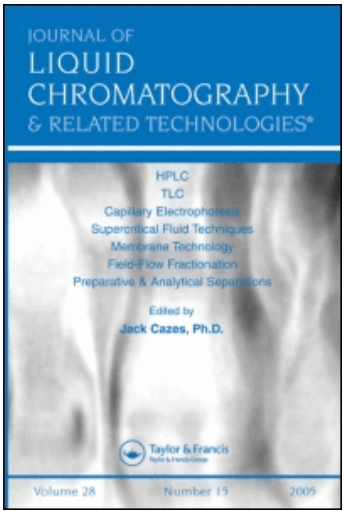

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Zs. Budvári-Bárány[a]; Gy. Szász[a]; G. Radeczky[a]; I. Simonyi[b]; A. Shalaby[c]
[a] Department of Pharmaceutical Chemistry Semmelweis Medical, University Budapest, Hungary [b] EGIS Pharmaceutical Works Budapest, Hungary [c] Pharmaceutical Chemistry Department, Zagazig University, Zagazig, Egypt

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SOME NEW DATA CONCERNING THE CHROMATOGRAPHIC PURITY TEST FOR NIFEDIPINE

ZS. BUDVÁRI-BÁRÁNY[1], GY. SZÁSZ[1], G. RADECZKY[1], I. SIMONYI[2], AND A. SHALABY[3]

[1]*Department of Pharmaceutical Chemistry*
Semmelweis Medical University
Budapest, Hungary
[2]*EGIS Pharmaceutical Works*
Budapest, Hungary
[3]*Pharmaceutical Chemistry Department*
Zagazig University
Zagazig, Egypt

ABSTRACT

The analysis of different Nifedipine commercial samples indicated the presence of impurities other than the nitroso- and nitrophenylpyridine analogues of Nifedipine generally are included in the pharmacopoeia-monographs. Besides the two latter photodegradation products isonifedipine and a tetrahydropyrimidine derivative as by--products of nifedipine-synthesis were identified. HPLC procedure is suitable for the separation Nifedipine and all of the four contaminants is published.

INTRODUCTION

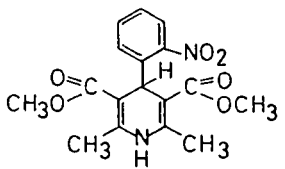
Nifedipine (Adalat^{R}, Procardia^{R}, Corinfar^{R}, etc.) is one of the most important antianginal, vasodilatory, anti-

arrhithmic Ca-channel blocking agent in our days. The substance is official in USP (1,2) as well as in several other pharmacopoeias.

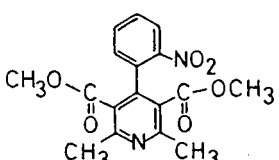
Nifedipine is a highly photosensitive substance, so its main impurities are formed by light-catalysed intramolecular reaction (3) and also by autooxidation (4,5). Besides the assay also the identification of degradation products of Nifedipine is mainly performed by chromatographic methods, e.g. TLC (1,3), GC (6-9) and especially HPLC (10-15), in substances, in pharmaceutical dosage forms, as well as in biological fluids.

Both in most of the quoted references and in USP two main impurities of Nifedipine are mentioned. These are the Nifedipine-nitro-, and nitrosophenyl-analogues (II and III). Further, Pötter and Hülm (16) report a liquid chromatographic identification for a third impurity, a tetrahydropyrimidine derivative (IV) may also be formed at the degradation of Nifedipine. The latter authors (16) succeeded to separate Nifedipine and all of the mentioned degradation products (II-IV) with satisfactory efficiency and detection limit, by HPLC method using silica gel impregnated with formamide as stationary phase.

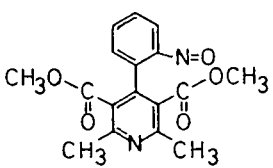
In the present paper a more simple HPLC method suitable for the separation of Nifedipine and II, III, IV degradation products is reported. A fourth impurity, a synthesis-by-product (named isonifedipine, V) was also identified and separated with the same method.



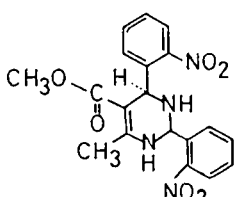
nifedipine
(I)



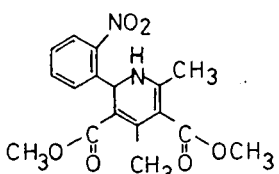
nitrophenylpyridine
analogue
(II)



nitrozophenylpyridine
analogue
(III)



tetrahydropyrimidine
derivative
(IV)



iso-nifedipine
(V)

Fig. 1.

Nifedipine and its degradation products.

EXPERIMENTAL

Materials

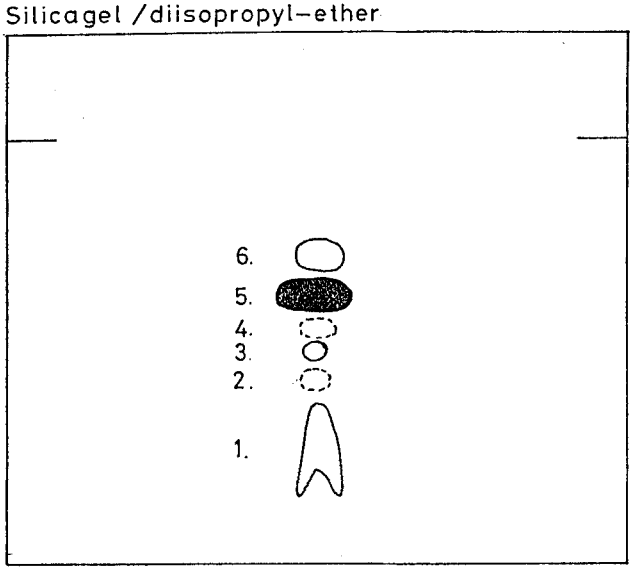
The Nifedipine (I) samples used for degradation and impurity study were commercial products from different sources, and also a Nifedipine reference standard (USP) with melting range 171-173 ^{o}C was applied. Reference substances nitrophenyl-pyridine, and nitrozophenyl-pyridine nifedipine-analogues were USP standard substances.

"Isonifedipine" (V) and dinitrophenylpyrimidine derivative (IV) were synthesized at our laboratory and identified through their IR, NMR and MS spectra.

All chemicals and solvents were of analytical grade (Merck) used without further purification.

Chromatography

The HPLC apparatus was comprised in an ISCO pump, model 2350 (USA) and an ISCO variable wavelength absorbance detector. The column effluent was monitored at 230 nm. Chromatographic system "A" included reversed phase C_8 (Zorbax, DuPont) in a column measured 250x4.6 mm i.d., and was prepacked with a material with particle size 5 μm. The mobile phase contained ethanol-water-tetrahydrofurane in a volume ratio 37:63:3. Chromatographic system "B" included the reversed phase C_{18} (Ultrasphere, Beckman) in a column measured 250x4.6 mm i.d., particle size 5 μm. Mobile phase: acetonitrile-methanol-water in a volume ratio x:50-x:50 (x = 5,10,15,20,25,30). The thin-layer chromatographic method was official in USP XXI, using silica gel/diisopropylether phases was applied.



1. nifedipine	R_f:	0,12
2.;3. unidentified		0,20 ; 0,26
4. nitrophenylpyridine analogue		0,32
5. nitrozophenylpyridine analogue		0,40
6. iso–nifedipine		0,52

Fig. 2.

Thin layer chromatogram of Nifedipine and its impurities

Irradiation

Nifedipine samples were exposed to the radiation of a UV lamp (600 w) or a Xenon lamp (OSRAM XBO 150 w) for different time, in a thin-layer.

RESULTS AND DISCUSSION

According to our experience Nifedipine exposed to the effect of sunlight or UV light degradates mainly with the

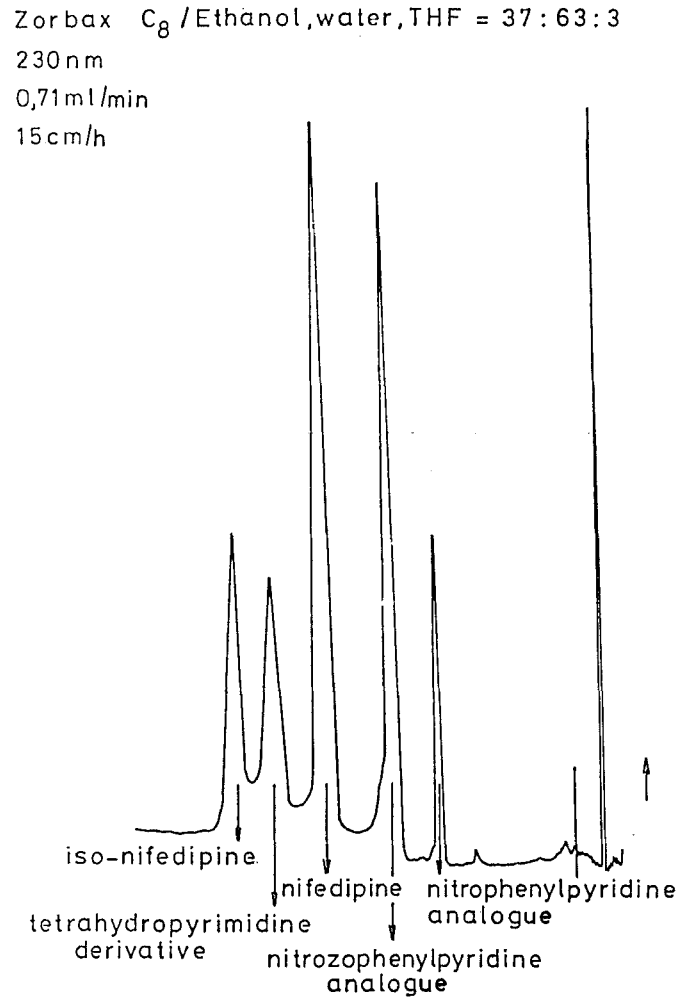


Fig. 3.

HPL Chromatogram of Nifedipine and its impurities

Table 1

Spectroscopic and Mass spectrometric data for Nifedipine and its two impurities

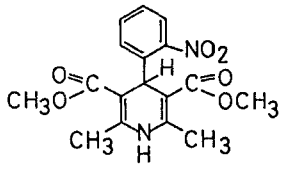
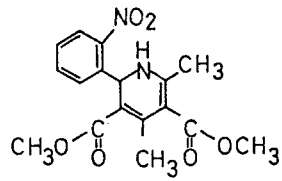
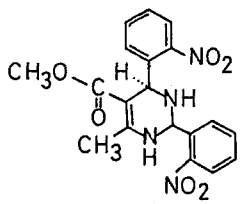
	IR	NMR	MS
nifedipine 		DMSO-d_6	int.%
	ν_{NH}:3340	CH_3 : 2.32	m^+ 346 (10)
	$\nu_{C=O}$:1690, 1680	CH_3O : 3.59	329 (100)
	ν_{NO_2}:as:1530 s:1350	CH(4): 5.73 s	284 (71)
		NH : 6.27	268 (35)
	ν_{COC}:1225, 1020	CH(3'): 7.67 dd	224 (70)
isonifedipine 			
	ν_{NH} :3280	CH_3 : 2.12 + 2.4	m^+ 346 (7)
	$\nu_{C=O}$:1695, 1665	CH_3O : 3.5 + 3.61	329 (10)
	ν_{NO_2}:as:1525 s:1350	CH(4) : 6.8 d	284 (38)
			268 (Ø)
	ν_{COC}:1200, 1045		224 (100)
tetrahydropyrimidine derivative 			
	ν_{NH} :3410, 3280	CH_3 : 2.38 s	m^+ 398 (Ø)
	$\nu_{C=O}$:1680	CH_3O : 3.42 s	381 (4)
	ν_{NO_2}:1530, 1350	CH(2) : 5.52 d	321(5)
		CH(4): 4.9 d)	

Table 2

The dependence of the retention (K') on the acetonitrile content of mobile phase

LiChrosorb RP_{18} / acetonitrile, methanol, water = x:50 - x:50

	K'					
	x = 5 %	10 %	15 %	20 %	25 %	30 %
nitrophenylpyridine analogue	10.67	9.22	9.11	7.6	7.0	5.7
nitrozophenylpyridine analogue	14.11	11.67	11.33	8.45	8.25	6.8
nifedipine	17.11	14.33	12.78	10.20	8.9	6.8
tetrahydropyrimidine derivative	16.10	13.44	12.11	10.1	9.2	8.2

formation of nitrosophenylpyridine analogue of Nifedipine (III): nitrozophenylpyridine content: UV (600 w) 4 hours 20%, Xenon 80 hours 39%, daylight 12 weeks 30-40%, aqueous suspension daylight 4 days 100%.

Fig. 2 and 3 show the TLC and HPLC chromatograms of a Nifedipine sample was previously illuminated by arteficial light. The thin-layer chromatogram (Fig. 2) indicates the presence of impurities other than II and III the only impurities are named in the USP monograph. The rather intense spot at R_F 0.52 was undertaken for further investigation and was identified as "isonifedipine" (see Table 1).

The peaks of the same three impurities separate sharply by HPLC too (Fig. 3) and in addition, a peak locating between the peaks of Nifedipine and isonifedipine is also observable. This peak was generated by a substance which was identified later as a tetrahydropyrimidine compound (IV). Table 1 includes some representative IR, NMR, MS data of Nifedipine and the compounds IV and V .

Finally, it seemed as an interesting task to study the relationship between the structure and HPL chromatographic behaviour. It is to be noted that isonifedipine imposes as less polar than nifedipine in the HPLC reversed system "A" (Fig. 3) and this observation is in accordance with the TLC picture (Fig. 2) too. This phenomenon can be interpreted by the steric shielding of the polar NH group by NO_2 standing nearby.

It was also interesting to observe the behaviour of tetrahydropyrimidine derivative when methanol-water-aceto-

nitrile as mobile phase was used. By altering the ratio of acetonitrile in the mobile phase also the selectivity of the eluent was changed. This is reflected by the inversion of the elution order for compound (IV) and Nifedipine at 25% acetonitrile content (Table 2).

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