A.M. Mattocks, *ibid.*, **47**, 329 (1958); *d*) J.E. Tingstad and E.R. Garrett. *ibid.*, **49**, 352 (1960); *e*) J.K. Guillory and T. Higuchi, *J. Pharm. Sci.*, **51**, 100 (1962); *f*) S.S. Kornblum and B.J. Sciarrone, *ibid.*, **53**, 935 (1964); *g*) J.T. Carstensen and M.N. Musa, *ibid.*, **61**, 1112 (1972); *h*) J.T. Carstensen and P. Pothisiri, *ibid.*, **64**, 37 (1975).
4) T.E. Eble and E.R. Garrett, *J. Am. Pharm. Assoc.*, **43**, 536 (1954).
5) S. Naito and S. Mizoguchi, *Yakuzaigaku*, **18**, 48 (1958).
6) *a*) E.R. Garrett and R.T. Carper, *J. Am. Pharm. Assoc.*, **44**, 515 (1955); *b*) C.J. Swartz and J. Autian, *ibid.*, **47**, 490 (1958); *c*) T. Hayashi, S. Yamazaki, S. Kaga, and Y. Takeya, *Yakuzaigaku*, **28**, 53 (1968).

those in the solution state. The most desirable thing in examining the solid-state stability is to follow the change of samples in the solid state as it is, without transferring them into a liquid phase for analysis, since they may exhibit a different behavior in the solution state due to the effect of a solvent. In order to satisfy this requirement, a new method for measuring the absorption spectra of a crystal in the gas phase was employed, and quantitation of a solid-state stability was made. The process of coloration of tablet surfaces followed by the colorimetric method and diffuse reflectance spectroscopy was related to the photolytic degradation based on the spectrophotometric method.

Experimental

Materials——One gram of sulfisomidine, Japanese Pharmacopeia, of under 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, Model IS-5000 (Shimadzu Seisakusho, Kyoto), and tablets of 15 mm in diameter and 4.5 mm in 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 in a desiccator over silica gel in the dark until exposure test.

Exposure Test——The samples were placed in the rack of the Fade-o-meter, Model MH-1 (Mitsubishi Denki, Tokyo) with a 400-Watt mercury vapor lamp,[7] described in the previous paper,[1] and exposed to the ultraviolet rays. The distance between the light source and the sample was 30 cm. The spectral distribution of radiation energy of this lamp[8] is given in Fig. 1.

To examine the effect of the intensity of ultraviolet rays on the coloration and chemical change of samples, a series of glass color filters (Toshiba Kasei Kogyo, Shizuoka) which have the property of shutting out the line spectra in Fig. 1 consecutively and as sharply as possible were placed in contact with the surface of each sample. The spectral transmittance curves of these filters are shown in Fig. 2.

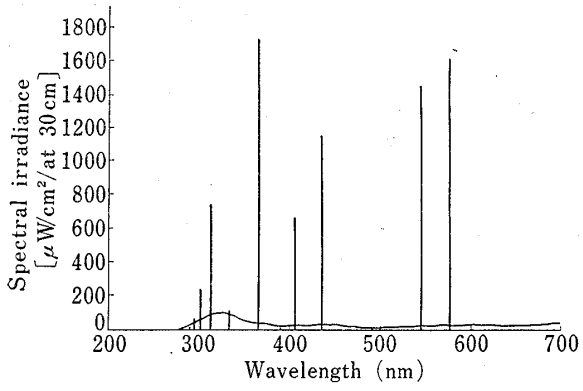

Fig. 1. Spectral Irradiance of High Pressure Mercury Vapor Lamp for Color Fading

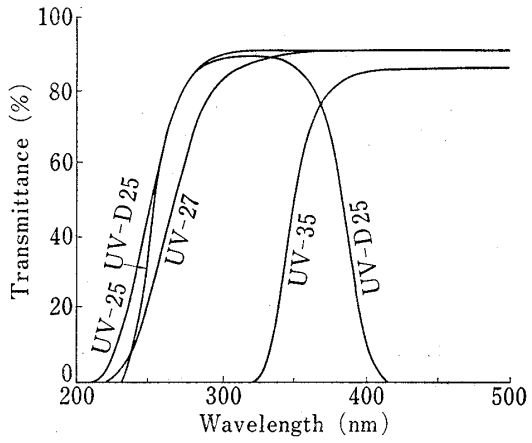

Fig. 2. Light Transmission Curves of Various Glass Color Filters

Among these, UV-D25 filter permits the transmission of ultraviolet rays alone, differing from the other. Samples were removed at periodic time intervals from the Fade-o-meter until analyzed by colorimetry and spectrophotometry.

Colorimetric Measurements——The surface color of the tablets in the *Lab* system[9] was measured with the integrating sphere-type color and color difference meter, Model ND-101 (Nippon Denshoku Kogyo, Tokyo). Barium sulfate plate was used as the reflectance standard. Hunter's color difference formula employed to evaluate the degree of coloration is expressed by the following equation (1).

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

where, $\Delta E(Lab)$: color difference in the *Lab* system; ΔL, Δa, Δb: difference between two lightnesses, 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 units.

7) JIS C 7604-1970: High Pressure Mercury Vapor Lamps for Color Fading.
8) Mitsubishi Electric Co., Ofuna Works, Technical Report.
9) JIS Z 8730-1970: Methods for Specification of Color Differences for Opaque Materials.

Diffuse Reflectance Measurements——The sample tablet was fixed in the sample holder, an attachment for the diffuse reflectance spectroscopy in the visible region, of the multipurpose recording spectrophotometer, Model MPS-50L (Shimadzu Seisakusho, Kyoto). Magnesium oxide tablet was used as the reflectance standard. After the initial reflectance spectrum was recorded, each sample was placed and exposed in the Fade-o-meter. The remission functions $f(r_\infty)$ were calculated from equation (2) according to the Kubelka-Munk theory.[10]

$$f(r_\infty) = (1-r_\infty)^2/2r_\infty \qquad (2)$$

where, r_∞ is the measured reflectance [—]

Absorption Measurements——In order to measure the absorption spectra of sample powders in the gas phase, a drop of acetone solution of pure sulfisomidine was placed on the quartz glass plate. The sample (particle size: 2—5 μm) was allowed to recrystallize on it by through evaporation of the solvent. These samples were placed in the attachment for film-like samples of the above-described spectrophotometer, and the absorption spectra, to be exact, the semi-integral attenuance spectra, were measured at every exposure at 24°. The semi-integral attenuance, ${}_pE_t$, is defined by the following equation (3).[11]

$${}_pE_t = \log (I_0/I_t) \qquad (3)$$

where, $I_o=I_r+I_a+I_t$, $I_t=I_p+I_d$, $I_r=I_{sr}+I_{dr}$. I_o, I_t, and I_r are the energy of incident, transmitted, and reflected light, respectively. The subscripts *a*, *p*, *d*, *sr*, and *dr* denote absorbed, parallel transmitted, diffuse transmttied, specularly reflected, and surface reflected light, respectively.

Results and Discussion

Coloration of Tablet Surface

Since it is known that the photochemical activity of the light radiation decreases with increasing wavelength, it would be expected in Fig. 2 that a glass color filter with a higher series number would give better protection against light than that with a lower series number. Fig. 3 shows the color change of tablet surfaces protected with these color filters. 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. The characteristic initial changes in the values of *L*, *a*, and *b* appeared within 20 min with any of the filters. After these marked changes, the color development followed a definite trend which was a function of time. Asymptotic values of *L*, *a*, and *b* were not obtained within the exposure time of the present work. Visual observation of these tablets indicated that they had taken on a yellow-tan color. However, there was no significant change in the colorimetric values, and visual observation showed no apparent darkening by the use of VY-48 and VR-62 filters, mentioned in the previous paper,[2] which permitted only visible light transmission. From this fact and from the result of the illuminance obtained by UV-D25 filter in the previous work,[2] it can be said that the coloration of sulfisomidine is strongly affected by ultraviolet ray absorption, and not significantly affected by light illuminance. Semi-logarithmic plots of the colorimetric values against time were also not linear. The kinetics are not zero- or first-order. The best linear relation of a function of the colorimetric values resulted when the reciprocal of these values were plotted in Fig. 4. These kinetics are apparent second-order with respect to the colorimetric values, and the following equation (4) may be applied:

$$1/L = k_L t + 1/L_0, \quad 1/a = k_a t + 1/a_0, \quad 1/b = -k_b t + 1/b_0 \qquad (4)$$

where, k_L, k_a, and k_b are the second-order rate constants with respect to *L*, *a*, and *b*, respectively.

However, the extrapolated values, L_o, a_o, and b_o, to the zero time in Fig. 4 did not agree with those of the initial observed values. This fact suggests that the complex coloration reaction is in progress in the earlier stage of exposure. The values of k_L, k_a, and k_b calculated from the regression lines in the region of the second-order kinetics are listed in Table I. It is interesting to note in this table that whereas k_L decreases with a decreasing amount of the

10) *a*) P. Kubelka and F. Munk, *Z. Tech. Phys.*, **12**, 593 (1931); *b*) P. Kubelka, *J. Opt. Soc. Amer.*, **38**, 448 (1948).

11) K. Shibata, *Tanpakushitsu, Kakusan, Kohso*, **13**, 344 (1968).

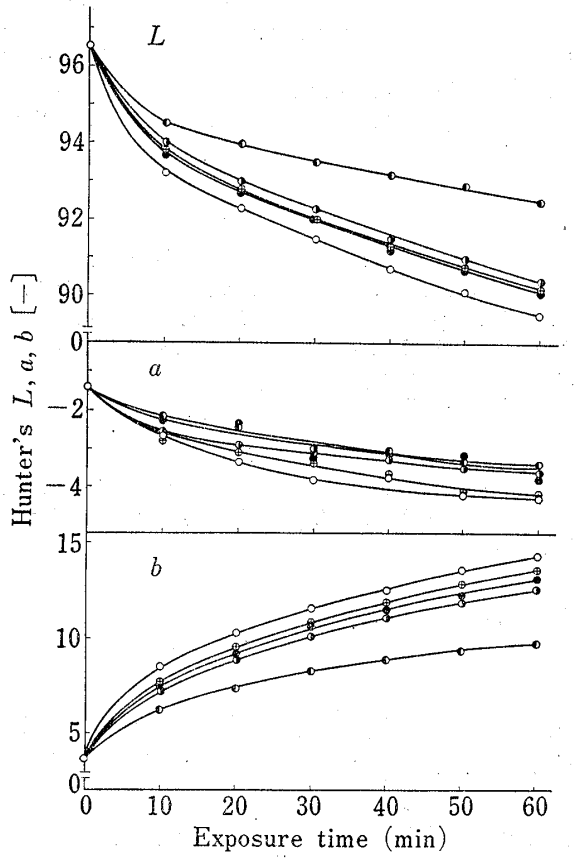

Fig. 3. Effect of Exposure Time on Hunter's Colorimetric Data

—○—: without filter —●—: UV-25 —⊕—: UV-D25
—◑—: UV-27 —◐—: UV-35

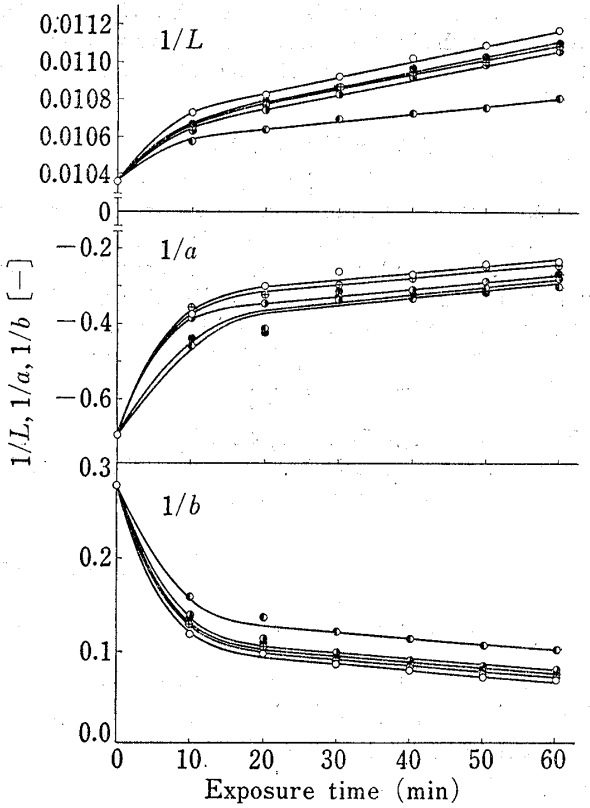

Fig. 4. Effect of Exposure Time on the Reciprocal of Hunter's Colorimetric Data

—○—: without filter —●—: UV-25 —⊕—: UV-D25
—◑—: UV-27 —◐—: UV-35

TABLE I. Kinetic Constants of Colorimetric Values

Color filters	k_L [NBS units^{-1}·min^{-1}]	k_a [NBS units^{-1}·min^{-1}]	k_b [NBS units^{-1}·min^{-1}]
Control	8.38×10^{-6}	1.88×10^{-3}	6.50×10^{-4}
UV-25	8.00	2.05	6.25
UV-D25	8.00	1.85	6.49
UV-27	7.63	1.88	6.49
UV-35	4.13	1.88	6.24

energy of ultraviolet rays, k_a and k_b remain constant regardless of the color filter used. However, effect of the amount of ultraviolet ray is already clearly shown before the critical time at which the initial coloration reaction turns to the subsequent second-order reaction, and, therefore, the initial period of coloration is considered to be more sensitive to light. It is, however, difficult to follow the color change in this region at shorter time intervals.

Changes in color difference between the original surface color and developed color are shown in Fig. 5. It is evident from this figure that the color differences have already reached a visually undesirable level of *ca.* 2 NBS units[2] within a few minutes after exposure. Fig. 5 also demonstrates the effect of the amount of ultraviolet rays on the rate of coloration.

Although the tristimulus reflectance method enables the quantitation of color change, it cannot follow the spectral color change.[12,13] In order to correct such a defect, spectral

12) J.L. Lach and M. Bornstein, *J. Pharm. Sci.*, **54**, 1730 (1965).
13) S.M. Blaug and W. Huang, *J. Pharm. Sci.*, **63**, 1415 (1974).

reflectances in the visible region were recorded, and its results are shown in Fig. 6. As is evident from equation (2), the remission function increases monotonously with decreasing reflectance. Fig. 6 indicates that although the original remission function curve showed equality in reflectance above 540 nm, it increased in the same manner with increasing exposure time with minimum and maximum at around 540 and 600 nm, respectively. The contribution of reflectance values to the color change is also shown in Fig. 7 in the form of $f_t(r_\infty)/f_0(r_\infty)$ against wavelength, in which the subscripts t and 0 denote the exposure time and the original state, respectively. From Fig. 7, it can be said that the drop in reflectance at 600 nm is greater than that in any other region of the wavelength. This suggests that the yellow-tan color is generated and promoted with increasing exposure time. Thus, the result of coloration obtained by visual observation was confirmed spectroscopically.

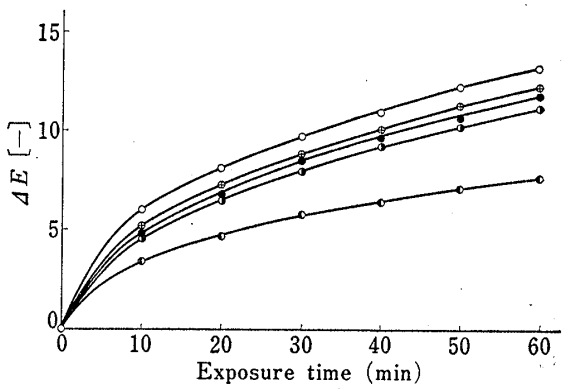

Fig. 5. Effect of Exposure Time on Color Difference

—○—: without filter —●—: UV-25 —⊕—: UV-D25
—◑—: UV-27 —◐—: UV-35

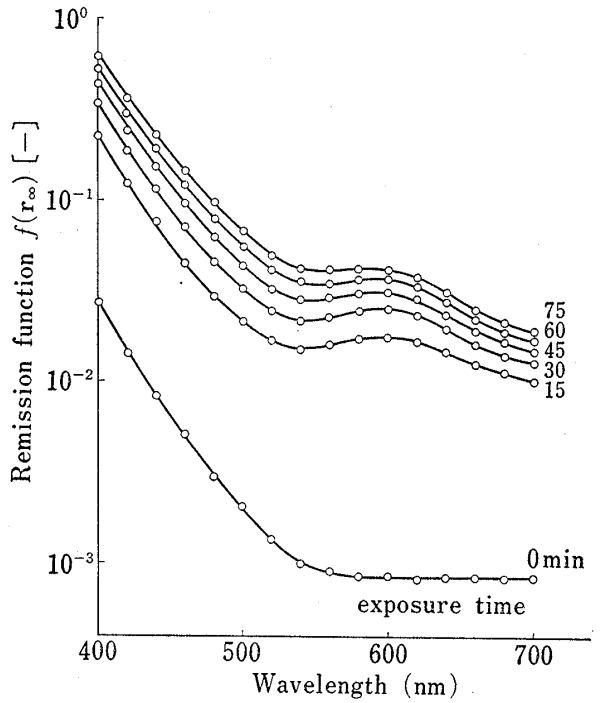

Fig. 6. Diffuse Reflectance Spectra as Remission Function of Sulfisomidine Tablets

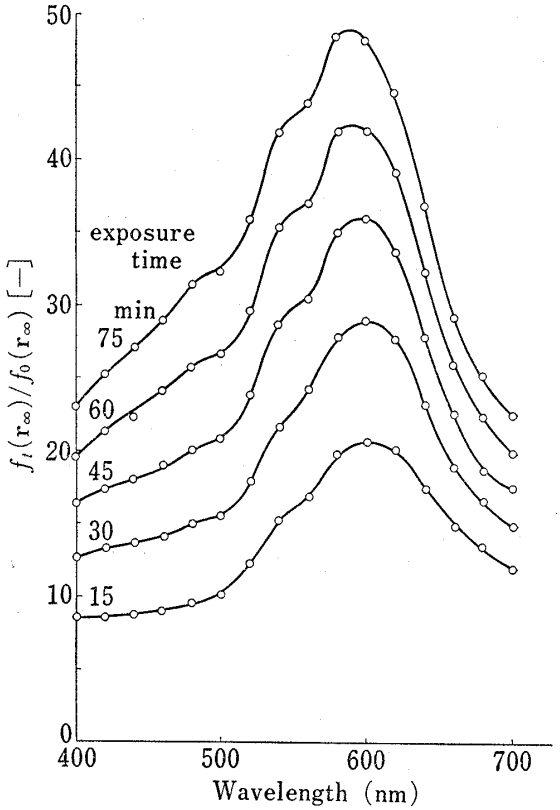

Fig. 7. Contribution of Reflectance Values to Coloration

Although the spectral shifts, shoulders, and development of new peaks in the ultraviolet region are generally considered to be in close relation to chemical degradation, it is yet difficult to discuss it in detail, because of the unreliability of the reflectance spectrum in this region.

Photolytic Degradation

Typical absorption spectra in the solid state are given in Figs. 8 and 9. The spectrum of the original state gave absorption maximum and minimum at 266 and 232 nm, respectively.

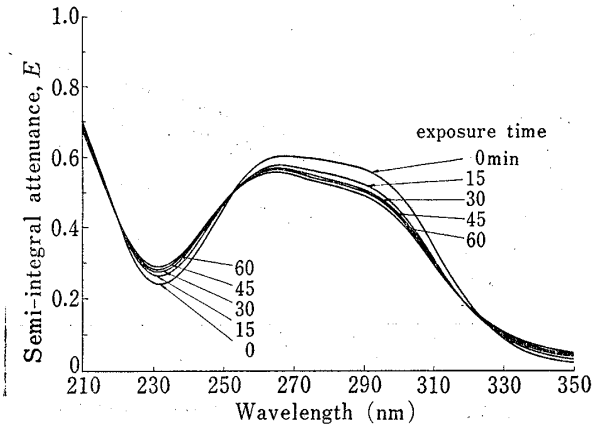

Fig. 8. Effect of Exposure Time on the Attenuance Spectrum without Filter

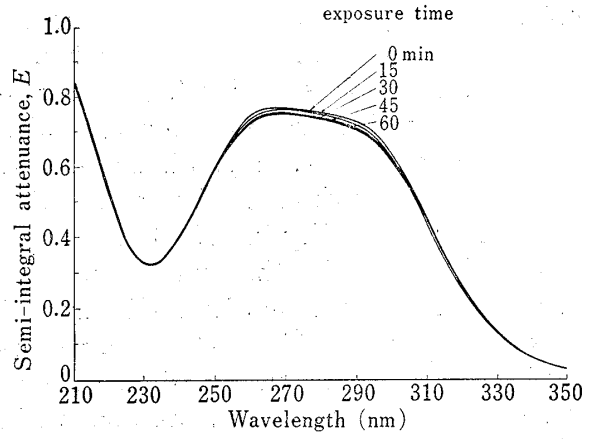

Fig. 9. Effect of Exposure Time on the Attenuance Spectrum with UV-35 Filter

As the exposure time extends, the absorption curve showed a flattening tendency of increasing at the minimum and decreasing at the maximum. The isosbestic points were confirmed at 219, 253, and 317 nm, but for UV-35 filter, these isosbestic points were not obtained, and the absorption curve gradually decreased without intersecting the original curve in any region of the wavelength. The photolytic degradation was not observed in the case of filters such as UV-39, VY-38, or VR-62 which did not permit transmission of ultraviolet rays. The presence and absence of isosbestic points may suggest induction of a photooxidation reaction on the tablet surface which has a selectivity with respect to wavelength.

To examine the degradation pattern quantitatively, the absorbance made dimensionless at 266 nm, E_t/E_0, is plotted against time in Fig. 10. In this graph, hyperbolic curves were likely to be given in the first portion of the photolytic degradation as shown by the broken lines, except for UV-35 filter, whereas almost linear relationship was obtained in the second portion as in Fig. 4. This suggests that the degradation follows an apparent zero-order kinetics from the beginning for UV-35 filter, while it has an induction period with different degradation mechanism before the subsequent zero-order reaction will proceed for other filters. The fact that the original absorption curve in Fig. 8 did not pass through any of these isosbestic points supports the above suggestion. The presence of an induction period in the absorption study is consistent with the data obtained on the coloration.

A characteristic feature of solid-state reaction is the total destruction of the reactant solid phases. Consequently, the notation of "order of reaction," as it is understood in the liquid phases, has only a limited applicability to solids, because they exist discontinuously throughout the reaction.[14] In a case like this absorption study in which the micronized and fixed sample powders are followed throughout the reaction, the attenuance defined in the solid state may be considered as the reactant concentration. Therefore, in the linear portion of each degradation curve, the kinetic equation (5) may be applied as follows:

$$d(E_t/E_0)/dt = -k, \text{ or } E_t/E_0 = 1 - kt \qquad (5)$$

where, k is the apparent zero-order rate constant [min^{-1}].

As shown in Fig. 10, degradation in the induction period proceeds at a much faster rate than the subsequent period. If a period of 15 min may be considered to be a critical time at which the degradation mechanism changes, $1-E_1$ should denote the amount of reactant in the induction period, and E_2-E_1, the amount of reactant in the same period assuming the zero-order degradation from the beginning. In this case, E_1 and E_2 are the values of E_t/E_0 at the critical time and extrapolated one to the zero time of the linear portion, respectively. The contribution of induction period to the degradation is shown in Fig. 11 in the form of $(1-E_1)/$

14) D.G. Pope and J.L. Lach, *Pharm. Acta Helv.*, **50**, 165 (1975).

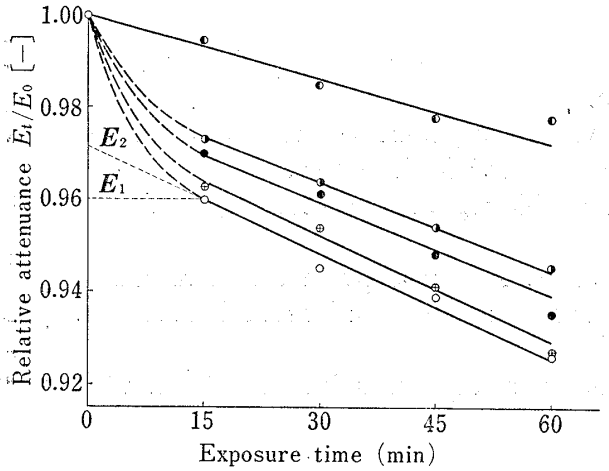

Fig. 10. Zero-order Plots of the Photolytic Degradation of Sulfisomidine Tablets

—○—: without filter —◉—: UV-25 —⊕—: UV-D25
—◑—: UV-27 —◐—: UV-35

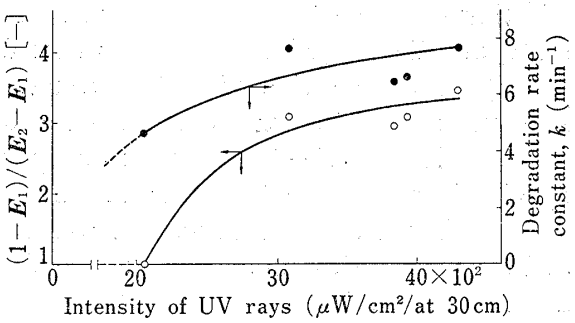

Fig. 11. Effect of UV Intensity on the Induction Period and Kinetic Constants in the Photolytic Degradation

●: degradation rate constant
○: contribution of induction period

(E_2-E_1) against ultraviolet intensity calculated from the data in Figs. 1 and 2, together with the k values in equation (5). It is evident from this figure that the contribution of induction period decreases with decreasing ultraviolet intensity and is not recognized in the region of lower intensity. This fact suggests that the degradation mechanism in earlier period is affected by the ultraviolet intensity. The tendency of the rate constant in the zero-order kinetic process was similar to that in the induction period.

Another purpose of the present work was to compare the degradation behavior in the solid state with that in the solution state. This is an important problem in choosing the desirable dosage form of the active ingredients. The ultraviolet absorption curves of *ca.* 5×10^{-5}M aqueous solution are shown in Fig. 12, which show absorption maxima at 260 and 282 nm, and minimum at 226 nm which do not correspond to those obtained in the solid state. Any changes in the absorption curve did not appear even after a 30 min exposure, in contrast to the solid state. Therefore, it can be considered that there is no effect of ultraviolet rays on the degradation of aqueous solution. Some of the solutions of sulfonamides undergo coloration on prolonged storage, and a reason for it has been considered to be due to oxidation or light intensity.[6b,6c,15] Effect of oxygen gas without exposure to ultraviolet rays on the absorption curve is also shown in Fig. 12. There appeared slight changes in the absorption intensity below 260 nm, but no effect was seen above this wavelength. It may be deduced from these evidences that the solution of sulfisomidine is not significantly affected by either the dissolved gaseous oxygen or ultraviolet rays. In the solid-state storage, no coloration and change in the absorption spectrum were observed in the dark. It may be adequate to estimate that the effect of air emerges only under the irradiation of light.

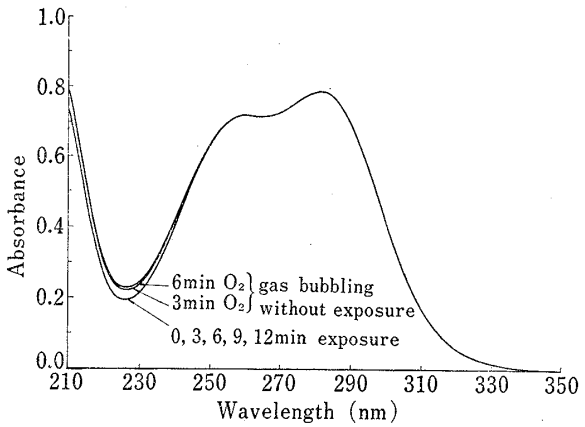

Fig. 12. Effects of Exposure Time and Oxygen on the Absorption Spectrum of Aqueous Solution of Sulfisomidine

15) P. Whitted, *Pharm. J.*, **165**, 309 (1950).

Conclusions

Sulfisomidine tablets were exposed to ultraviolet rays for stability studies in the solid state, and the following conclusions were drawn.

1) The coloration of tablet surfaces followed an apparent second-order kinetics in the *Lab* system, and the rate constants depend on the ultraviolet intensity.

2) Diffuse reflectance spectroscopy in the visible region supported the results obtained by visual and colorimetric observation.

3) The process of coloration was confirmed by spectroscopy in the ultraviolet region, and the photolytic degradation was found to fit an apparent zero-order reaction accompanying an induction period.

4) Photolytic degradation was not observed in the aqueous solution state, and the effect of oxygen did not appear significantly.