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# Photostability of Indomethacin in Model Gelatin Capsules: Effects of Film Thickness and Concentration of Titanium Dioxide on the Coloration and Photolytic Degradation[1]

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The dependence of the photostability of indomethacin on the capsule shell thickness and on the concentration of titanium dioxide used as an opacificient was investigated using gelatin films prepared by casting as models of hard gelatin capsules. The film thickness and concentration of opacificient were varied in the ranges of 50—150 μm and 0—1.5% of the amount of dried films, respectively. Films and indomethacin tablets were exposed to a 400 W mercury vapor lamp for 120 min, then coloration of the enclosed indomethacin was measured by tristimulus colorimetry, and evaluated as Hunter's color difference. The chemical stability of the drug was determined by following the ultraviolet spectrophotometric change of a solid sample.

There was a good linear relationship between color difference values and the square root of exposure time at all concentrations and thicknesses. The coloration rate constants calculated from the slopes of these lines were affected by both parameters, and decreased significantly as the film thickness was increased at every concentration of opacificient. However, the effect of concentration seemed to disappear above 1% addition. The coloration rate was directly dependent on the average transmittance of films over the wavelength range relating to the photostability of indomethacin.

Degradation of indomethacin followed apparently sequential first-order kinetics. Apparent conversions after 120-min exposure as determined from the UV spectra were also affected by both parameters and were below 3% at thicknesses above 80 μm at every opacificient concentration tested; this represents excellent protection of indomethacin.

**Keywords**——indomethacin; gelatin capsule; gelatin film; photostability; photostabilization; effect of film thickness; effect of opacificient; coloration; photolytic degradation; solid dosage form

Many pharmaceutical products require light-resistant containers to protect them from photochemical deterioration. In most instances, a container made of good quality amber glass will reduce the light transmission sufficiently, and may protect light-sensitive pharmaceuticals. Hard gelatin capsules are solid dosage forms which may be considered as "primary" containers. For better protection against light, the formulations of capsule shells should therefore be considered from the viewpoint of light transmission. Titanium dioxide has been widely used in these formulations as an opacificient. Although this filler material has been recognized to modify the moisture permeability of polymer films,[3,4] very little information actually exists concerning its opacificient role.

In the present study, titanium dioxide was incorporated into gelatin films, and the effect of the light transmission properties of the films on the coloration and photolytic degradation of indomethacin protected by these films was investigated under ultraviolet irradiation.

1) This paper forms Part VII of "Stability of Solid Dosage Forms." Part VI: Y. Matsuda, K. Kouzuki, M. Tanaka, Y. Tanaka, and J. Tanigaki, *Yakugaku Zasshi*, **99**, 907 (1979).
2) Location: *Motoyama-Kitamachi, Higashinada, Kobe 658, Japan.*
3) J.W. Parker, G.E. Peck, and G.S. Banker, *J. Pharm. Sci.*, **63**, 119 (1974).
4) K. Bayer, M. Soliva, and P. Speiser, *Pharm. Ind.*, **34**, 677 (1972).

## Experimental

**Preparation of Indomethacin Tablets**——Indomethacin JP (below 200 mesh) was compressed into 0.5 g flat-faced tablets, 15 mm in diameter, as models of the enclosed active ingredient, using a compression-tension testing machine. In order to obtain reproducible changes in the surface color of these tablets in subsequent experiments, a constant compression force of 200 kg was used. Samples were stored over silica gel in a desiccator in the dark until used.

**Preparation of Gelatin Films**——As described in the previous study,[1] titanium dioxide was added to molten gelatin aqueous solution and dispersed thoroughly using a homogenizer. The concentrations used were 0.5, 1.0, and 1.5 w/w% of the amount of dried films. Solutions were poured onto horizontal flat polyvinyl chloride plates. Rings made of the same material, with a diameter of 5 cm, were used to control the area of spreading and the thickness of films. The solvent was allowed to evaporate for 15 hr at constant temperature and humidity (25°, 50±2% R.H.). Dried films were peeled from the plate and sample films of 3×3 cm were cut off.

The thickness of films was varied from 50 to 150 μm; it was calculated as the mean of the measured values at five fixed points on a film using an electromagnetic thickness meter (Permascope type ES-8, Helmut Hischer GMBH, West Germany). These films were fixed on the front of the holders for sample tablets reported previously,[5] as models of capsule dosage forms.

**Ultraviolet Irradiation**——For kinetic studies, a sample film and tablet were exposed to UV irradiation in a fading tester with a 400 W mercury vapor lamp, as reported previously,[1,5–7] and subjected to colorimetric measurement at appropriate intervals. A grating monochromator[8] (model CRM-50, Japan Spectroscopic Co., Tokyo) with a 5 kW xenon lamp adjustable for wavelength in the range of 295—475 nm was also employed to obtain spectra for coloration and photolytic degradation of unprotected indomethacin. A bandwidth of 5 nm was used at all wavelengths for irradiation.

**Colorimetric Measurements**——The surface color of the tablets was measured using a color and color difference meter.[6] After each exposure, Hunter's color difference, $\Delta E$,[9] was calculated from three colorimetric values to evaluate the degree of coloration.

**Absorption Measurements**——Transmittance curves of films and ultraviolet absorption spectra of indomethacin in the solid state were recorded by the method described previously.[7] The average transmittance of the film, as discussed below, was obtained by calculating the area under the transmittance curve in related wavelength ranges.

## Results and Discussion

### Photosensitivity of Indomethacin

Indomethacin is photosensitive[10a] and becomes colored on exposure to light,[10b] and photodegradation has been reported in aqueous solution under UV light.[11] However, there are no data on the effect of light on solid-state indomethacin. Therefore, we required fundamental data on its photosensitivity before beginning the encapsulation studies.

Figure 1 shows action spectra for coloration and photolytic degradation under a fixed irradiation energy of $3.82\times10^8$ erg/cm$^2$. In this graph the degree of photolytic degradation was evaluated in terms of apparent conversion, as discussed later; it was defined as the ratio of absorption intensity at 270 nm after to that before irradiation in the UV absorption spectrum. Within the wavelength range observed and under normal storage conditions for drugs, the action spectrum for coloration exhibited a characteristic band which showed the greatest effectiveness at around 372 nm. In the region above 372 nm, $\Delta E$ decreased rapidly, but coloration still remained appreciable above 400 nm. The pattern of the action spectrum for photolytic degradation was in good accord with that for coloration. Based on these

5) Y. Matsuda, H. Inouye, and R. Nakanishi, *J. Pharm. Sci.*, **67**, 196 (1978).
6) Y. Matsuda and Y. Minamida, *Yakugaku Zasshi*, **96**, 425 (1976).
7) *Idem*, *Chem. Pharm. Bull.*, **24**, 2229 (1976).
8) Y. Matsuda and M. Itoh, *Asian J. Pharm. Sci.*, **1**, 107 (1979).
9) R.S. Hunter, *J. Opt. Soc. Am.*, **38**, 661 (1948).
10) *a*) "The United States Pharmacopeia," XX, Mack Publishing Company, Easton, PA., 1980, p. 399; *b*) "The Pharmacopeia of Japan," IX, Yakuji Nippo Ltd., Tokyo, 1975, p. 281.
11) *a*) E. Pawelczyk, B. Knitter, and K. Knitter, *Pharmazie*, **32**, 483 (1977); *b*) E. Pawelczyk and B. Knitter, *ibid.*, **32**, 698 (1977).

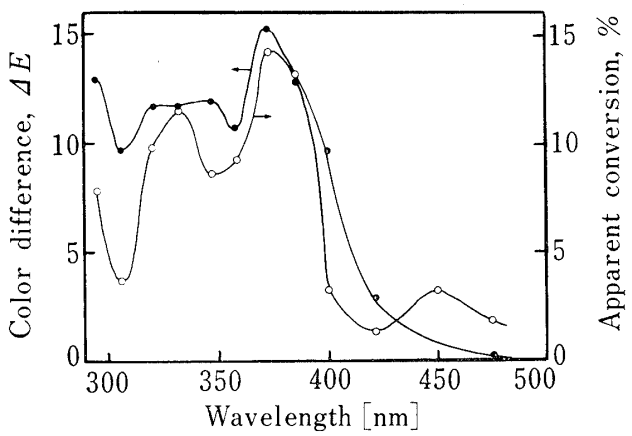


Fig. 1. Action Spectra for Coloration and Photolytic Degradation of Indomethacin

○, apparent conversion; ●, color difference.

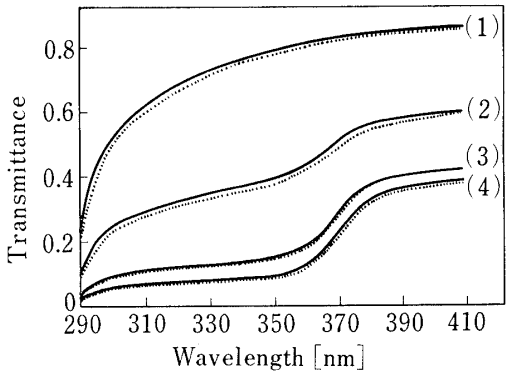


Fig. 2. Effect of Ultraviolet Irradiation on the Transmittance Curves of Gelatin Films

Film thickness: 80 μm. Numbers (1)—(4) in the figure represent the concentrations of opacificient, 0, 0.5, 1.0, and 1.5%, respectively.
——: before exposure;
------: after 120-min exposure.

results, it can be deduced that the action of lower wavelengths in the visible region should not be neglected in assessing the photosensitivity of indomethacin.

**Light Transmission Properties of Gelatin Films**

If the transmittance of gelatin films is changed by exposure to light, it would be difficult to determine the protection provided by these films. Figure 2 shows the effect of UV irradiation on the transmittance curves of gelatin films having a thickness of 80 μm after 120-min exposure. The light transmission properties of film without opacificient were not affected much even under severe exposure conditions. It is evident that the film without opacificient exhibits a rather high transmittance in the ultraviolet region below 400 nm. Such transmittance was greatly reduced, especially below 350 nm, with increasing concentration of opacificient. The transmittance curves were hardly affected, even by 120-min exposure, at any concentration of opacificient. Thus gelatin films can be considered photostable as regards light transmission properties.

The effects of film thickness and concentration of opacificient over the whole range investigated on the light transmission properties of films are summarized in Fig. 3, in which the cut wavelength, $\lambda_{T50}$, denotes the 50% transmission point on the transmittance curve.

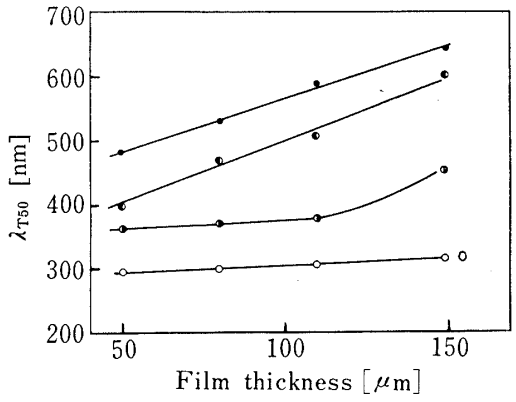


Fig. 3. Effect of Film Thickness on the Cut Wavelength of Films, $\lambda_{T50}$

Concentration of opacificient:
○, 0%; ◑, 0.5%; ◐, 1.0%; ●, 1.5%.

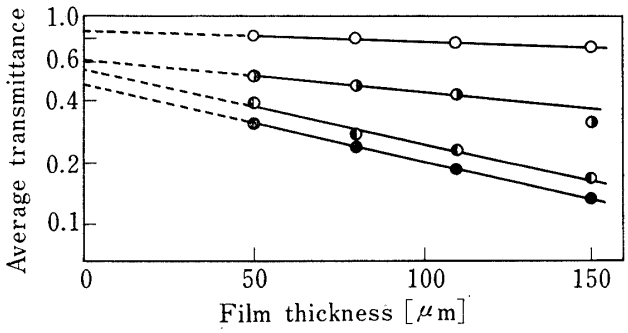


Fig. 4. Semi-logarithmic Plots of Average Transmittance of Films against Film Thickness

Concentration of opacificient:
○, 0%; ◑, 0.5%; ◐, 1.0%; ●, 1.5%.

The $\lambda_{T50}$ values of films without opacificient were not significantly affected by film thickness, indicating poor protective effectiveness against UV light. In contrast, at any concentration of opacificient, changes in the value of $\lambda_{T50}$ were proportional to film thickness, and the higher the concentration, the more satisfactory was the shielding effect. Referring to the results shown in Fig. 2, it would be expected that film formulations giving $\lambda_{T50}$ values of more than 450 nm would show desirable protective effectiveness. However, to evaluate the protective effectiveness more precisely, determination of the average transmittance over the wavelength range where indomethacin is photosensitive would be preferable to $\lambda_{T50}$.

The values of average transmittance between 290 and 450 nm are plotted in relation to the film thickness in Fig. 4. As is clear from Fig. 4, it decreases with the increase of either film thickness or concentration of opacificient. It appears that both parameters are directly and linearly related on a semi-log scale over the whole range of film thickness used. This relationship indicates that the following equation[12] can be applied to a semi-transparent material such as that used in the present work.

$$T = (1-R)^2\exp(-\alpha x),\ R = \left(\frac{n-1}{n+1}\right)^2 \qquad \text{(Eq. 1)}$$

where, $T$: average transmittance
$R$: reflectance
$x$: film thickness
$\alpha$: apparent extinction coefficient
$n$: refractive index of film

Reflectance and apparent extinction coefficient calculated from Eq. 1, using the slope and the extrapolated value at zero thickness (Fig. 4), are plotted in Fig. 5. The reflectance value of about 0.062 for the film without opacificient was approximately equal to that of the plate glass ($R$=0.042)[13] having a refractive index of 1.52. The reflectance increased monoto-

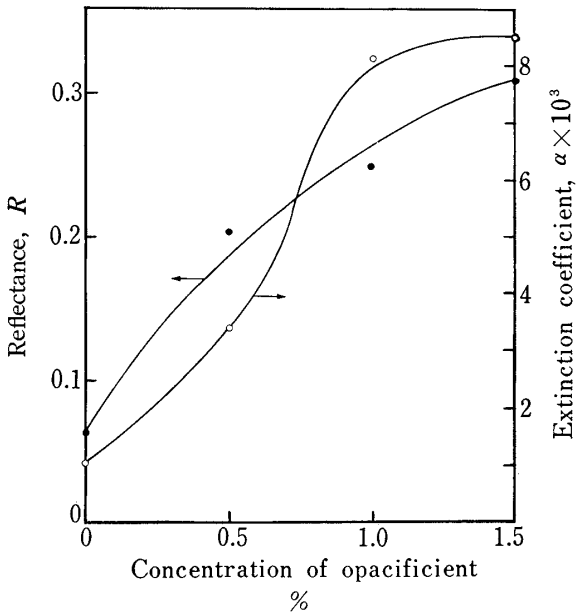


Fig. 5. Dependency of the Reflectance and Apparent Extinction Coefficient of Films on the Concentration of Opacificient

●, reflectance; ○, apparent extinction coefficient.

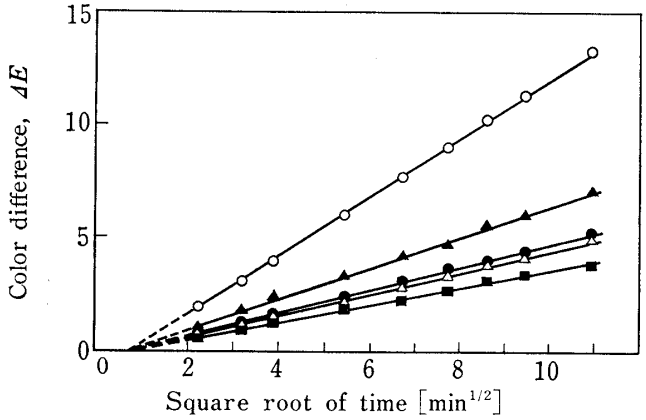


Fig. 6. Linear Plots of Color Difference as a Function of Square Root of Exposure Time

Concentration of opacificient: 1.5%.
○, without film; ▲, 50 μm; ●, 80 μm; △, 110 μm; ■, 150 μm.

12) S. Naruse, "Glass Engineering," Kyoritsu Publishing Co., Tokyo, 1966, p. 307.
13) K.A. Connors, G.L. Amidon, and L. Kennon, "Chemical Stability of Pharmaceuticals," John Willey and Sons Inc., New York, 1979, p. 90.

nously with increasing concentration of opacificient. On the other hand, the increase in apparent extinction coefficient seemed to level off somewhat above 1% addition. Since the coloration and photolytic degradation of an enclosed drug are affected only by the light transmitted through the capsule film, the results in Fig. 5 indicate that the combined effects of both reflectivity and absorptivity should result in good photostabilization in the higher concentration range.

**Effects of Film Thickness and Concentration of Opacificient on Coloration**

Figure 6 shows the effect of film thickness on the coloration of enclosed indomethacin for 1.5% addition of opacificient. Unprotected indomethacin showed more than 12 NBS units of color difference after 120-min exposure, which was quite clear visually.[14] Reduced coloration was observed with increasing film thickness, but even at 150 μm thickness, coloration was still nearly 4 NBS units, which is appreciable. The plots of color difference values against square root of exposure time, $t$, gave a good linear relation at all concentrations and thicknesses, and, therefore, equation 2 may be applied:

$$\Delta E = k(\sqrt{t} - 0.82) \qquad \text{(Eq. 2)}$$

where $k$ is regarded as a coloration rate constant. The protective effectiveness can be evaluated in terms of $k$.

Figure 7 shows the effects of film thickness and concentration of opacificient on the coloration rate constant. A good linear relationship exists between the logarithmic value of rate constant and film thickness. The coloration rate constant fell significantly as the film thickness was increased at every concentration of opacificient, but the effect of concentration seemed to level off somewhat above 1% addition, as is evident in this figure. It is clear from this evidence and the results obtained in Fig. 5 that the coloration rate is affected more significantly by the absorptivity than by the reflectivity of the film. The graphical behavior of the coloration rate constant closely resembles that of the average transmittance in Fig. 4, suggesting a strong correlation between these parameters. The coloration rate constant is plotted against

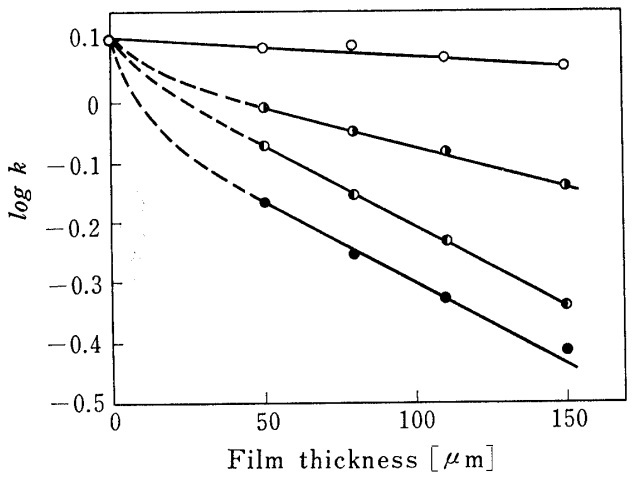


Fig. 7. Effect of Film Thickness on Logarithmic Coloration Rate Constant

Concentration of opacificient:
○, 0%; ◑, 0.5%; ◐, 1.0%; ●, 1.5%.

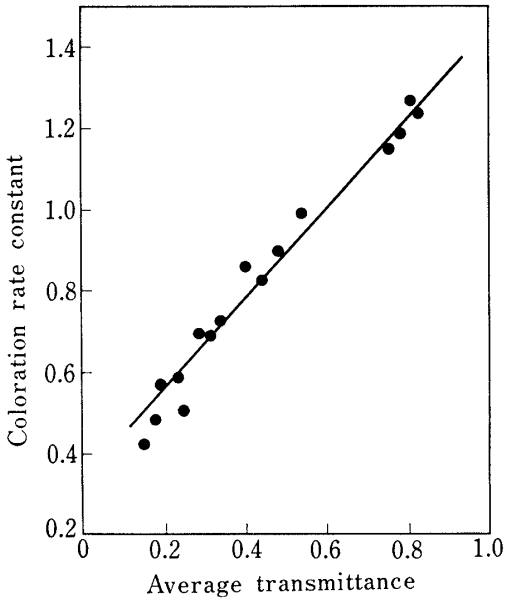


Fig. 8. Relationship between Coloration Rate Constant and Average Transmittance of Film

14) E.I. Stearms, *Am. Dyestuff Rep.*, **40**, 563 (1951).

average transmittance in Fig. 8. There was a correlation coefficient of 0.988 ($n=16$, $p<0.001$), regardless of film thickness and concentration of opacificient, indicating that the coloration rate is directly controlled only by the average transmittance.

**Photolytic Degradation**

Photochemical degradation of indomethacin in phosphate buffer solution has been found to be a sequential reaction consisting of a series of zero-order processes;[11] there are three processes having different rate constants.

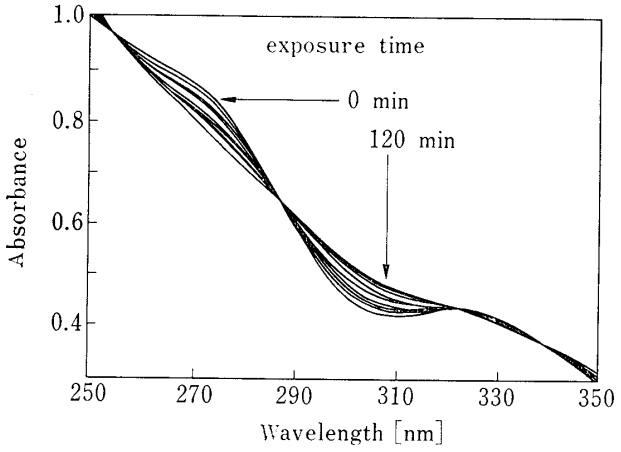


Fig. 9. Effect of Exposure Time on the Absorption Spectrum of Solid Indomethacin used as a Control

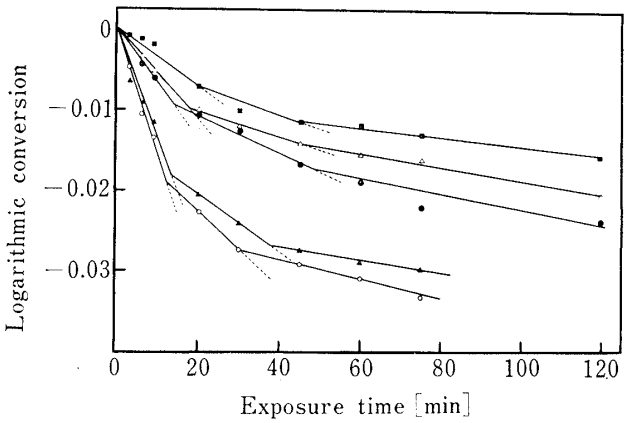


Fig. 10. Typical Apparent First-order Plots of Photolytic Degradation at Various Film Thicknesses

○, without film; ▲, 50 $\mu$; ●, 80 $\mu$m; △, 110 $\mu$m; ■, 150 $\mu$m.

For the reason described in our previous report,[7] spectrophotometric analysis of indomethacin was done in the solid state, and a typical absorption spectrum for the control is shown in Fig. 9. In the original state before exposure, there was an absorption maximum and a minimum at 323 and 308 nm, respectively, with a weaker absorption band as a shoulder at 270 nm, which corresponds to the maximum absorption wavelength for the solution. As the exposure time increased, the absorption curve tended to flatten out, increasing the minimum and decreasing the maximum. Neither the maximum nor the minimum could be seen after 120-min exposure. The isosbestic points were at 254, 287, 322, and 339 nm. These points were observed for films showing higher average transmittance.

The ratio of absorbance after to that before exposure at 270 nm was taken as a measure of the apparent conversion, because the changes in absorption intensity were most marked at this wavelength. The values of these ratios are plotted against time in Fig. 10 for films without opacificient. The plots obtained were linear on the semi-log scale, indicating that the degradation of indomethacin in the solid state followed apparently sequential first-order kinetics in all the steps. Among the three degradation rate constants calculated from the slopes of individual lines, the rate constant of the first process was the greatest. It was about 3.4 times the rate constant of the second and 17.9 times that of the third process.

The effects of film thickness on these degradation rate constants are given in Fig. 11 in the form of the rate of stabilization ($R_i$), defined by the following equation 3:

$$R_i = \frac{k_{oi}-k_{li}}{k_{oi}} \times 100\ (\%) \qquad \text{(Eq. 3)}$$

where, $k_{oi}$: rate constant in the $i$ th degradation process for the control

$k_{li}$: rate constant in the $i$ th degradation process for the film having a thickness $l$

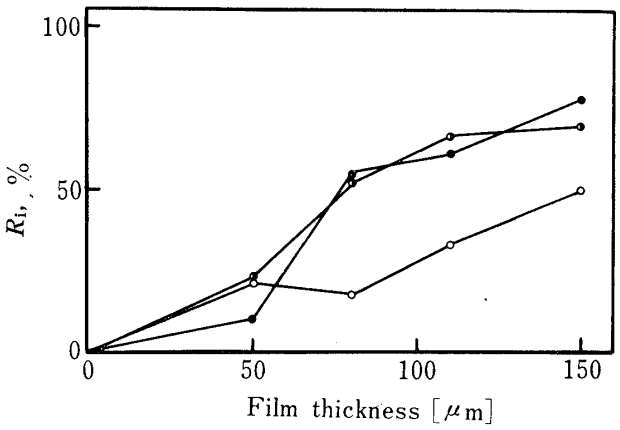


Fig. 11. Effect of Film Thickness on the Rate of Stabilization

●,first process; ◑, second process; ○, third process.

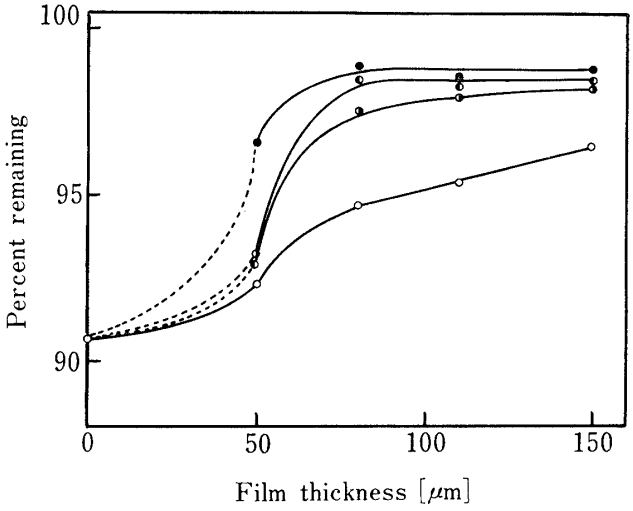


Fig. 12. Effect of Film Thickness on Percentage remaining in Photolytic Degradation

Concentration of opacificient:
○, 0%; ◑, 0.5%; ◐, 1.0%; ●, 1.5%.

In this plot, although the film thickness affects all the degradation processes, its effect seems to be most marked in the earliest process.

Since the spectrophotometric change was small even for the control (Fig. 9), it is difficult to follow this change precisely at short time intervals for films having lower average transmittance. Therefore, the photostability was evaluated in terms of the conversion after a long exposure time of 120 min. These conversion are plotted against thickness in Fig. 12 for every concentration of opacificient tested. In spite of the strong UV irradiation, conversions were below 3% at thicknesses above 80 $\mu$m at every concentration. Judging from the results in Fig. 12, the usual additive concentration of opacificient and film thickness used in commercially available capsules should give excellent protection of indomethacin.

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