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Comparative evaluation of photostability of solid-state nifedipine under ordinary and intensive light irradiation conditions

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Summary

The solid-state photodegradation of nifedipine was investigated using mercury vapor and fluorescent lamps as light sources. Nifedipine was decomposed concurrently to 4 components by either lamp, quite differing from the results of the past investigations in a liquid phase. The main photoproduct was a nitrosopyridine derivative and the others were minor. The wavelength of light significantly affected the degradation; the drug was easily decomposed by UV and visible lights below 500 nm and the degree of degradation reached the maximum at around 380 nm corresponding to the absorption band of the nitro group and dihydropyridine ring in the molecule. The degradation process followed apparent first-order kinetics. Although the degradation rate constant was much higher for the mercury vapor lamp than for the fluorescent lamp, the degradation profiles were, irrespective of kinds of light sources, enough expressed as a definite function of the total irradiation intensity over the wavelength range relating to the degradation The coloration profiles of the drug powder, which were evaluated by Hunter's color difference before and after exposure, ΔE, were also equivocally controlled by the total irradiation intensity over the same wavelength range as that for the degradation. The total irradiation intensity was thus proved to be a useful parameter for estimating the photostability under ordinary irradiation condition from the results obtained in an accelerated stability test.

Introduction

Nifedipine (dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate) known well as an effective calcium antagonist is widely used for the treatment of coronary heart disease. Because the drug is extremely photolabile, strict illumination control is necessary to maintain the chemical potency during the manufacturing process of its preparations. Colorants or light-resistant package systems have been also applied to photostabilize its tablets, and hard or soft elastic gelatin capsules. The photostabilities of several solid dosage forms have been evaluated for their quality assurance under fluorescent lamp or daylight irradiation condition (Kudo et al., 1972; Sugimoto and Matsuda et al., 1981; Binda and Dondi, 1981; Terui et al., 1984; Inoue et al., 1985).

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There have been several reports (Kudo et al., 1972; Ebel et al., 1978; Testa et al., 1979; Jacobsen et al., 1979; Thoma and Klimek, 1985a, 1985b; Majeed et al., 1987) dealing with the photo-degradation of nifedipine and its degradation mechanism in some organic or inorganic solvents. In these reports nifedipine was proved to show a characteristic degradation profile; it decomposed to different photoproducts upon exposure to daylight and UV light. However, due to the complexity of pharmaceutical reaction and inaccurate irradiation condition, most of these investigations have been only qualitative in nature. It is of value to perform extensive evaluation for the solid-state photostability of nifedipine in view of the present situation of commercial dosage forms. This paper describes a preformulation study to provide basic information which can be used for achieving more reasonable and reliable photostabilization of the drug. From the pharmaceutical point of view, the emphasis is placed on the quantitative interpretation of degradation profiles under different light source conditions. The degradation mechanism of nifedipine was not elucidated in this investigation. A photostabilization of the drug in a model film-coating system will be reported elsewhere.

Materials and Methods

Materials

Nifedipine (200 mg) was dissolved in 50 ml of ethyl acetate. A few drops (50 μl) of the solution was placed with a microsyringe to spread on a glass plate (47 × 26 mm), and evaporated at room temperature. The sample was then cooled at 0 °C for 24 h to accomplish thorough recrystallization. The fine crystals of 200 μg separated on the glass plate were discrete enough for uniform exposure to light.

Irradiation test

Three irradiation apparatuses were employed; two of them, a grating monochromator (model CRM-FA, Japan Spectroscopic Co., Tokyo, Japan) equipped with a 5-kW xenon lamp and a fading tester (model MH-1, Mitsubishi Electric Co., Tokyo, Japan) equipped with a 400 W high-pressure mercury vapor lamp, were the same as those described in our previous paper (Matsuda and Masahara, 1983). To investigate the effect of wavelength of light on the photodegradation, the former apparatus was adjusted for irradiation of monochromatic light (band width: 3 nm) at 10-nm intervals within the wavelength range of 290–500 nm. The samples were exposed to light at each wavelength until the irradiation reached the same designed intensity level (5×10^4 J/m^2). Since the spectral irradiation energy of this lamp varied depending on the wavelength, the irradiation time required for obtaining the same intensity level differed for every wavelength (Table 1). In this table the irradiation time t at a wavelength λ to obtain the designed irradiation intensity E was calculated by:

$$t = E/I_\lambda \qquad (1)$$

where I_λ is the irradiation intensity of monochromatic light measured at the sample position (this

TABLE 1

The time required for obtaining a designed irradiation intensity (5×10^4 J/m^2)

Wavelength λ(nm)	Irradiation intensity (J/m^2·s)	Irradiation time (s)
290	0.40×10^2	1250
300	0.47	1064
310	0.50	1000
320	0.57	877
330	0.64	781
340	0.72	694
350	0.78	641
360	0.82	610
370	0.79	633
380	0.74	676
390	0.82	610
400	0.84	595
410	0.84	595
420	0.84	595
430	0.80	625
440	0.78	641
450	0.83	602
460	0.88	568
470	0.98	510
500	0.69	725

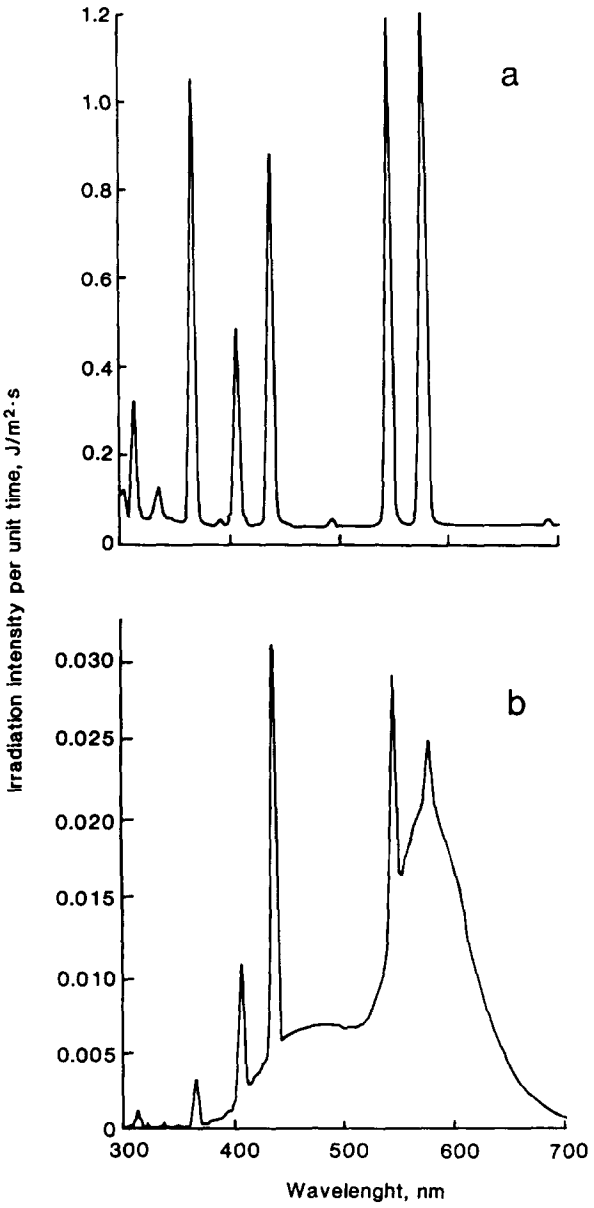

Fig. 1. Spectral irradiation intensity of mercury vapor lamp (a) and fluorescent lamp (b).

value can be obtained from the spectral irradiation intensity curve of the lamp). The illuminance on the surface of a sample fixed in the fading tester was 11,450 lux as measured with an illuminometer (model UVR-365, Tokyo Optical Instruments Co., Tokyo, Japan) and the distance between the lamp and sample was 30 cm. Unless otherwise specified, the accelerated irradiation tests using these lamps were carried out at room temperature. Samples for the ordinary irradiation tests at various temperatures were fixed in the same thermostated jacket in an instrumented irradiation cabinet as that reported previously (Matsuda and Masahara, 1983) and exposed to light of a 20 W fluorescent lamp. The distance between the lamp and sample was 47 cm. The illuminance on the surface of any one sample was 1066 lux. The spectral irradiation intensity curves of mercury vapor and fluorescent lamps, measured on the surface of a sample under these irradiation conditions with a portable spectroradiometer (model LI-1800, LI-COR Inc., NE, U.S.A.), are shown in Fig. 1.

Colorimetric measurements and diffuse reflectance spectrometry

To trace the quantitative change in appearance of nifedipine powder after exposure to light, 300 mg of the drug was compressed to a tablet of 15 mm diameter by a single set of flat-faced punches and die at a constant compression force of 2000 kg, which was equipped with a compression tension testing machine (model IS-5000, Shimadzu Co., Kyoto, Japan). The tablet was fixed on a glass plate and irradiated with the mercury vapor or fluorescent lamps. The surface color of the tablet in the Lab system was measured using a 0°–45° method (JIS Z 8722) after irradiating for a certain period of time with an integrating sphere-type color difference meter (model SZ-Σ80, Nippon Denshoku Kogyo Co., Tokyo, Japan). The Hunter color difference ΔE was calculated according to the method of our previous paper (Matsuda et al., 1978) to evaluate the degree of coloration.

Diffuse reflectance spectrum of the drug before irradiation was recorded on a multi-purpose spectrophotometer (model MPS-2000, Shimadzu Co., Kyoto, Japan) using barium sulfate disk as a reflectance standard.

HPLC analysis

Nifedipine and its photoproducts were analyzed by a HPLC system (model LC-3A, Shimadzu, Co., Kyoto, Japan); the prepacked column (Chem-

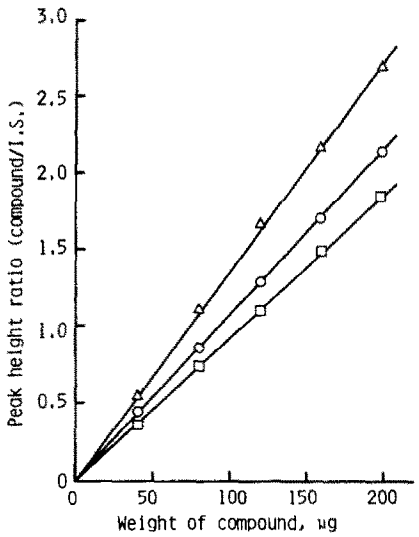

Fig. 2. Calibration curves for unchanged nifedipine and two photoproducts, the nitroso- and nitro-derivatives. ○, nifedipine; □, nitroso-derivative; △, nitro-derivative.

copak $5C_{18}$, 15 cm × 4.6 mm i.d., Chemco Co., Tokyo, Japan) was operated at 40 °C at a flow rate of 0.8 ml/min. The mobile phase consisted of a solvent system of methanol–water (5 : 3). An antipyrine solution (400 μg/ml) was used as an internal standard. After irradiation, samples on the glass plate were washed away several times with ethyl acetate, 140 μl of the internal standard solution was added, and the mixture was evaporated to dryness under vacuum. The residue was then dissolved in 200 μl of ethyl acetate and 0.6 μl of this solution was injected onto the chromatograph to simultaneously determine the concentrations of both unchanged nifedipine and two photoproducts. The values were determined in triplicate at 254 nm and the mean of these determinations was used. The calibration curves for nifedipine and the photoproducts are given in Fig. 2. Good linearity was established for any compound ($r > 0.999$; $n = 5$), and the reproducibility of the data was invariably good.

Isolation and spectrometry of photoproducts

Nifedipine was irradiated under the same conditions as described in the section on irradiation tests, and 3 photoproducts were isolated with a preparative HPLC system (Waters Ltd., Tokyo, Japan) equipped with a column (μBondasphere C_{18} 15 μm, 30 cm × 7.8 mm i.d.). Operating conditions were as follows: mobile phase, methanol: water (5 : 3); flow rate, 2.8 ml/min; detection wavelength, 254 nm; column temperature, 35 °C.

UV-spectra of these products in methanol were taken by a spectrophotometer (UV-160, Shimadzu Co., Kyoto, Japan). PMR spectra in $CDCl_3$ + TMS were recorded on a Varian XL-200, and mass spectra were obtained with a Hitachi M-80 (Hitachi Co., Tokyo, Japan). All procedures were performed under the irradiation of a photo-flood red lamp in a dark room.

Results and Discussion

Establishment of chemical structure of photoproducts

Fig. 3 shows a typical chromatogram of the sample irradiated by a mercury vapor lamp for 8 min. Similar results were obtained from the irradiation tests using a fluorescent lamp. It exhibited 4 peaks (**II, III, IV**, and **V**) which were attributable to photoproducts other than (**I**) of the recovered

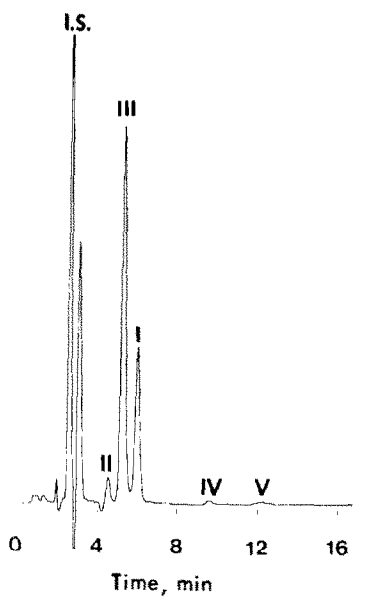

Fig. 3. Typical HPLC chromatogram of photodegraded nifedipine after 8-min irradiation by mercury vapor lamp. **I**, Recovered nifedipine; **II**, nitro-derivative; **III**, nitroso-derivative; **IV**, unknown product; **V**, azoxy-derivative.

TABLE 2

The spectrometric data of photoproducts

Spectrum	II	III	V
UV	260 (shoulder)	280	325
(nm)		309	
PMR	6H 2.66 ($C-CH_3$)	6H 2.64 ($C-CH_3$)	6H 2.58 ($C-CH_3$)
(ppm)	6H 3.52 ($O-CH_3$)	6H 3.40 ($O-CH_3$)	6H 2.62 ($C-CH_3$)
	4H 7.20–8.32 (aromatic H)	4H 6.40–7.80 (aromatic H)	6H 3.38 ($O-CH_3$)
			6H 3.40 ($O-CH_3$)
			8H 6.70–8.10 (aromatic H)
MS	313 (5%) (M^+-OCH_3)	328 (27%) (M^+)	640 (69%) (M^+)
(m/z)	298 (100%) (M^+-NO_2)	298 (5%) (M^+-NO)	581 (17%) (M^+-CO-N_2-H)
		269 (100%) ($M^+-COOCH_3$)	298 (100%) ($M^+-C_{17}H_{16}O_5N_2$)
HRMS		calcd for $C_{17}H_{16}O_5N_2$: 328.1057	calcd for $C_{34}H_{32}O_9N_4$: 640.2167
		found 328.1057	found 640.2173

nifedipine. The retention times for products **II** and **III** agreed exactly with those of the authentic samples of a nitro-derivative, 4-(2-nitrophenyl)-2,6-dimethyl-3,5-dimethoxycarbonylpyridine corresponding to the dehydrogenated form of nifedipine, and a nitroso-derivative, 4-(2-nitrosophenyl)-2,6-dimethyl-3,5-dimethoxycarbonylpyridine. The spectral data of these products isolated (Table 2) gave excellent agreement with those of the above-mentioned authentic samples and the results obtained by Ebel et al. (1978). The major photoproducts **II** and **III** were thus confirmed to be the nitro- and nitroso-derivatives, respectively,

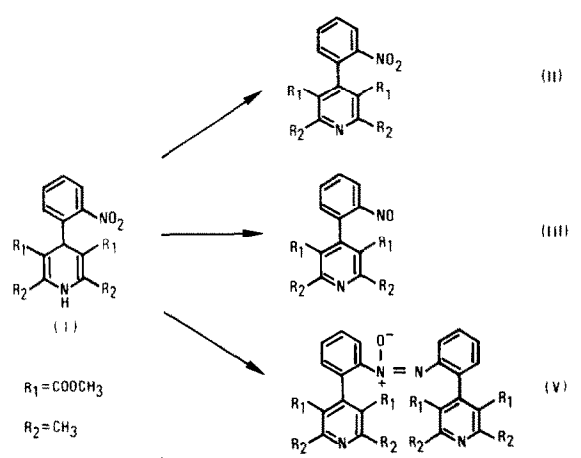

Fig. 4. The chemical structures of nifedipine (**I**) and three photoproducts (**II, III** and **V**). The roman numerals in parentheses are the same as those in Fig. 3.

as represented in Fig. 4. The chromatograms of the two authentic samples irradiated by a mercury vapor lamp for 10 min did not show any peak other than that of the recovered sample, suggesting no more occurrence of photodegradation.

The mass spectrum of the minor unknown photoproducts V showed typical fragments m/z 581 (M^+-CO-N_2-H) characteristic of azoxy derivatives and m/z 298 ($M^+-C_{17}H_{16}O_5N_2$). In the PMR-spectrum the signals were assigned as follows: singlet at 2.58 ppm (6H) from C-CH_3; singlet at 2.62 ppm (6H) from C-CH_3; singlet at 3.38 ppm (6H) from O-CH_3; singlet at 3.40 ppm (6H) from O-CH_3 and a multiplet at 6.70–8.10 ppm (8H) from aromatic ring protons. It is therefore deduced from these data that an azoxy-derivative, 2,2′-bis-(2,6-dimethyl-3,5-dimethoxycarbonylpyridine-4-yl)azoxybenzene, is formed as represented in Fig. 4. The structure of another unknown product **IV** could not be established due to its trace amount.

Common results obtained by earlier investigations (Kudo et al., 1972; Ebel et al., 1978; Testa et al., 1979; Jacobsen et al., 1979) dealing with the photodegradation in the liquid phase indicate that under daylight or normal laboratory light nifedipine decomposes only to the nitroso-derivative (**III**), and only to the nitro-derivative (**II**) by UV light (254 nm). The United States Pharmacopeia (1985) also describes that the drug, when exposed to daylight and certain wavelengths of artificial

light, converts to a nitrosopyridine derivative, and to a nitropyridine derivative upon exposure to UV light. In the present study, irrespective of the spectral irradiation intensity of light sources, nifedipine simultaneously decomposed in the solid state to at least 4 compounds. This finding is quite different from the results obtained in a solution where the formation of products was selective and wavelength-dependent.

Photodegradation profiles under ordinary and intensive irradiation conditions

Fig. 5 shows the time-course changes in molar fractions of intact nifedipine, and both nitroso- and nitro-derivatives formed under the irradiation by mercury vapor and fluorescent lamps. Nifedipine decomposed very rapidly as exposed to a mercury vapor lamp; its fractional remaining decreased down to less than 0.30 after only a 10-min irradiation. A rapid increase in fractional formation of the nitroso-derivative was found in an early stage of irradiation by any lamp, but the rate of formation began to level off at 8–10 min (mercury vapor lamp) and 5–6 h (fluorescent lamp). The fractional formation of the nitro-derivative by the irradiation even after almost completing the degradation was still very slow, indicating the formation of a minor product. The sum of the molar fractions for the 3 components did not remain constant and decreased gradually. This was caused by the formation of the products **IV** and **V**.

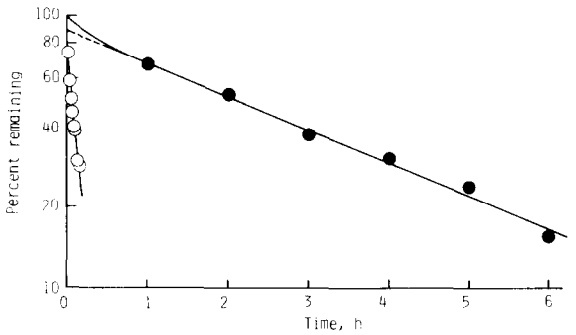

Fig. 6. The apparent first-order degradation profiles of nifedipine under mercury vapor lamp (○) and fluorescent lamp (●).

To quantitatively interpret the degradation profiles of nifedipine in Fig. 5, the residual percentage was plotted against time on semilogarithmic paper (Fig. 6). Good linear relationships existed between both variables for any lamp, suggesting that the solid-state photodegradation followed the apparent first-order kinetics. The degradation rate constants obtained from the slope of the straight lines for mercury vapor and fluorescent lamps were 6.18 and 0.28 h^{-1}, respectively. The significant difference of degradation rates between the two kinds of lamps as shown in Figs. 5 and 6 should naturally be ascribed to the entire difference of the intensities for the light and spectral irradiation of these lamps. These variables (intensities of both light and spectral irradiation) can be integrated as the total irradiation intensity over a certain limited wavelength range. Fig. 7, in which the data are identical to those shown in Fig. 6, illustrates the plots of logarithm of percent

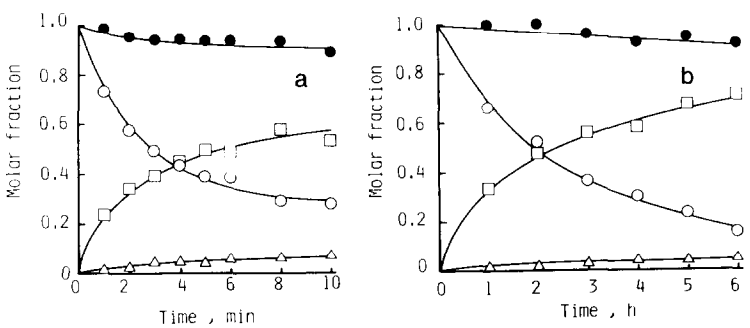

Fig. 5. The time courses for the degradation of nifedipine (○) and the formation of nitroso- (□) and nitro- (△) derivatives under mercury vapor lamp (a) and fluorescent lamp (b). The solid circles indicate the total molar fraction of unchanged nifedipine and the two photoproducts.

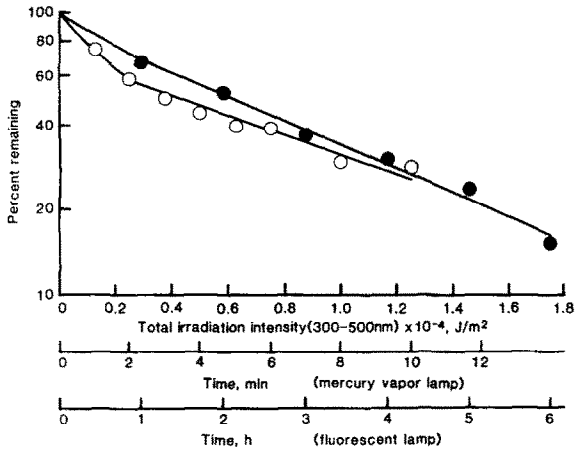

Fig. 7. The time courses for the degradation of nifedipine based on the total irradiation intensity under mercury vapor lamp (○) and fluorescent lamp (●) (cf. Fig. 5).

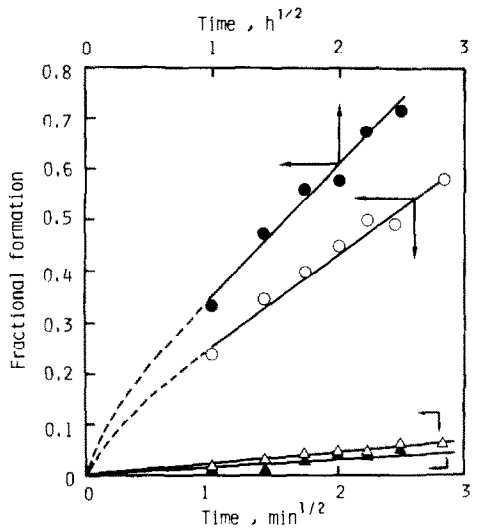

Fig. 8. The plots of fractional formation of nitroso- (○, ●) and nitro- (△, ▲) derivatives against square root of irradiation time under mercury vapor and fluorescent lamps. Open and solid symbols represent the data obtained under mercury vapor and fluorescent lamps, respectively (cf. Fig. 5).

remaining of nifedipine in Fig. 6 against the total irradiation intensity of light in the wavelength range of 300–500 nm where the chemical potency of nifedipine tablet lowered significantly (Sugimoto and Matsuda et al., 1981) and was also confirmed in the next section; the total irradiation intensity I_T (J/m^2) was calculated by:

$$I_T = t\int_{300}^{500} I_\lambda d\lambda \qquad (2)$$

where t is irradiation time(s) and I_λ is irradiation intensity per unit time (J/m^2 · s) at wavelength, λ in Fig. 1. These plots were also satisfactorily regressed by a straight line for any lamp except for the initial period of irradiation, because the total irradiation intensity for individual lamps is proportional to irradiation time. The two lines were very close to each other, indicating that irrespective of the kinds of the light sources, the percent remaining of nifedipine could be expressed as a definite function of the total irradiation intensity. The total irradiation intensity was calculated by Eqn. 1 using a computer-aided integration circuit attached in the spectroradiometer. The values thus integrated were 20.8 and 80.9×10^{-2} (J/m^2 · s) for mercury vapor and fluorescent lamps, respectively. This result strongly suggests that the photostability of nifedipine can be estimated unequivocally by the total irradiation intensity of a light source.

Fig. 8 shows the result of plotting for the fractional formation of the nitroso- and nitro-derivatives in Fig. 5 against square root of time. All were good straight lines except for the earlier period of irradiation by any one lamp. The ap-

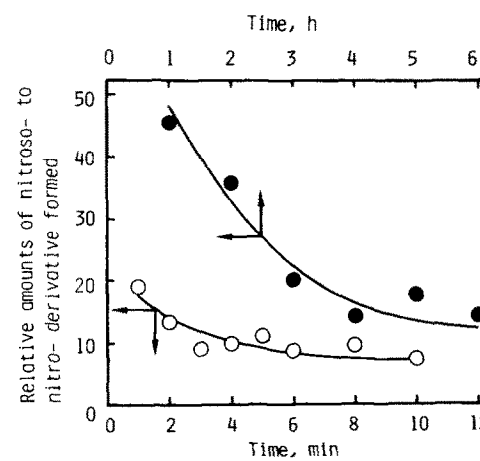

Fig. 9. The time dependency of the relative amounts of nitroso- and nitro-derivatives. ○, Mercury vapor lamp; ●, fluorescent lamp.

TABLE 3

The apparent first-order degradation rate constants at various temperatures obtained under fluorescent lamp

Temperature (°C)	k (h^{-1})
25	0.211
35	0.229
45	0.207
55	0.200

parent formation rate constants for the nitroso- and nitro-derivatives, which were obtained from the slopes of lines after irradiation of a mercury vapor lamp, were ~ 5.4 and ~ 10.2 times as great as those of a fluorescent lamp, respectively. The plots of relative amounts of formation of the nitroso- to nitro-derivative against time are given in Fig. 9. The values were much greater after the irradiation of a fluorescent lamp than after that of a mercury vapor lamp. With the lapse of time, the values decreased and approached gradually equilibrium values which were by far greater than unity. This finding indicates that the nitro-derivative still remains a minor product even after long irradiation.

Table 3 summarizes the temperature-dependency of the degradation rate constant obtained under the irradiation by fluorescent lamp. No significant difference was found among the values obtained at 4 temperatures, suggesting the activation energy for the degradation to be negligibly small. The energy available in a photochemical reaction is much greater than that for a thermal reaction. Therefore, photochemical reaction depends very rarely on temperature in activating molecules except for a few cases (Zimmerman et al., 1969; Matsuda and Masahara, 1983). This also suggests that nifedipine will be easily decomposed by light even at very low temperature.

Effect of irradiation wavelength on photodegradation

It is well known that photodegradations depend on the intensity of light and its wavelength (Lin and Lachman, 1969; Matsuda and Masahara, 1983; Allwood and Plane, 1986). Fig. 10 shows the effect of wavelength of light on the degradation of

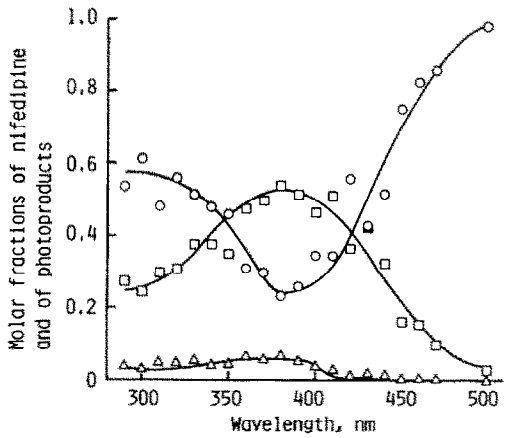

Fig. 10. The effect of wavelength on the photodegradation of nifedipine after exposure to light intensity of 5×10^4 J/m^2. ○, Nifedipine; □, nitroso-derivative; △, nitro-derivative.

nifedipine and the formation of the nitroso- and nitro-derivatives under a constant irradiation intensity (5×10^4 J/m^2) shown in Table 1. No photodegradation occurred at wavelengths above 500 nm which was almost consistent with the wavelength for the photodegradation of the drug in tablet (Sugimoto and Matsuda et al., 1981). The action spectrum for the degradation of nifedipine depicted a characteristic pattern corresponding

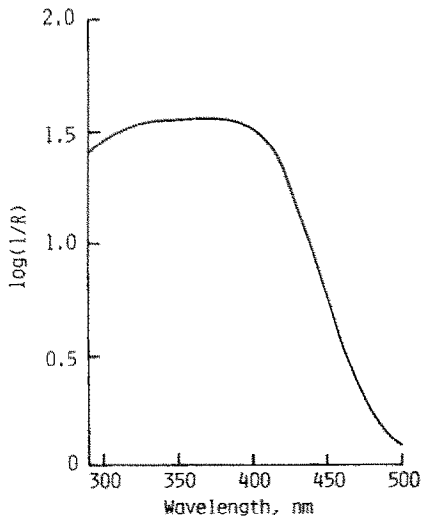

Fig. 11. The diffuse reflectance spectrum of nifedipine powder before irradiation. In this graph the diffuse reflectance, R, is recorded as $\log(1/R)$.

well with the diffuse reflectance spectrum of the drug before irradiation (Fig. 11); the decrease in the fractional remaining of nifedipine became noticeable as the irradiation wavelength was shifted toward the side below 500 nm, reaching the minimum at ~ 380 nm followed by increasing again at further lower wavelengths. This fact suggests that the drug must be thoroughly protected from not only UV but also from visible light.

The critical wavelength at ~ 380 nm was very close to the characteristic absorption band attributable to the nitro group and the dihydropyridine ring (325–370 nm (Ebel et al., 1978) or 330–360 nm (Thoma et al., 1985a) in ethanol) in the molecule of nifedipine. The fractional formation of the nitroso-derivative exhibited a maximal value at ~ 380 nm, depending on the degradation of nifedipine, and kept higher levels even in the visible region. The nitro-derivative was formed preferentially by UV light, showing a maximal formation at around 380 nm as well as the nitroso derivative, and no appreciable formation was detected at wavelengths above 420 nm. Therefore, the light of 314, 366 and 402 nm irradiated from a fluorescent lamp (Fig. 1) must contribute to the result that the nitro-derivative was also formed under the irradiation by the lamp (Fig. 5). The effect of wavelength on the relative amounts of formation of nitroso- to nitro-derivative in Fig. 10 is clearly shown in Fig. 12; although the value was constant independently of wavelength below 380 nm, it increased sharply above this critical wavelength. The reason why this value was much higher for a fluorescent lamp than for a mercury vapor lamp (Fig. 9) can be fully explained by the distinct difference for the relative intensity of UV to the intensity of visible light between the lamps and by the result of Fig. 12.

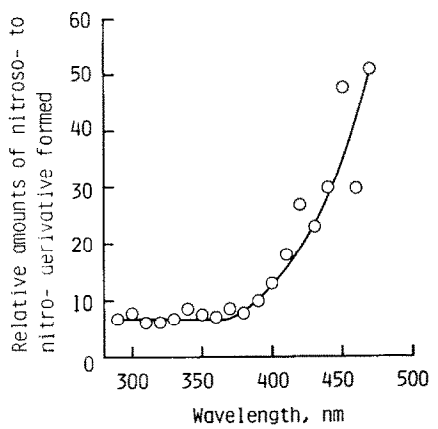

Fig. 12. The effect of wavelength on the relative amounts of nitroso- and nitro-derivatives formed (cf. Fig. 10).

Appearance change under ordinary and intensive irradiation conditions

The surface color of nifedipine tablet turned gradually from fresh yellow to dark yellow upon exposure to light. In this sense it is possible to qualitatively estimate the photostability of the drug by the extent of coloration or color darkening. The progress of darkening was examined by color difference, ΔE. For the kinetic interpretation of these color changes, the increase in ΔE against time may be expressed by (Matsuda and Masahara, 1980):

$$\frac{d\Delta E}{dt} = k(\Delta E)^n \tag{3}$$

where t and k are irradiation time and the color-darkening rate constant, respectively, and n is constant. Integrating Eqn. 2 under the initial condition ($\Delta E = 0$ at $t = 0$), we obtain:

$$\log \Delta E = \frac{1}{1-n}\log t + \frac{1}{1-n}\log[(1-n)k]$$

$$(n \neq 1) \tag{4}$$

Eqn. 3 indicates that a linear relationship with a slope of $1/(1-n)$ should hold between ΔE and t on the double-logarithmic scale. The double-logarithmic plot of color darkening processes under these lamps gave excellent straight lines nearly parallel to each other over the whole range of irradiation time investigated (Fig. 13). The time required for ΔE to reach the same color difference level was much shorter in a mercury vapor lamp than in a fluorescent lamp. Similarly to the results obtained in Fig. 5, the difference in color change depending on the chemical degradation is also attributable to the irradiation properties of light sources. These two straight lines could be super-

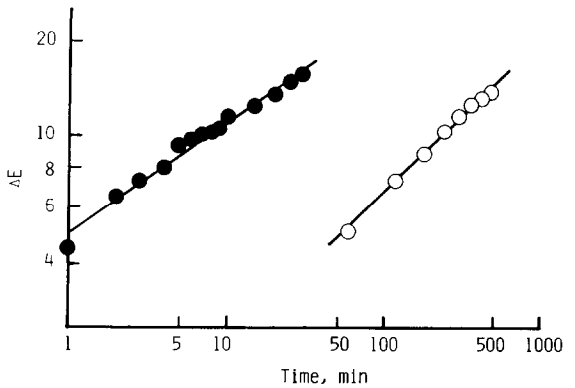

Fig. 13. The double logarithmic plot for the color change process under mercury vapor lamp (●) and fluorescent lamp (○) (cf. Eqn. 4).

posed satisfactorily by replacing irradiation time with the total irradiation intensity in the same wavelength range as in Fig. 7 (Fig. 14). If the irradiation characteristics of light sources are already clarified, the establishment of similarities in degradation and color change shown in Figs. 7 and 14 strongly suggests that the photostability under ordinary irradiation condition can be roughly estimated from the results obtained in an accelerated stability test.

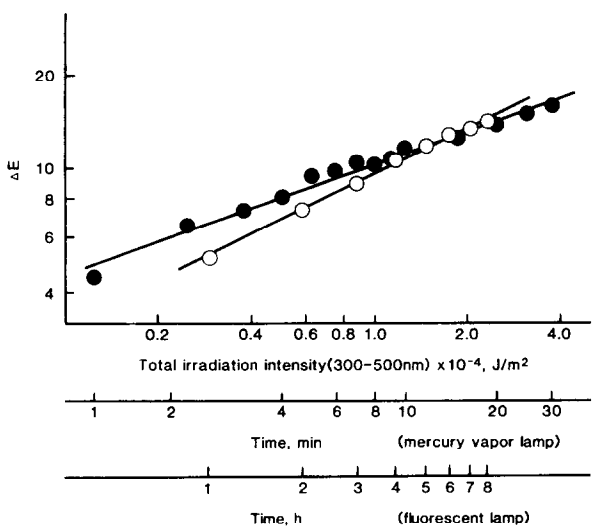

Fig. 14. The double-logarithmic plot for the color change process based on the total irradiation intensity under mercury vapor lamp (●) and fluorescent lamp (○).

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