COMPARATIVE STUDY ON THE PHOTOSTABILITY OF NIFEDIPINE AND NITRENDIPINE

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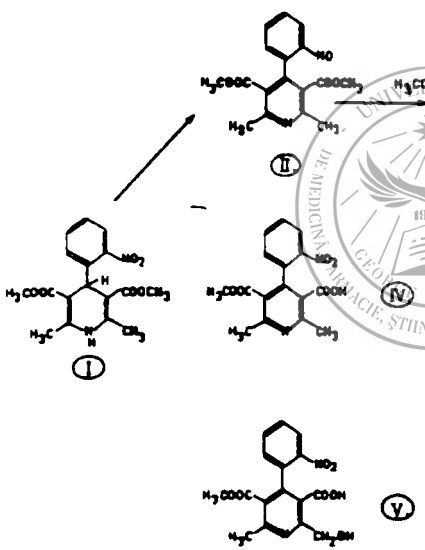
In treating cardiovascular disorders, among drugs introduced in the past 15 years, calcium-antagonists are of great importance (19). An outstanding place has been attributed to the group of 4-aryl - 1, 4-dihydropyridine (1,4-DHP) since nifedipine was started in therapy in 1975. Several compounds of this series have already been applied in therapy, including nitrendipine (19).



It is known that nifedipine (I)- 1,4 - dihydro - 2,6 - dimethyl - 4- (o - nitrophenyl) - 3,5 - pyridinedicarboxylate - (18) is extremely photosensitive, and its decomposition – even if in solid stategoes on at 450 nm radiation (14). During this first nitroso (II) - and later nitropyridine (III) - derivatives are formed by intramolecular redox- reaction; these have no effect (see: Scheme of decomposition).

Therefore, it is necessary to ensure a rather good protection against light in the production, storage, processing and analysis of nifedipine.

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The higher photosensitiveness of nifedipine (o - nitrophenyl - derivative) may be due to the characteristic spatial structure of the molecule. The DHP-cycle is not planar, but its conformation is bathshaped. The electron pair of the nitrogen atom in such a manner coming near in space to carbon atom No. 4 plays an important part in the redox processes. On the other hand, the ortho-positioned nitrogroup of the aromatic ring in position 4 has a significant role. In addition to the redox-process, the hydrolysis of the ester group in the solution should also be considered (IV).

A lot of authors (1, 3-9, 11, 12, 14-17) have studied the descomposition of nifidipine, as well as the action of various factors upon the process of decomposition.

The aim of our investigations was the study of the in-time decomposition of the substance exposed to sunlight and UV radiation (254 and 366 nm). Comparatively we have studied another therapeutically very important compound of the group: nitrendipine (m-nitrophenyl derivate).

Materials and Methods

Of the substances studied, nifedipine is the product of the factory "Terapia" in Cluj, Romania. Nitrendipine was obtained from "Baypress" tablets by extraction.

1. Assays by HPLC-method

Apparatus: Waters Millipore
Column: μ-Bondapack C 18 RP-18
Eluent: acetonitrile-water (7:3)
Flow rate of eluent: 0,8 ml/min.
Speed of paper: 0,5 cm/min.
Sensibility: 0,2
Detector: UV-254nm
Solutions studied: 0,1% solutions of nifedipine and nitrendipine (in: acetonitrile-water 7:3)
Amount injected: 50 μl

The solutions of nifedipine and nitrendipine were radiated by UV light (wavelengths: 254 and 366 nm) from 10 cm distance (making use of Camag UV lamp). At the same time other solution parts were kept in sunlight. The assays in UV-radiated solutions were carried out in 5, 15, 35, 75, 155 minutes and 4 hours, and those in solutions kept in sunlight were made daily.

We have found that of the decomposition products of nifedipine (RT = 5,20 min.) that with 4-minute retention time was prevailing, and it has proved to be a nitrosopyridine derivative when compared with the other methods used by us (TLC, UV-spectrophotometry, NMR). The change of height and area of the peak characteristic of this derivative was followed up as for length of time and wavelength.

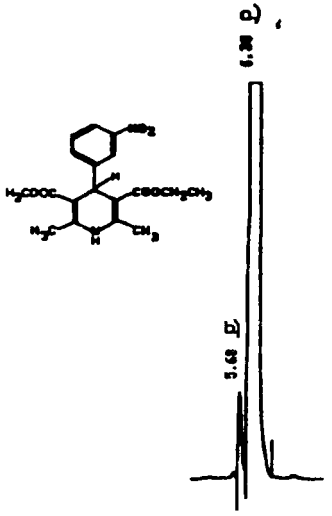

Fig. no. 1: HPLC-gram of Nitrendipine after 75 min UV radiation (366 nm); a - nitrendipine; b - product of decomposition

It was pointed out that decomposition took place much faster at 366 nm, within 1 hour at almost three times higher speed than in the sample radiated at 254 nm.

The nitrosopyridine derivative was isolated by quantitative HPLC-method, and after that it was identified by UV - spectrophotometrical and TLC-method.

It is of interest that the nitrendipine solution did not show any significant decomposition when radiated for 4 hours by UV or kept in sunlight for 1 day (fig. No.1).

2. UV-spectrophotometrical Analysis

It is known that nifedipine shows maximum absorption in the 237 and 360 nm UV regions (2, 3, 9, 14) (fig. No. 2).

It is easy to follow up, in case of nifedipine-solution, the shifting of the above maximums towards shorter wavelengths, and at the same time, at 280 nm there occurs a new maximum characteristic of the decomposition product - nitrosopyridine (fig. No.2).

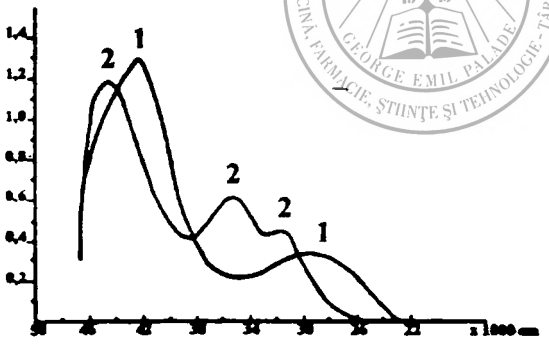

Fig.no. 2 :UV - Spectrum of Nifedipine (sol. 0,002% in acetonitrile water 7 : 3) .1.- Fresh solution; 2. - Solution radiated at UV 254 nm for 4 hours

The latter could be proved by comparing the spectrum of the decomposition product isolated by HPLC-technique, and it seemed to be the same.

The absorption curve of the nitrendipine solution did not show any significant change after 4 hours UV radiation, either.

3. Thin-layer Chromatographic Analysis

During our preliminary investigations we examined the stability of nifedipine solutions on silicagel (content zinc powder) by using mixture of chloroform-methanol (9 : 1). The detection was made with hydrochloric acid p-DABA reactant.

The technique used also by THOMA and KLIMEK (15) proved to be simpler, and it used basic mixture of slight polarity, on plates Kieselgel 60 F254 "Merck" (Fertigplatten).

Through this method – just like in the case of the following NMR-method – four main decomposition products could be isolated. Among them, besides the spot of nifedipine (Rf=0.15), quantitatively the 0.75 Rf value is praivaling undoubtedly, and this is very suitable to follow up the decomposition dynamics of native substance.

Through TLC-method, we studied - depending upon length of time-, the action of the UV wavelength (254 and 366 nm) and the distance from the light source (5 and 10 cm) upon the decomposition of nifedipine and nitrendipine.

In figure No. 3 it is seen that decomposition is much more greater - at the same values of time and wavelength - if the solution- is placed 5 cm from the source of light.

Otherwise, it is quite obvious, – according to HPLC investigations –, that decomposition at 366 nm is faster and stronger than at 254 nm. Thus, as for the intensity, the decomposition after 35 minute radiation at 366 nm took place at 254 nm approximately in 4 hours.

The nifedipine solution kept in daylight for five days was completely decomposed.

On the contrary, the nitrendipine solution kept in sunlight for one day did not show any significant decomposition.

4. NMR - method

The change in the structure due to the photodecomposition of nifedipine was studied by NMR - method, $CDCl_3$ medium, at 400 MHz.

The basic resonance signs of the protons in the original structure of nifedipine are to be found in the following ppm values:

a) CH_3 groups in positions 2 and 6 on DHP - cycle 2.35 ppm;

b) CH_3 groups in ester - bonds in position 3 and 5 on DHP - cycle 3.59 ppm;

c) H in position 4 on DHP - cycle 5.73 ppm;

d) hydrogens on the aromatic ring 7.2-7.7 ppm.

When the solution was kept in sunlight for 15 days - for full transformation - four decomposition products may be identified:

- doublet at 6.55 ppm shows that the original subtituent of the aromatic ring was changed (see formation of nitroso-group);

- simultaneously it could be seen that because of the aromatization of the DHP - cycle, the disappearence of the 5.73 ppm value peak is characteristic of H in position 4;

- the estimation of NMR-spectrum indicates other transformation too: such as the hydrolysis of the ester-group, as well as perhaps the oxidation of the CH_3 group in position 2 and 6, respectively (V).

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Key: pharmacy; drug; photostability; nifedipine; nitrendipine

Summary

COMPARATIVE STUDY ON THE PHOTOSTABILITY OF NIFEDIPINE AND NITRENDIPINE

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By chromatografic (TLC, HPLC), UV-spectrophotometric and NMR methods we have studied the photostability of the calcium - antagonists : nifedipine and nitrendipine.

The 0.1% (acetonitrile - water 7:3) solutions of the compounds studied were exposed to sunlight and UV - radiation (254 and 366 nm). The effect of the length of time of light action, as well as of the distance from the light-source upon the intensity of decomposition was also followed up. We found that decomposition took place most rapidly at 366 nm (in 2 hours in case of nifedipine), and it was increasing on approaching the light-source. The following processes were pointed out: intramolecular redox-reaction, formation of nitroso- and nitropyridine derivatives, hydrolysis of ester-bonds. The solution exposed to sunlight underwent complete decomposition in 5 days. The NMR analysis showed 4 main derivatives of decomposition. Besides the above processes, the oxidation of methyl group should be taken into consideration, too.

The chromatograms recorded in our HPLC examinations (Waters Millipore apparatus: μ-Bondapack column C 18 RP-18, eluent acetonitrile- water 7:3, UV-254 nm detector) showed rather well separated peaks in case of nifedipine (RT = 5.20 min) and nitrendipine (RT=6.30 min). The derivatives of decomposition were also identified.

Studying the stability of the active principle nitrendipine of "Baypress" tablets, we pointed out that it was much more resistent to light action.