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Some factors affecting the photodecomposition of nifedipine

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Summary

Nifedipine, like most nitrophenyldihydropyridine derivatives, undergoes rapid photochemical oxidation to the corresponding nitrophenylpyridine when exposed to light. This is accompanied by a remarkable diminution of the pharmacological activity. In this report, the stability of the drug in different organic solvents and in the presence of an antioxidant was investigated. The UV-spectral properties of the oxidized and reduced forms of the drug were similar in acetonitrile, ethanol and chloroform. In cyclohexane the oxidized form showed absorption characteristics different from those in other solvents. Kinetic parameters for the disappearance of the reduced form or the appearance of the oxidized form as a function of bisulfite concentration were determined and the half-lives calculated. The degradation of two structural analogues of nifedipine was also studied. The results have shown that an electron donating substituent in the position of the nitro group imparts high light resistance to this group of substances.

Introduction

Nifedipine, an oral calcium-blocking agent, is absorbed rapidly and almost completely after oral administration (Palzschke et al., 1972). It undergoes metabolism in the liver to inactive acid or lactone derivatives which show a pH-dependent equilibrium in aqueous solutions (Kondo et al., 1980).

Like most 4-(2-nitrophenyl)-1,4-dihydropyridine derivatives nifedipine undergoes photochemical oxidation when exposed to light (Berson and Brown, 1955a; Testa et al., 1979). It is more sensitive to light when in solution than in the crystalline form. In contrast, the 4-(4-nitrophenyl) compounds are stable even when irradiated by intense sun light or a mercury arc (Phillips, 1951).

The photochemical reactions of many 4-(2-nitrophenyl)-1,4-dihydropyridines were studied by Berson and Brown (1955a) who found that irradiation of ethanolic solutions of these compounds convert them to the corresponding 4-(2-nitrosophenyl)-pyridine. The ultraviolet spectral changes for those compounds in 95% ethanol were also determined by these workers. The yellow color of such materials was found to change to brown on exposure to normal light.

Pietta et al. (1981) developed a high-performance liquid chromatography procedure for identification and separation of nifedipine and its metabolites in the biological fluids.

Furthermore, their method enabled them to

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analyze the photooxidation products, nitrophenylpyridine and nitrosophenylpyridine in the pharmaceutical preparations even in the presence of nifedipine as a bulk component. The nitrophenyl pyridine and nitrosophenyl pyridine products are obtained by irradiation of nifedipine with ultraviolet or day light, respectively.

The photo-oxidation of nifedipine to the pyridine derivative leads to a remarkable diminution of the pharmacological activity (Iwanami et al., 1979; Schlossman, 1975). Therefore, a study of this reaction is important to further characterize conditions that affect the photodecomposition.

In a previous report (Majeed et al., 1987) we investigated the reaction kinetics and the effects of concentration, light intensity and pH on the stability of nifedipine. This study primarily deals with the stability of the drug in different organic solvents and in the presence of antioxidants.

Materials and Methods

Materials

Nifedipine was donated by Pfizer Company (New York, U.S.A.). All reagents were analytical or spectrograde. Water used in solutions was doubly distilled and deionized.

Methods

A stock solution of 1.0×10^{-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. Lowere nifedipine concentrations used for experiments were prepared by suitably diluting the stock solution.

Effect of antioxidant

Triplicate solutions of 6×10^{-5} M nifedipine with 6×10^{-5} to 5×10^{-3} M of sodium bisulfite were prepared in phosphate buffer (0.2 M) at pH 7. A stock soluton of 1×10^{-2} M sodium bisulfite was prepared in doubly distilled water and aliquots were added to nifedipine solutions to obtain the required final concentration of the antioxidant.

Solutions containing both nifedipine and sodium bisulfite were irradiated by a fluorescent lamp (15 W, 43 cm long) placed 30 cm away from the samples in a darkened room at $25 \pm 3°$C. Aliquots were removed at 15-min intervals over a 6-h period and the absorption spectra were determined at 360, 280 and 237 nm.

The absorbance values at those 3 wavelengths were measured over a 6-h period. The degree of photo-oxidation of the dihydropyridine derivative was determined. A control solution of nifedipine without bisulfite was prepared in phosphate buffer (0.2 M, pH 7). Sodium bisulfite solution of the same concentration was used as reference.

Effects of organic solvents

Suspensions of nifedipine in cyclohexane, chloroform, acetonitrile and carbon tetrachloride were prepared in a darkened room by adding 10 mg of the compound to 100 ml of solvent and were then stirred for 30 min. Following this, solutions were filtered using an organic millipore membrane.

The solutions were irradiated using the method described above. Aliquots were taken at 0, 4 and 20 h and assayed spectrophotometrically to determine the changes in the spectra of nifedipine.

Nifedipine analogues

Concentrations of 1×10^{-4} M of two structural analogues of nifedipine, the unsubstituted and the *o*-methyl substituted phenyl derivatives in 95% ethanol were prepared.

The solutions were irradiated using the above procedure, and the spectra of both analogues were recorded over 5 days.

In another set of experiments, solutions were irradiated in tightly sealed quartz cuvettes. The light source was positioned 15 cm horizontally from the cuvettes. Mirrors were placed 20 cm on the opposite side to enhance irradiation. Also, the quartz cuvettes containing the solutions were irradiated in an UV chamber with UV light of fixed wavelength. The spectra of both compounds were run after 6 h.

Effect of amber glass

Brown volumetric flasks were used to prepare 6×10^{-5} M nifedipine in 95% ethanol. The solutions were kept in a darkened room under the

fluorescent light. Aliquots were taken daily and assayed spectrophotometrically.

Statistical analysis

Two-way comparison of data utilized Student's *t*-test. A *P*-value less than 0.05 was considered significant.

Results and Discussion

To determine the effect of the inclusion of an antioxidant, such as sodium bisulfite, on the photo-decomposition of nifedipine, UV spectra at zero time and after 6 h of irradiation were obtained for both a control solution and a solution of the drug containing the antioxidant. The UV spectrum of the control showed two maxima at 237 and 360 nm before irradiation, however, on irradiation a hypochromic shift was observed and two absorption maxima for the oxidized form at 280 and 310 nm appeared. Similar results were obtained by Berson and Brown (1955a and b) 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 nitrosophenyl-pyridine derivative. Other studies (Testa et al., 1979) have also shown that the derivative produced by UV irradiation was the same compound produced by chemical oxidation.

In the presence of bisulfite there was a decrease in the absorption maxima at 237 and 360 nm after irradiation and a new absorption maximum at 274 nm appeared. There was no absorption peak at 310 nm. This change in the spectrum of nifedipine was found at all concentrations of bisulfite.

Table 1 shows the molar absorptivity values which were used to calculate the corresponding concentrations of nifedipine. There was no significant change in the rate of disappearance of the reduced form with respect to sodium bisulfite concentration according to one-way analysis of variance. The rate of appearance of the oxidized form did not show significant changes with varying concentrations of sodium bisulfite.

TABLE 1

Molar absorptivities of oxidized and reduced forms of nifedipine

Molar absorptivity	Value	Sodium bisulfite concentration
E^R_{274}	2620	6×10^{-5} M to 5×10^{-4} M
E^R_{360}	3152	6×10^{-5} M to 5×10^{-4} M
E^R_{274}	2839	10^{-3} M
E^R_{360}	3322	10^{-3} M
E^R_{274}	3022	5×10^{-3} M
E^R_{360}	3739	5×10^{-3} M
E^O_{360}	1052	all concentrations
E^O_{274}	5140	all concentrations

Each molar absorptivity value is useful for the corresponding concentration only. E^R and E^O are the molar absorptivities, at the specified wavelength, of the reduced and oxidized forms of nifedipine, respectively.

Statistical and kinetic parameters for the disappearance of the reduced form or the appearance of the oxidized form as a function of bisulfite concentration are depicted in Tables 2 and 3, respectively. The minimum $T_{1/2}$ (disapp.) was 153.75 ± 5.85 min observed at 1×10^{-3} M bisulfite and the minimum $T_{1/2}$ (app.) was 171.80 ± 2.11 min observed at 6×10^{-5} M bisulfite.

The photodecomposition of nifedipine was also studied in different media. The spectra of the drug in chloroform and acetonitrile were similar to that in 95% ethanol. There were two absorption maxima, at 237 and 360 nm, at zero time. After irradiation a decrease in the absorption maxima at 237 and 360 nm was observed with the appearance

TABLE 2

Statistical and kinetic parameters for the disappearance of the reduced form at 237 nm as a function of the antioxidant concentration at 6×10^{-5} M nifedipine in phosphate buffer (pH 7)

Sodium bisulfite concentration (M)	$K \pm$S.E.M (M/min)	$T_{1/2}$ (disapp.) min $\pm$ S.E.M.	r
6×10^{-5}	$16.40\pm1.55\times10^{-8}$	186.07 ± 16.25	0.98
10×10^{-5}	$16.85\pm0.69\times10^{-8}$	178.58 ± 7.17	0.98
50×10^{-5}	$17.92\pm0.56\times10^{-8}$	167.71 ± 5.36	0.98
100×10^{-5}	$19.57\pm0.77\times10^{-8}$	153.75 ± 5.86	0.98
500×10^{-5}	$16.32\pm1.56\times10^{-8}$	186.87 ± 16.34	0.98

TABLE 3

Statistical and kinetic parameters for the appearance of the oxidized form at 280 nm as a function of the antioxidant concentration at 6×10^{-5} M nifedipine in phosphate buffer (pH 7)

Sodium bisulfite concentration (M)	$K \pm$S.E.M. (M/min)	$T_{1/2}$ (app.) min $\pm$ S.E.M.	r
6×10^{-5}	$17.46\pm0.21\times10^{-8}$	171.80± 2.11	1.0
10×10^{-5}	$15.61\pm0.16\times10^{-8}$	192.18± 1.99	1.0
50×10^{-5}	$17.38\pm1.01\times10^{-8}$	173.74± 9.74	0.99
100×10^{-5}	$16.75\pm1.02\times10^{-8}$	180.40±10.72	0.99
500×10^{-5}	$15.47\pm1.39\times10^{-8}$	196.74±16.24	0.99

of new absorption maxima at 280 and 310 nm. However, in cyclohexane the spectrum did not show a new absorption maximum at 310 nm. Spectral changes in aqueous solutions after 3 h of irradiation were similar to those in ethanol.

The spectral properties of the two structural analogues of nifedipine, the unsubstituted and *o*-methyl-substituted phenyl derivatives showed no changes on exposure to light for 5 days. Both substances exhibited two absorption maxima at 245 and 360 nm before and after irradiation. No absorption peak was observed at 280 nm.

Samples of the same concentrations were also irradiated with a high intensity of light in a quartz cuvette for 6 h. The results showed no detectable spectral changes in the UV-visible region. Furthermore, an ultraviolet lamp of short wavelength was used to irradiate both compounds in quartz cuvettes. Again, no spectral changes were observed. The results indicate that both compounds were resistant under laboratory conditions to light and confirm that the nitro group is required for the photo-oxidation of nifedipine (Berson and Brown, 1955a).

Previous studies (Berson and Brown, 1955a and b; Phillips, 1951) have shown that 4-(*p*-nitrophenyl) substituted dihydropyridines were stable even if irradiated by intense sunlight or mercury arc. Also, *o*-nitrobenzaldehyde is photochemically unstable whereas *p*- or *m*-isomers are stable (Lucy and Leighton, 1934). Such structural requirement for the nitro group of the nitrophenyl-1,4-dihydropyridine to be in the ortho position implies that the photochemical reaction is intramolecular. The structural substitution of different ester or ketone groups in the 3,5-positions of dihydropyridines was established not to affect the photochemical sensitivity of these compounds (Berson and Brown, 1955a).

When solutions of nifedipine in 95% ethanol were prepared in amber glass bottles and irradiated, no spectral changes were observed. Spectrophotometric analysis over more than two months revealed no significant loss in the reduced form of the drug. This indicates that nifedipine is very stable to degradation when protected from light.

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