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Spectrophotometric study of the photodecomposition kinetics of nifedipine

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Nifedipine is a photosensitive compound. Irradiation for 4 h under a fluorescent lamp placed 30 cm from a solution of nifedipine in 95% ethanol leads to complete photo-oxidation as determined spectrophotometrically. The disappearance of the reduced form and appearance of the oxidized form is best described by zero-order kinetics at concentrations higher than 4×10^{-4} M. At lower concentrations pseudo-first order kinetics are followed. Monochromatic irradiation of nifedipine at wavelengths 400 to 700 nm in 25 nm increments showed no change in the absorbance at 280 nm, and, except for a hyperchromic effect at 237 nm, no other spectral changes were observed. Its photo-oxidation was dependent on the intensity of light and increased exponentially as solutions were irradiated progressively closer to a fluorescent light source. The pH studies showed that aqueous solutions of nifedipine photo-oxidized fastest at pH 2.

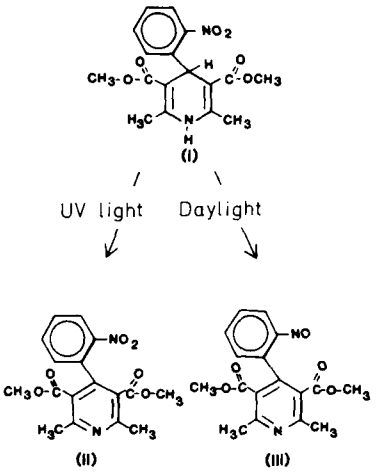
Nifedipine, an orally active calcium blocking agent, is a 4-(2-nitrophenyl)-1,4-dihydropyridine derivative (I). As such, it undergoes photochemical oxidation when exposed to light (Berson & Brown 1955; Testa et al 1979). Berson & Brown (1955) have reported that irradiation of ethanolic solutions of 4-(2-nitrophenyl)-1,4-dihydropyridines convert these compounds to the fully aromatic nitroso derivatives.

Depending on the source of irradiation, two photo-oxidation products of nifedipine have been reported (Testa et al 1979; Jacobsen et al 1979; Pietta et al 1981). One is the nitrophenylpyridine product (II) elicited by ultraviolet light, and the other the nitrosophenylpyridine product (III) caused by daylight irradiation.

The possibility of the photo-oxidation of nifedipine has been pointed out by several investigators (Testa et al 1979; Jacobsen et al 1979; Pietta et al 1981; Dokladalova et al 1982) and by the manufacturer (Greenslade personal communication). However, extensive studies on the kinetics or a detailed examination of conditions that might affect the kinetics of the photo-oxidation process have not been reported. The purpose of these studies was to determine the reaction kinetics, and to investigate the effects of concentration, light intensity, and pH on the stability of nifedipine.

Materials and methods

Materials. Nifedipine (I) (lot 19324-04010) was donated by Pfizer Company, Brooklyn, NY, USA. All reagents were analytical or spectro-grade. Water used in solutions was doubly distilled and deionized. Buffers were prepared at 0·2 M and adjusted to pH 2, 5, 7 and 9 by addition of 0·1 M NaOH and/or 0·1 M HCl using a Markson Model 85 pH meter.



Scheme. Photo-oxidation products of nifedipine under ultraviolet and daylight exposure.

Methods. A stock solution of $1{\cdot}0 \times 10^{-2}$ M nifedipine was prepared in 95% ethanol, transferred to an amber glass bottle, wrapped with aluminum foil, and stored tightly closed in the dark at room temperature. Lower concentrations used for experiments were prepared by dilution of the stock solution.

The effect of monochromatic light on the photoconversion of nifedipine was studied using a Spectronic 20 Spectrophotometer (Bausch and Lomb, Rochester, NY). Solutions were irradiated over a wavelength range of 400–700 nm at increments of 25 nm. Samples were placed in a quartz cell and covered with a Teflon cap to prevent evaporation of ethanol. Ultraviolet-visible spectra were obtained after irradiation for 0, 12 and 24 h (Beckman ACTA Spectrophotometer, Palo Alto, CA). The absorbance values at 237, 280 and 360 nm were used to determine absorbance changes at each time interval.

The effect of concentration on the kinetics was studied using triplicate solutions in a concentration range of 2×10^{-5} to 1×10^{-4} M. These solutions were irradiated by a fluorescent lamp (15 W, 43 cm long)

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placed 30 cm above the samples in a darkened room at 25 ± 3 °C. Samples were taken every 15 min for 4 h and assayed spectrophotometrically at 236, 280 and 360 nm.

To study the effect of light intensity on the kinetics of photo-oxidation, triplicate solutions of 8×10^{-5} M nifedipine were placed at 22, 30, 55, and 75 cm below the fluorescent light source and irradiated in an otherwise darkened room. Samples were assayed at 15 min intervals for 4 h.

The effect of pH was studied using triplicate solutions of 2×10^{-5} M nifedipine prepared in aqueous buffered solutions (pH 2, 5, 7 and 9). Samples were irradiated by the fluorescent light source 30 cm from the sample container. Aliquots were collected over 24 h and assayed spectrophotometrically.

Results and discussion

The effect of photo-oxidation of nifedipine under fluorescent light was studied. The spectra of 2×10^{-4} M I in 95% ethanol showed absorbance maxima at 237 and 360 nm before irradiation with fluorescent light. With the photoconversion of the reduced form to the oxidized form, the absorbance spectrum of the same solution following 3 h of irradiation showed a decrease in the absorbance maxima at 237 and 360 nm and the appearance of a new maximum at 280 nm. These results are summarized in Fig. 1. Similar results were obtained

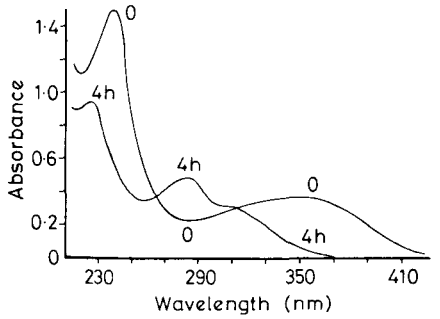

FIG. 1. Spectral changes in the photo-oxidation of 2×10^{-2} M nifedipine in 95% ethanol at time 0 and 4 h after irradiation with fluorescent light.

by Berson & Brown (1955) in their studies of dihydropyridines with different ester or ketone functional groups at the 3,5-positions. Based on their studies, the reduced form is deduced to be the non-aromatic nitrophenyl-dihydropyridine compound and the oxidized form is the compound resulting from conversion to the fully aromatic nitrosophenylpyridine derivative (Berson & Brown 1955).

When nifedipine was irradiated with monochromatic light in 25 nm increments from 400 to 700 nm, the only change observed was a hyperchromic effect at 237 nm when the solution was irradiated at 400, 475 and 550 nm. Photo-oxidation does not appear to be caused by any specific wavelength in this range.

A series of nifedipine concentrations (1×10^{-5} to 1×10^{-4} M) were irradiated under fluorescent light. Beer plots were constructed at 237, 280 and 360 nm at 0 time and at 4 h, from which time no further changes in the spectra were noted. From the slope of each graph the molar absorptivities of both nifedipine species, reduced and photo-oxidized forms, were determined for each wavelength (Table 1).

Table 1. Molar absorptivities of nifedipine at 237, 280 and 360 nm before and after irradiation under fluorescent light. The molar absorptivities were determined from the slope of the graph of absorbance vs molar concentration for each wavelength given. The graphs represent before and 4 h after irradiation.

Irradiation time (h)	Molar absorptivity (nm)		
	237	280	360
0	15 700	2300	3600
4	10 200	6300	1000

From the molar absorptivity data, multicomponent analysis was used to determine the concentration of both molecular species at each time. The kinetic order of the reaction was determined graphically as described by Frost & Pearson (1961). The data were analysed statistically by the linear regression model, and the correlation coefficient and standard error of the estimate were used in evaluating the results for concentration and logarithmic concentration vs time.

Two spectral relationships may be used in determining concentrations of reduced, C_R, and oxidized, C_O, forms of nifedipine by multicomponent analysis: 237 and 280 nm, and 280 and 360 nm, respectively. The advantage of using the 280 and 360 nm wavelengths for the calculation of C_R and C_O lies in the change in molar absorptivities at these two wavelengths being very similar (Fig. 1). There is also a broader wavelength range over which the slope is zero than at 237 nm. Moreover, at 237 nm there is a shift to a shorter λ_{max} as the oxidized form appears. Thus, the major advantage of using the 280 nm and 360 nm wavelengths is greater accuracy; the major disadvantage is a relative lack of sensitivity, requiring higher concentrations of the drug to achieve low errors in measurement.

When triplicate solutions of 1×10^{-4} were irradiated under fluorescent lighting and C_R and C_O determined at 280 and 360 nm, the statistically best fit for the disappearance kinetics of the reduced form was zero-order. Jacobsen et al (1979) reported that photo-degradation of nifedipine in toluene follows first-order kinetics. However, they used a very low concentration and did not take into consideration the effects that higher concentrations or other parameters may have had on the reaction. Berson & Brown (1955) found that the decomposition of 2,6-dimethyl-3-carboethoxy-5-acetyl-4-(2-nitrophenyl)-1,4-dihydropyridine followed zero-order kinetics until the reaction was 60% complete, after which time the rate decreased. The authors

attributed this decrease in rate as being due to the inhibition of the reaction by the product, the 4-(2-nitrosophenyl)pyridine derivative.

The dependency of the rate of photodecomposition with respect to nifedipine concentration was studied, and the results are summarized in Fig. 2. The zero-order rates of its disappearance and appearance of the oxidized product increased as the nifedipine concentration increased in the range of 2×10^{-5} to 6×10^{-5} M. Over the concentration range of 6×10^{-5} to 1×10^{-4} the reaction rate became concentration-independent as indicated by the plateau shape of both graphs (Fig. 2).

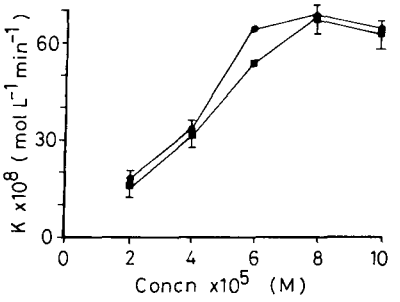

FIG. 2. Effect of molar concentration of nifedipine on the photo-oxidation of nifedipine. Plot of rate constant vs distance of light source from sample (cm). Concentration of nifedipine determined using (●) 237 and 280 nm, and (■) 280 and 360 nm.

Table 2 summarizes the disappearance half-life, $t_{\frac{1}{2}}$ (disapp), at various concentrations. As shown in Table 2, the $t_{\frac{1}{2}}$ (disapp) was concentration-independent at initial concentrations of 2 to 6×10^{-5} M, while at concentrations higher than 6×10^{-5} M it became concentration-dependent. It was 54·9 ± 2·3 min at 2×10^{-5} M and increased to 71·9 ± 2·5 min with a 5-fold increase in concentration.

Table 2. Kinetic parameters for the disappearance of nifedipine as a function of concentration.

[a]$C_R \times 10^5$ mol L^{-1}	$10 \times$ [b]K s.e. mol L^{-1} min^{-1}	[c]$t_{\frac{1}{2}}$ (disapp) min ± s.e.
2	18·22 ± 0·70	54·91 ± 2·13
4	33·34 ± 0·34	50·17 ± 2·47
6	64·13 ± 1·50	46·82 ± 1·06
8	68·44 ± 3·55	58·75 ± 2·98
10	64·30 ± 2·09	77·91 ± 2·47

[a] C_R = concentration of nifedipine.
[b] K = zero-order rate constant.
[c] $t_{\frac{1}{2}}$ (disapp) = time of the disappearance of 50% of the reduced form (nifedipine).

The results of variation in the light intensity are summarized in Fig. 3. The maximum rate of photo-oxidation was at the highest light intensity, i.e. when nifedipine was irradiated 22 cm from the fluorescent lamp. The rate decreased exponentially as the light intensity decreased, i.e. when irradiation distance increased. Furthermore, as Table 3 shows, the $t_{\frac{1}{2}}$ (disapp) was 40·4 min under intensive light and increased to more than 5 h when the light source was 75 cm above the samples. The $t_{\frac{1}{2}}$ (app) was 46·1 ± 3·2 min at 22 cm and increased to 310·6 ± 7·2 min at 75 cm.

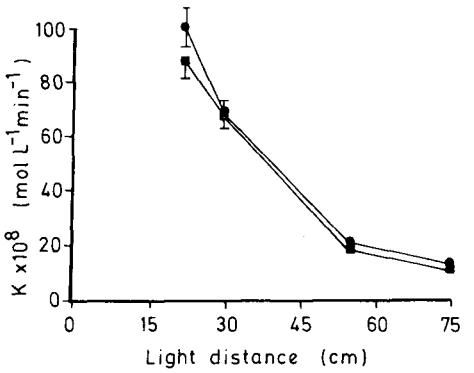

FIG. 3. Effect of light intensity on the photo-oxidation of nifedipine. Plot of rate constant vs distance of sample from light source (cm). Key as in Fig. 2.

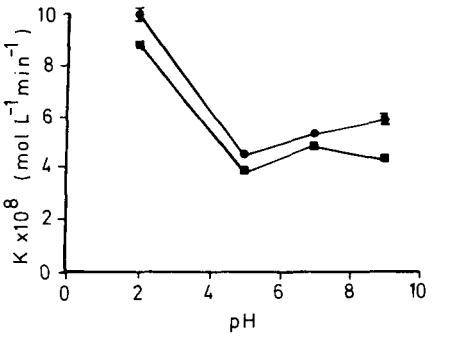

FIG. 4. Effect of pH environment on the photo-oxidation of nifedipine. Plot of rate constant vs pH. Key as in Fig. 2.

Fig. 4 shows the pH vs photo-oxidation rate constant profile. The maximum rate was found at pH 2. When the pH was increased to 5 the photo-oxidation rate reached a minimum. The high rate of photo-oxidation at pH 2 may be due to the formation of an ionized pyridine ring.

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