# Method of Kinetic Analysis of Photodegradation: Nifedipine in Solutions

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**A rate equation for photodegradation was derived from Lambert–Beer's law and Grotthus–Draper's law:**

$$-dc/dt=k_1(1-\exp(-(k_2c+k_3(c_0-c))))k_2c/(k_2c+k_3(c_0-c))$$

**where $c$ is the concentration of reactant, $c_0$ is the initial concentration of reactant, $t$ is time, $k_1$ is the rate constant, and $k_2$ and $k_3$ are the absorption coefficient of reactant and its photodegradation product, respectively.**

**In a case where the photodegradation products have no photoabsorption, $k_3$ assumes the value of zero in the above general equation. In a case where the photodegradation products have the same spectrum and molar absorptivity as that of the reactant, $k_3$ assumes the value of $k_2$, and hence the photodegradation is not a first-order reaction; however, the equation itself gives the pseudo-first-order reaction rate equation. In a case where the concentration of reactant is high enough, the equation approaches a zero-order reaction rate equation.**

**The photodegradation rate of nifedipine in solutions under a germicidal lamp, near an ultraviolet fluorescent lamp and a fluorescent lamp was analyzed using the above equation. The photodegradation rate was directly proportional to the amount of light absorbed, and fitted well with the equation. The above theoretical equation was substantiated by the photodegradation of nifedipine, and hence is expected to apply to other photosensitive drugs.**

**Keywords** photostability; photodegradation; kinetics; nifedipine; kinetic theory; solution; photodecomposition

Many investigation results on the kinetics and the mechanisms of photodegradation have been reported. For nifedipine alone, kinetics and mechanisms have been investigated by Berson,[1] Ebel,[2] Jakobsen,[3] Sugimoto,[4] Thoma,[5,6] Majeed,[7] Al-Turk[8] and Akimoto.[9] However, most of these investigators analyzed the photodegradation as the zero-order or the first-order reactions without extensive consideration. In fact, theoretical investigations on the photodegradation rate have been rather limited.

In this study, a photodegradation rate equation has been theoretically derived, and using this equation, the photodegradation of nifedipine in solutions has been analyzed.

## Theory

The amount of light absorbed by a solution is given by subtracting the amount of light transmitted from the amount of incident light, and can be expressed by Eq. 1:

$$A_i=I_{0i}-I_i \tag{1}$$

where $A_i$ is the amount of light absorbed by wavelength $i$, and $I_{0i}$ and $I_i$ are the intensity of the incident light and the transmitted light by wavelength $i$, respectively.

If Lambert–Beer's law holds, the amount of light transmitted can be expressed by Eq. 2.

$$I_i=I_{0i}\exp(-\gamma_i cl) \tag{2}$$

where $\gamma_i$ is a coefficient, $c$ is the concentration of reactant and $l$ is the path length.

Therefore, Eq. 1 can be transformed to Eq. 3.

$$A_i=I_{0i}(1-\exp(-\gamma_i cl)) \tag{3}$$

If Grotthus–Draper's law holds and the photodegradation rate is proportional to the amount of light absorbed, Eq. 4 can be derived under constant radiant conditions:

$$-\frac{dc}{dt}=k_{0i}I_{0i}(1-\exp(-\gamma_i cl)) \tag{4}$$

where $k_{0i}$ is a constant and $t$ is time.

When Eqs. 3 and 4 hold over a wide range of wavelengths, and the radiant light source is not a monochromatic beam, Eq. 5 can be derived.

$$-\frac{dc}{dt}=\sum k_{0i}I_{0i}(1-\exp(-\gamma_i cl)) \tag{5}$$

where $\sum$ is the sum from the short wavelength to the long wavelength of $k_0\times I_0$ sub $i$.

The photodegradation can be classified into four cases.

**Case 1: The Photodegradation Products Have No Absorption Spectrum** When the photodegradation products have no absorption spectrum within the wavelength region in which the reactant undergoes a photodegradation, Eq. 5 can be written as Eq. 6.

$$-\frac{dc}{dt}=k_1(1-\exp(-k_2c)) \tag{6}$$

where $k_1$ is the rate constant and $k_2$ is the absorption coefficient of the reactant.

**Case 2: The Photodegradation Products Have an Absorption Spectrum** In the case where the photodegradation products absorb the light, the amount of light absorbed by the reactant decreases with the increase in quantity of photodegradation products. That is, the amount of light absorbed by the reactant is equal to the amount of light absorbed by the solution times the ratio of the amount of the light absorbed by the reactant. Consequently, Eq. 7 can be derived as the general rate equation for the photodegradation.

$$-\frac{dc}{dt}=k_1(1-\exp(-(k_2c+k_3(c_0-c))))\frac{k_2c}{k_2c+k_3(c_0-c)} \tag{7}$$

where $k_3$ is the absorption coefficient of the photodegradation products.

**Case 3: The Reactant and the Photodegradation Products Have the Same Absorption Spectrum and Molar Absorptivity** In the case where the photodegradation products have the same or almost the same absorption spectrum as the reactant, $k_3$ is equivalent to $k_2$ in Eq. 7.

Hence, substituting $k_3=k_2$ into Eq. 7 gives Eq. 8.

$$-\frac{dc}{dt}=k_1(1-\exp(-k_2c_0))\frac{c}{c_0}=Kc \quad (8)$$

where $K$ is the pseudo-rate constant.

**Case 4: The Concentration of Reactant Is High** When the concentration of the reactant is high, the value of $\exp(-(k_2c+k_3(c_0-c)))$ approaches zero, and then the photodegradation rate can be given by Eq. 9.

$$-\frac{dc}{dt}=k_1 \quad (9)$$

## Calculation

**Case 1** It is apparent from Eq. 6 that $k_1$ and $k_2$ can be obtained by determining the degradation rate from at least two concentrations.

Integration of Eq. 6 yields Eq. 10.

$$c+\frac{1}{k_2}\ln(1-\exp(-k_2c))=c_0+\frac{1}{k_2}\ln(1-\exp(-k_2c_0))-k_1t \quad (10)$$

where $c_0$ is the initial concentration of the reactant. Consequently, $k_1$ and $k_2$ can also be obtained by tracing the concentration of the reactant after radiation of light on the solution.

Equation 10 is expressed as the linear equation of Eq. 11.

$$Y=A+BX \quad (11)$$

where $A$ is the constant and $B$ is the slope.

Substitute experimental data and $k_2$ for Eq. 10, and compute $A$ and $B$ by the least squares method. And then compute $F$. $F$ is used for the significance test of linearity.

$$F=\frac{B^2\sum(X_i-X)^2\times(N-2)}{\sum(Y_i-Y)^2-B^2\sum(X_i-X)^2} \quad (12)$$

where $N$ is the number of the experiment.

The value of $F$ changes in accordance with $k_2$. The value of $k_2$ is changed so as to give maximum $F$ value. The value of $k_2$ that gives maximum $F$ value is the absorption coefficient, and then $k_1$ may be obtained from the slope.

**Case 2** Equation 7 cannot integrate analytically but can be solved numerically. Therefore, $k_1$, $k_2$ and $k_3$ can be estimated by the nonlinear least squares parameter estimation method.

In order to evaluate the rate constant and the absorption coefficients, it is necessary to observe at least two experiments by changing the initial concentrations, and then to solve simultaneous differential equations.

**Case 3** Integration of Eq. 8 yields Eq. 13.

$$\ln c=\ln c_0-Kt \quad (13)$$

thus, in this case the remaining reactant decreases exponentially with time.

The pseudo-rate constant $K$ at the initial concentration $c_{0i}$ is calculated using Eq. 13.

The rate constant $k_1$ and absorption coefficient $k_2$ can be evaluated by determining $K$ at more than two initial concentrations, because Eq. 14 is:

$$\frac{k_1(1-\exp(-k_2c_{0i}))}{c_{0i}}=K_i \quad (14)$$

where $K_i$ is the pseudo-rate constant at the initial concentration $c_{0i}$.

If the initial concentration $c_{02}$ is higher than the initial concentration $c_{01}$, and if $c_{01}$ multiplied by $k_1$ is larger than $c_{02}$ multiplied by $k_2$, then $k_1$ and $k_2$ cannot be obtained. In this case, the assumption that $k_2$ equals $k_3$ is incorrect.

**Case 4** Integration of Eq. 9 yields Eq. 15.

$$c=c_0-k_1t \quad (15)$$

Thus, when the concentration is high enough that the value of $\exp(-(k_2c+k_3(c_0-c)))$ can approximate zero, the remaining reactant decreases linearly with time.

## Experimental

**Light Source** A germicidal lamp (Toshiba Electric Co., Ltd., Tokyo, 20 W GL15), a near ultraviolet (UV) fluorescent lamp (Toshiba Electric Co., Ltd., 20 W FL20SBL) and a fluorescent lamp (Toshiba Electric Co., Ltd., 40 W FLR40SW) were employed as the light sources. The spectral intensity of the lamps is shown in Fig. 1.

The intensity of radiation was determined with a UV radiometer (Tokyo Optical Instruments Co., Ltd., UVR-25, UVR-36) for the germicidal lamp and the near UV fluorescent lamp, and an illumination meter (Tokyo Optical Instruments Co., Ltd., 1M-2D) for the fluorescent lamp.

**Samples** Nifedipine was accurately weighed and dissolved in ethanol to make 2.5 mg/ml to 50 mg/ml solutions. Three ml of the solution was placed in a quartz cell and covered with a glass stopper; this was used as the sample for the germicidal lamp radiation. Subsequently, 5 ml of the solution was placed in a 5 ml vial and sealed with a rubber stopper; this was used as the sample for the near UV fluorescent lamp and fluorescent lamp radiations.

**Photo-Radiation** Photo-radiation was carried out at room temperature. The samples were swung forty five times per min at an angle of $\pm 6$ degrees to the horizontal during radiation of the near UV fluorescent lamp and fluorescent lamp. (Taiyo Kagaku Kogyo Co., Ltd., TAIYO MONOSIN-A)

**Assay** The concentrations of nifedipine were determined by high performance liquid chromatography. The liquid chromatograph (Shimadzu Co., Ltd., LC-6A series) was equipped with a 228 nm detector and a 4.6 mm × 150 mm column. The column's packing consisted of octadecyl silane, chemically bonded to porous silica, and was 5 $\mu$m in diameter. The column temperature was maintained constant at about 35 °C. The mobile phase was a degassed mixture of water and methanol (42 : 58, v/v), which was filtered through a 0.45 $\mu$m membrane filter. The flow rate of the mobile phase was 0.7 ml/min. The internal standard was *sec*-butyl paraben.

## Results and Discussion

**Absorption Spectrum of Nifedipine and Its Photodegradation Product** The absorption spectra of nifedipine and its photodegradation products in ethanol were measured and are shown in Fig. 2.

The absorption spectra of the photodegradation products of nifedipine in ethanol under the light of three lamps were identical.

**Photodegradation of Nifedipine under the Germicidal Lamp** The rate constant $k_1$ and the absorption coefficients $k_2$ and $k_3$ under the radiation of the germicidal lamp were estimated by the nonlinear least squares parameter estimation method (NLSPE method). To clarify the dependence of solution concentration on the rate constant and the absorption coefficients, estimation was done using the data from three different initial concentrations and solving three degree simultaneous differential equations. For example, to estimate the rate constant $k_1$ and the absorption coefficients $k_2$ and $k_3$, data of 2.5, 5 and 7.5 mg/100 ml were used and analyzed at the value of

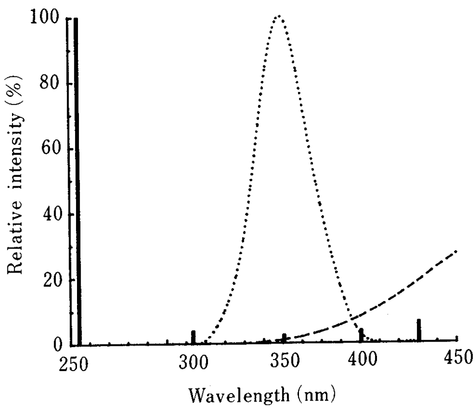


Fig. 1. Radiation Spectrum of Lamps

——, germicidal lamp; ····, near UV fluorescent lamp; ------, fluorescent lamp.

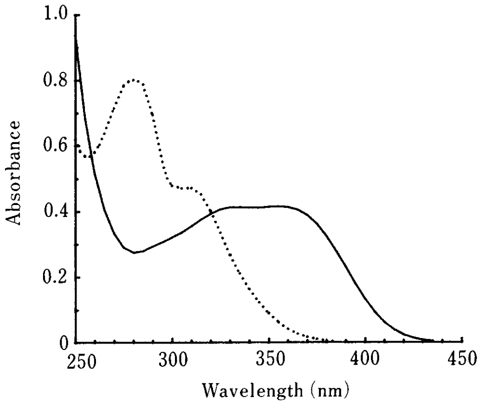


Fig. 2. Absorption Spectrum of Nifedipine and Its Photodegradation Products in Ethanol

——, nifedipine (3 mg/100 ml ethanol); ····, photodegradation products of nifedipine with the germicidal, the near UV fluorescent and the fluorescent lamp.

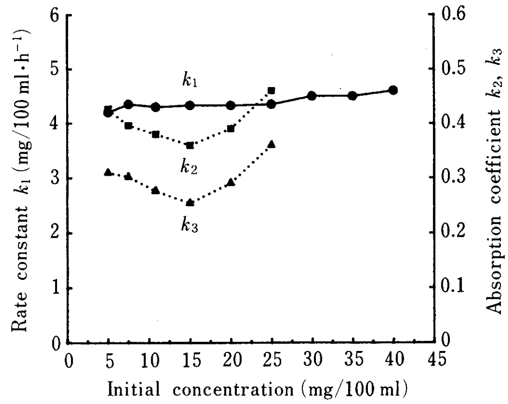


Fig. 3. Dependence of the Initial Concentration on the Rate Constant and Absorption Coefficients for the Photodegradation of Nifedipine in Solutions under the Germicidal Lamp

The radiation intensity is $30\,mW/cm^2$. —●—, rate constant $k_1$; ···■···, absorption coefficient of nifedipine $k_2$; ···▲···, absorption coefficient of photodegradation product $k_3$.

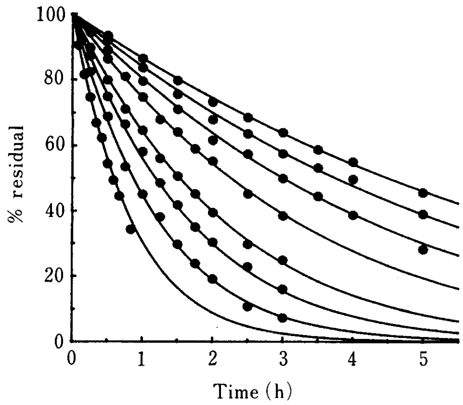


Fig. 4. Experimental Data and Theoretical Curves of Photodegradation of Nifedipine in Solutions under the Germicidal Lamp

The radiation intensity is $30\,mW/cm^2$. The theoretical curves are calculated by substituting $k_1=4.28\,mg/100\,ml\cdot h^{-1}$, $k_2=0.432$, $k_3=0.320$ and $c_0$ into Eq. 7. The substituted initial concentrations $c_0$ of nifedipine are 2.5, 5, 7.5, 10, 15, 20, 25 and 30 mg/100 ml from lower curve to upper curve, respectively.

5 mg/100 ml. Data of 5, 7.5 and 10 mg/100 ml were similarly used and analyzed at the value of 7.5 mg/100 ml and so on.

The rate constant of photodegradation of nifedipine, $k_1$, under the radiation intensity of $30\,mW/cm^2$ was almost constant or slightly higher at a higher solution concentration, but the absorption coefficient values of nifedipine, $k_2$, and the photodegradation product of nifedipine, $k_3$, were somewhat scattered as shown in Fig. 3. At higher concentrations of nifedipine, even with substitution of any initial value for $k_1$, $k_2$ and $k_3$ using the NLSPE method, the rate constant $k_1$ converged at a constant value. The absorption coefficients $k_2$ and $k_3$, however, did not converge at a constant value but changed slightly. The dependence of concentration on the rate constant and absorption coefficients is still considered to be small.

The rate constant $k_1$ and absorption coefficients $k_2$ and $k_3$ that were estimated from the eight different initial concentrations, (namely, 2.5, 5, 7.5, 10, 15, 20, 25 and 30 mg/100 ml) were $4.28\,mg/100\,ml\,h^{-1}$, 0.432 and 0.320, respectively. The experimental data and theoretical curves that were calculated by substituting the above rate constant and absorption coefficients into Eq. 7 are shown in Fig. 4.

The absorption coefficient $k_3$ was nearly 75% that of $k_2$, and almost coincided with the ratio of the absorption at 254 nm of nifedipine to the photodegradation products of nifedipine.

$k_2$ is now equivalent to the absorption coefficient for concentration in 1 mg/100 ml of nifedipine per path length of cell, and in this case $k_3$ is the absorption coefficient of photodegradation product of nifedipine.

With respect to absorption spectrophotometry, the absorbance is defined as Eq. 16.

$$A=\log_{10}(1/T)=abc \tag{16}$$

where $A$ is absorbance, $T$ is the transmittance, $a$ is absorptivity, $b$ is a constant and $c$ is the concentration.

The absorption coefficients $k_2$ and $k_3$ were defined as natural logarithms, and, unifying the definition, they were respectively roughly equal to the absorptivity of nifedipine and its photodegradation product at 254 nm (the germicidal lamp is the polychromatic light source with a main emission wavelength of 254 nm, as shown in Fig. 1).

Theoretically, the absorption coefficients $k_2$ and $k_3$ under monochromatic radiation can be estimated by multiplying 2.303 by the absorptivity of the reactant and its photodegradation product, respectively. When the absorption coefficients $k_2$ and $k_3$ are estimated from the absor-

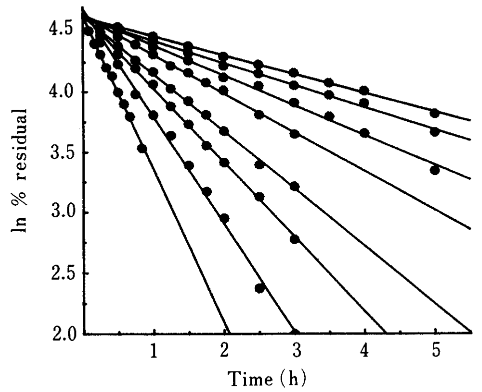


Fig. 5. ln%–Time Plots for the Photodegradation of Nifedipine in Solutions under the Germicidal Lamp

The radiation intensity is $30\,mW/cm^2$. Initial concentrations of nifedipine are 2.5, 5, 7.5, 10, 15, 20, 25 and 30 mg/100 ml from lower linear line to upper linear line, respectively.

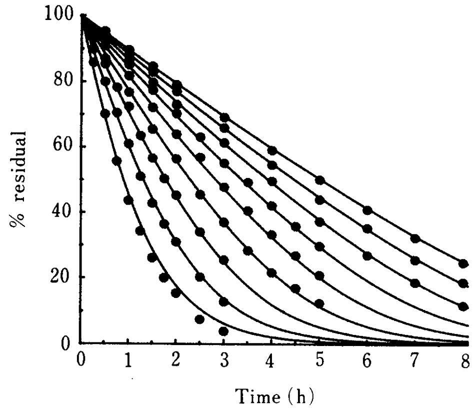


Fig. 7. Experimental Data and Theoretical Curves of Photodegradation of Nifedipine in Solutions under the near UV Fluorescent Lamp

The radiation intensity is $30\,mW/cm^2$. The theoretical curves are calculated by substituting $k_1=4.74\,mg/100\,ml\cdot h^{-1}$, $k_2=0.255$, $k_3=0.0341$ and $c_0$ into Eq. 7. The substituted initial concentrations $c_0$ of nifedipine are 5, 10, 15, 20, 25, 30, 35, 40 and 45 mg/100 ml from lower curve to upper curve, respectively.

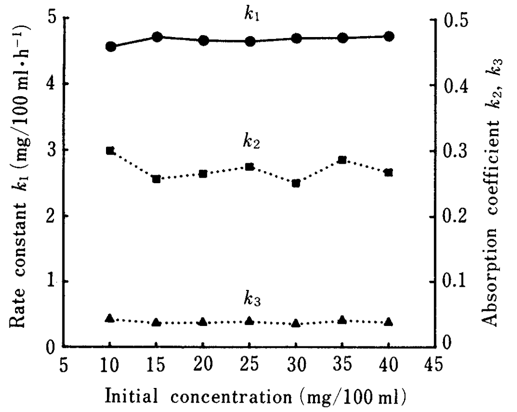


Fig. 6. Dependence of the Initial Concentration on the Rate Constant and the Absorption Coefficients for the Photodegradation of Nifedipine in Solutions under the Near UV Fluorescent Lamp

The radiation intensity is $30\,mW/cm^2$. —●—, rate constant $k_1$; ····■····, absorption coefficient of nifedipine $k_2$; ····▲····, absorption coefficient of photodegradation product $k_3$.

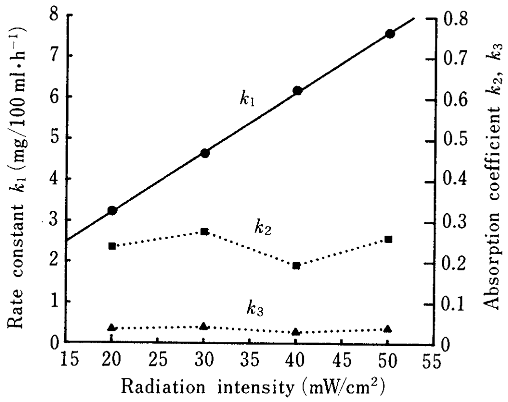


Fig. 8. The Effect of the Radiation Intensity on the Rate Constant and Absorption Coefficients for the Photodegradation of Nifedipine in Solutions under the near UV Fluorescent Lamp

—●—, rate constant $k_1$; ····■····, absorption coefficient of nifedipine $k_2$; ····▲····, absorption coefficient of photodegradation product $k_3$.

bance, the rate constant $k_1$ can easily be estimated by Eq. 7, because $k_1$ is the only unknown in this equation. The rate constant $k_1$ can also be estimated by testing at a concentrated solution that is considered to be a zero-order reaction. Therefore, we can estimate the rate constant $k_1$ and the absorption coefficients $k_2$ and $k_3$ without using the NLSPE method. Moreover, we can estimate them by observing a single photodegradation experiment. Once $k_1$, $k_2$ and $k_3$ are determined, photodegradation can be simulated at any initial concentration using Eq. 7.

Because the absorption coefficient $k_3$ is close to $k_2$ ($k_3=0.75\ k_2$), the plots of the percent remaining the time gave relatively good linearity, as shown in Fig. 5. However, since the half life or pseudo-rate constant depends on the initial concentration, it is clear that the photodegradation is not a first-order reaction.

In the present study, the rate constant $k_1$ and the absorption coefficients $k_2$ and $k_3$ were estimated by solving simultaneous differential equations using the Runge-Kutta method for numerical integration, and the Marquardt method for nonlinear parameter estimation. This took one to two minutes computing time with a Yokogawa Hewlett-Packard 9845B 16 bit desk top computer.

**Photodegradation under the Near UV Fluorescent Lamp** The rate constant $k_1$ and the absorption coefficients $k_2$ and $k_3$ under the radiation of the near UV fluorescent lamp were estimated by the NLSPE method.

Each rate constant $k_1$ and each absorption coefficient $k_2$ and $k_3$ under the radiation intensity of $30\,mW/cm^2$ were almost constant for every initial concentration tested, as shown in Fig. 6. The absorption coefficient $k_3$ was about fifteen percent that of $k_2$ for every initial concentration. This percentage is considered to be reasonable from the radiation spectrum of the lamp, and from absorption spectra of nifedipine and its photodegradation products. The rate constant $k_1$ and the absorption coefficients $k_2$ and $k_3$ that were estimated from nine different initial concentrations, (namely, 5, 10, 15, 20, 25, 30, 35, 40 and 45 mg/100 ml) were $4.74\,mg/100\,ml\,h^{-1}$, 0.255 and 0.0341, respectively. The experimental data and calculated curves that were calculated by substituting the above values into Eq. 7 are shown in Fig. 7. The calculated curves showed a good agreement with the experimental data, and hence Eq. 7 can be regarded as the theoretical equation for photodegradation.

With respect to the germicidal lamp, if the initial concentration is high, the absorption coefficients $k_2$ and $k_3$

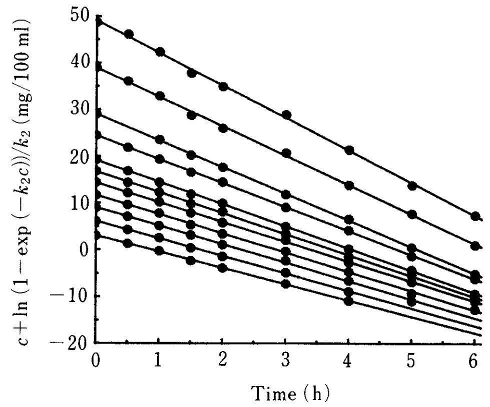


Fig. 9. Experimental Data and Plots of $c+\ln(1-\exp(-k_2c))/k_2$ against Time for the Photodegradation of Nifedipine in Solutions under the Fluorescent Lamp

The radiation intensity is 1000 lux. The initial concentrations of nifedipine are 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 30, 40 and 50 mg/100 ml, from lower linear line to upper linear line, respectively.

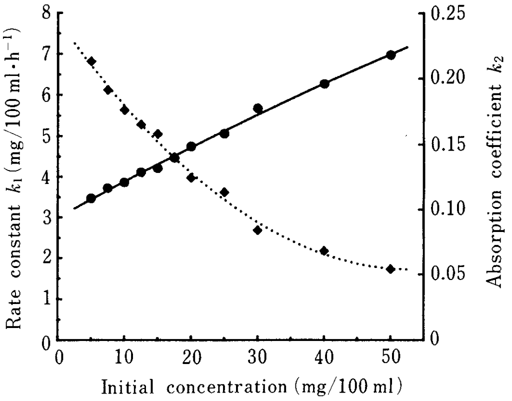


Fig. 10. Dependence of the Initial Concentration on the Rate Constant and Absorption Coefficient for the Photodegradation of Nifedipine in Solutions under the Fluorescent Lamp

The radiation intensity is 1000 lux. —●—, rate constant $k_1$; ···◆···, absorption coefficient of nifedipine $k_2$.

cannot be estimated, however in this case, estimation was possible. They converged at a constant value.

The effect of the radiation intensity on the rate constant $k_1$ and the absorption coefficients $k_2$ and $k_3$ was tested. The rate constant $k_1$ was directly proportional to the radiation intensity, but the absorption coefficients $k_2$ and $k_3$ were not influenced by the radiation intensity and were almost constant, as shown in Fig. 8. In this experiment, three initial concentrations (20, 25 and 30 mg/100 ml) of nifedipine solutions were used to estimate the rate constant and the absorption coefficients.

**Photodegradation under the Fluorescent Lamp** The rate constant $k_1$ and the absorption coefficients $k_2$ and $k_3$ under the radiation of the fluorescent lamp were estimated using the NLSPE method. The absorption coefficient $k_3$ was approximately zero for every initial concentration sample. This result can be explained by the absorption spectrum of the photodegradation product and the radiation spectrum of the fluorescent lamp, as shown in Figs. 1 and 2. The photodegradation products have almost no absorption of light at a wavelength more than 370 nm, and the fluorescent lamp has almost no radiation of light at a wavelength less than 370 nm.

Because the absorption coefficient $k_3$ was assumed to be zero, the rate constant $k_1$ and the absorption coefficient $k_2$ under the radiation intensity of 1000 lux were calculated from the linear equation of Eq. 10, and are shown in Figs. 9 and 10.

Theoretically, if the radiation conditions are constant, the rate constant $k_1$ and the absorption coeffiicient $k_2$ must be constant, even if the initial concentration is changed. However, the rate constant $k_1$ increased and the absorption coefficient $k_2$ decreased with increasing concentration of nifedipine. The reason for the decrease in $k_2$ in this condition, in spite of the constant path length under the experimental conditions, is as follows: the short wavelength of ligh that influences the photodegradation strongly is weak with respect to the fluorescent lamp; the short wavelength of light is all absorbed it traverses through the concentrated solution; a similar reason holds when the path length of short wavelength light is shortened. The absorption coefficient $k_2$ is derived from Eq. 5, and hence is proportional to the path length of the light.

The reason that the rate constant $k_1$ increased with the increasing concentration of nifedipine is as follows: the short wavelength of light is more effectively used for the photodegradation of concentrated solutions than dilute solutions. That is to say, the proportion of the absorption of the short wavelength of light is relatively higher in concentrated solutions than in dilute solutions.

In conclusion, a theoretical equation for the kinetic analysis· of photodegradation was derived and was substantiated by demonstrating the photodegradation of nifedipine.

This equation is expected to apply to other photosensitive reactants.

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