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Mechanistic studies on photolytic degradation of nifedipine by use of ^{1}H-NMR and ^{13}C-NMR spectroscopy

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Summary

To understand the photolytic degradation of nifedipine (**I**), a method based on ^{1}H-NMR and ^{13}C-NMR spectroscopy has been used for the simultaneous determination of nifedipine and its decomposition products, 4-(2-nitrosophenyl)pyridine (**II**) and 4-(2-nitrophenyl)pyridine (**III**) homologues. The ^{1}H-NMR technique has been used quantitatively in photodecomposition studies of nifedipine in solid form and in solution, however, the ^{13}C-NMR method is used for confirmatory identification of decomposition products. The extent and mechanism of photolytic degradation were investigated as a function of concentration, solvent polarity, light intensity and irradiation time in solution. The degradation of bulk drug was also studied in detail under different light conditions.

Nifedipine (**I**) [dimethyl-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine dicarboxylate] belongs to a class of drugs having calcium antagonist activity. It is widely used clinically as a coronary vasodilator. The pharmaceutical preparations are available in the form of capsules, tablets and solutions, and are usually given orally or intravenously and the therapeutic range in plasma is 25–100 μg/l. The drug is reported to be highly light sensitive, and there exists controversy regarding its degradation products and extent of degradation under different light conditions, particularly in solution. Jacobson et al. (1979) and Testa et al. (1979) reported the formation of 4-(2-nitrosophenyl)pyridine (**II**) under visible light and 4-(2-nitrophenyl)pyridine (**III**) when exposed to ultraviolet light; however, Ebel et al. (1978) reported formation of only **II** under both ultraviolet and visible light conditions. On the other hand, Squella et al. (1989) have reported formation of both the derivatives depending on the duration of exposure to light. Similarly, regarding the extent of degradation, Ebel et al. (1978), Tucker et al. (1985) and Greiner et al. (1987) have observed faster degradation (half-life 4–5 h) while Squella et al. (1989) have observed no degradation up to 580 min on exposure to daylight in solution. In USP XXII NF XVII, it has been reported to

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undergo degradation even in solid form and extra precautions are recommended in the analysis of the bulk drug and its formulations.

Therefore, a detailed investigation was required regarding its degradation in solution and in solid form in its preformulation studies for optimal design of conditions in pharmaceutical preparations and the basis for pharmaceutical analysis.

The present communication describes the extent and mechanism of degradation in solid and in solution. The stability was tested in solution using sodium benzoate as a stabiliser.

Nifedipine USP reference standard was obtained from Ana Lab, Bombay; sodium benzoate, AR grade (Glaxo Chemical, Bombay), carbon tetrachloride, spectroscopy grade (E. Merck, Bombay) chloroform, methanol, benzene, water, and all deuterated solvents with 99.80% purity (Fluka chemie AG, Switzerland) were used in the study.

A Jeol Fx-90Q, 90 MHz Fourier Transform NMR spectrometer with a 5 mm C/H dual switchable probe with deuterium internal lock operating at $30 \pm 1°C$ was used for the study. The data processing was acquired by a Hewlett Packard computer with 16K memory and a single pulse with pulse angle of 45°. The ^{1}H-NMR spectra were recorded at 89.55 MHz magnetic field, 54.51 kHz offset, 900 Hz spectral width and 18 μs pulse width with 4 s pulse delay and 1.02 s acquisition time. However, ^{13}C-NMR spectra were recorded at 22.50 MHz magnetic field, 33.51 kHz offset, 5000 Hz as spectral width and 5 μs pulse width with 2 s pulse delay and 0.4 s acquisition time. Degradation studies were performed in the UV-visible chamber of a Specord instrument (Germany).

To study solvent polarity effects on photolytic degradation, solutions of **I** at 5×10^{-2} M concentration were prepared in various deuterated solvents such as methanol, chloroform, benzene, methanol:water (75 : 25) in 5 mm NMR tubes (0.5 ml each) and exposed to light from a 100 W lamp.

However, to investigate the concentration effect on photodegradation, solutions of **I** in 40% deuterated chloroform in carbon tetrachloride of 10^{-1} and 10^{-2} M concentrations were prepared in NMR tubes (0.5 ml each) while 10^{-3} and 10^{-4} M solutions were prepared in stoppered volumetric flask (25 ml each). The solutions were exposed to artificial room light (400–650 nm, mercury tube) and the degradation was studied by ^{1}H-NMR spectroscopy.

The extent of degradation of nifedipine under different light conditions was studied by exposing the solutions of 5×10^{-2} M concentration in 40% deuterated chloroform in carbon tetrachloride (0.5 ml in NMR tube) and bulk drug to daylight (room light), artificial daylight, 100 W lamp light, 300 W lamp light, sunlight, UV light chamber (190–350 nm) and visible light chamber (350–600 nm).

The extent of degradation of nifedipine was observed at intervals of 0.5 h for all the above samples by ^{1}H-NMR spectroscopy. Only the bulk drug exposed to artificial room light conditions was investigated after every 12 h.

The solutions of **I** of $\geq 10^{-2}$ M concentration were taken directly for ^{1}H-NMR analysis, while the lower concentration solutions were concentration by purging with nitrogen and brought to 10^{-2} M concentration for ^{1}H-NMR analysis and 10^{-1} M for ^{13}C-NMR analysis. Each sample was analysed in triplicate under the described experimental conditions and integrated in the range of 2–4 ppm at least five times. The singlets of methoxyls of **I**, **II** and **III** integrated for six protons each are very intense and distinct, and do not interfere with each other (Table 1). Hence these singlets which can be readily detected and accurately quantitated were chosen for quantitative ^{1}H-NMR spectroscopic analysis in the photodecomposition study of nifedipine.

From the integral areas of analyte protons of the drug and the degradation products, the percentage of intact nifedipine was calculated from the formula: $100\ (MW_I \times A_I)/(MW_{II} \times A_{II}) + (MW_{III} \times A_{III})$, where MW_I, MW_{II} and MW_{III} are the molecular weights and A_I, A_{II} and A_{III} are the integral values for **I**, **II** and **III**, respectively. The content of degradation products was also calculated using the same equation. The method has the advantages of speed, and easy sample preparation. For the sample of 10^{-2} M concentration, $S/N > 10$ was observed within 25 transients and thus it takes less than 5 min to analyse the sample in ^{1}H-NMR spectroscopy. The method has a great advantage as it does not require separation

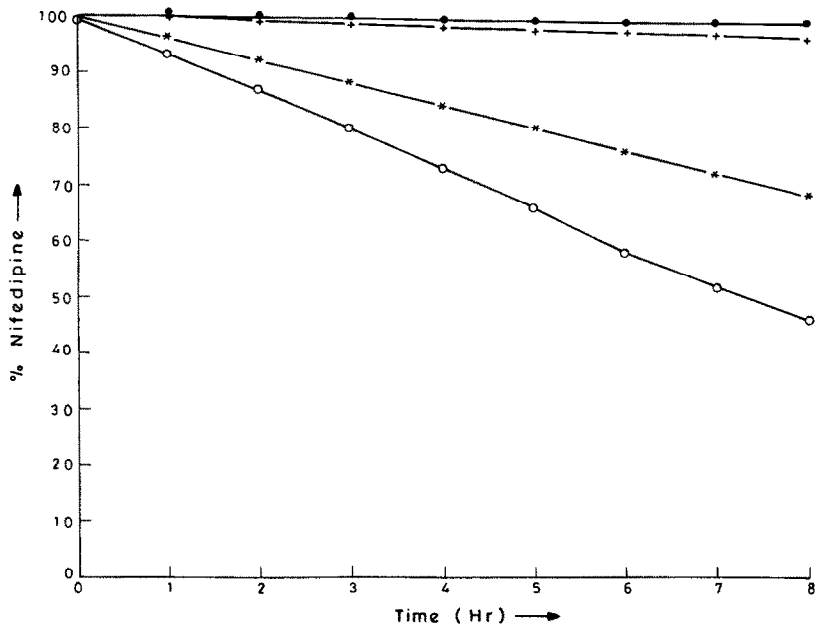


Fig. 1. Effect of concentration on rate of degradation of nifedipine in solution. (●) 10^{-1} M, (+) 10^{-2} M, (*) 10^{-3} M, (○) 10^{-4} M nifedipine solutions.

of degradation products for structural identification of these compounds. ^{13}C-NMR spectroscopy was used for the confirmatory identification of the degradation products developed in the photolytic study. Table 1 lists the chemical shifts for carbons of nifedipine and its degradation products **II** and **III**. The carbon signals of nifedipine and degradation products which do not interfere with each other, and the methyl and methoxyl groups resonating for two equivalent carbons each with a high NOE effect are very intense and hence readily detectable at low concentrations and were used for investigation.

Fig. 1 shows the concentration effect on photolytic degradation of nifedipine in solution. The study indicates that the solutions of lower concentrations ($< 10^{-2}$ M) are more susceptible to degradation. The 10^{-1} M solution of **I** shows no significant degradation and the 10^{-2} M solution displays only 4.2% degradation when exposed to an artificial room light for 8 h, while the solutions of 10^{-3} M and 10^{-4} M **I** show 35 and 55% decomposition, respectively, under the same roomlight conditions.

Solvents of different polarities do not show significant differences in degradation as predicted by Squella et al. (1989). The least polar, non-protic benzene shows only 2–3% excess degradation compared to the most polar methanol : water (75 : 25) solution in the series.

Fig. 2 shows the extent of degradation of **I** in solution under various light conditions. The solution exposed to UV light (190–350 nm) shows only 6–7% degradation even after 8 h and formation of **II** as a degradation product. The solution of **I** exposed to sunlight shows 100% quantitative degradation within 1 h, while exposure to room light conditions for 8 h produced only 4.5% decomposition and showed a half-life of 7 days. The sunlight degradation product was exclusively **II**, however, under room light conditions the degradation products after 100% disappearance of **I** on the 14th day showed a mixture of **II** (94%) and **III** (6%). The same solution kept further for 1 month shows 88% of **II** and 12% of **III**. Thus, slow degradation follows the initial photolytic degradation to yield product **II** and then slow oxidation of **II** to product **III**. It was also observed that the

TABLE 1

^{1}H and ^{13}C chemical shifts of nifedipine (I) and its photodecomposition products II and III

Carbon No.	I		II		III	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1 N-H	5.82 (1H)	–	–	–	–	–
2 and 6	–	145.092	–	156.041	–	155.632
3 and 5	–	103.594	–	127.108	–	128.515
4	5.63 (1H)	34.784	–	139.462	–	138.913
2 and 6-CH_3	2.32 (6H)	19.288	2.66 (6H)	23.080	2.63 (6H)	24.158
COO	–	167.632	–	167.311	–	167.926
$\underline{COOCH_3}$	3.58 (6H)	50.930	3.37 (6H)	51.688	3.68 (6H)	53.153
1′	–	142.275	–	144.225	–	146.746
2′	–	148.023	–	161.459	–	163.281
3′		132.743		107.711		132.635
4′		123.857		134.694		124.631
5′		131.118		130.468		130.914
6′		127.000		128.625		126.536
Arom-H (3′H-6′H)	7.1–7.7 (4H)		6.5–7.7 (4H)		7.1–8.2 (4H)	

All spectral data are based on tetramethylsilane (TMS) as an internal standard referenced to zero and $CDCl_3$ as a solvent.

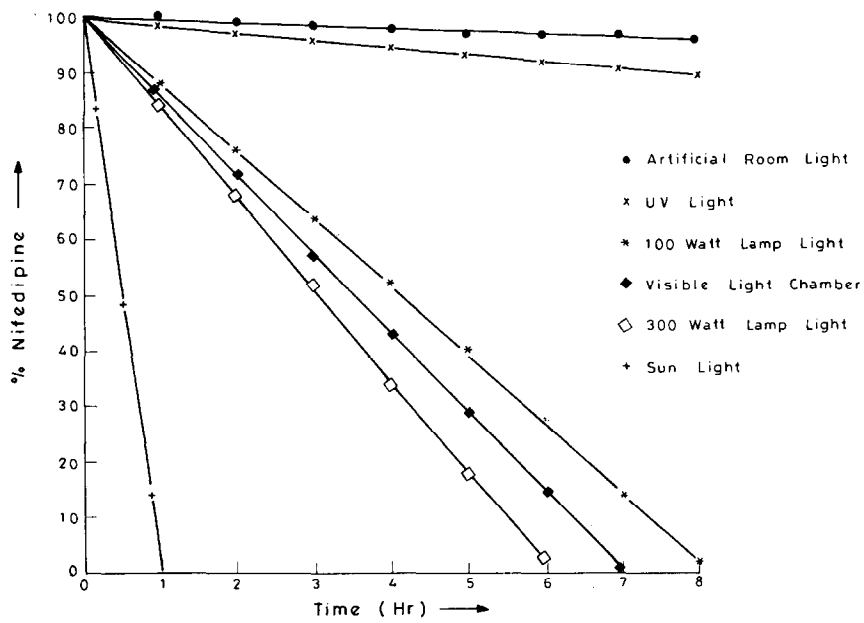
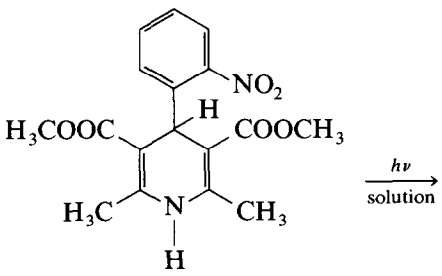
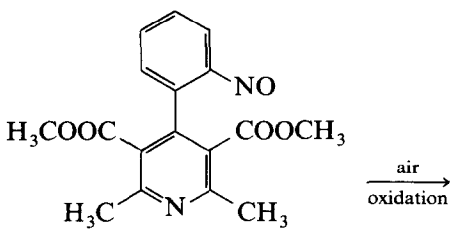


Fig. 2. Rate of degradation of nifedipine in solution under different light conditions.

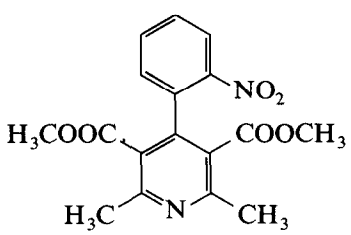
initial conversion of **II** to **III** is fast and attains equilibrium after 12–14% conversion. Therefore, the mechanistic route can be given as:



(I)



(II)



(III)

Furthermore, it was also observed that the addition of sodium benzoate ($< 10^{-2}$ M) as a quenching agent retards the photolytic degradation of nifedipine in solution and can be used as stabilizer.

The photolytic degradation of nifedipine in the form of bulk drug is slow compared to the solution form, but the degradation is significant even in room light conditions. The nifedipine solid when exposed to sunlight shows complete 100% photodecomposition within 6 h. The degradation products investigated by ^{1}H-NMR and ^{13}C-NMR spectroscopy show a different pathway of degradation from the solution forms. Both **II** (85%) and **III** (15%) were formed as degradation products. The formation of **III** was faster during the initial period and attained equilibrium after some time while formation of **II** is linear and follows first-order kinetics. Under artificial room light conditions, the bulk drug after 24 h shows only 3.2% conversion and the half-life is 58 days. However, in a visible light chamber the drug was completely decomposed within 30 h and formed **II** as a major degradation product. In a UV light chamber, we observed formation of **II** and **III** but **II** was the major component. The half-life for bulk drug in the UV chamber is 32 days.

This degradation study is of value in predicting the stability of nifedipine in formulations and will provide a basis for optimal design of dosage forms.

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