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EPR INVESTIGATION OF ILLUMINATED AND UV IRRADIATED NIFEDIPINE*

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Abstract
The aim of the present work is to study by Electron Paramagnetic Resonance (EPR) spectroscopy the behavior of the illumination- and UV irradiation-induced free radicals in the nifedipine [$C_{17}H_{18}N_2O_6$, 3,5-pyridine dicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitro-phenyl)- dimethyl ester], to characterize the specific features of these radicals. Powder samples of nifedipine were investigated for a comparison between radiation damage in commercial tablet and in active substance. The nifedipine has not EPR signal before illumination or before UV irradiation, but the relative yielding of free radicals, appeared after irradiation, depends on the exposure time. Some spectroscopic properties and suggestions concerning possible structure of the free radicals are discussed in this paper.
Keywords: EPR spectroscopy, free radicals, nifedipine.

1. Introduction

It is well known that, the radiation on the drugs produces chemical and physical alterations and even to loss their biological activity [1]. In this paper was study nifedipine, which is a light sensitive substance and is decomposed under daylight (natural) to give nitroso-phenylpyridine homologue, and under UV irradiation to give the nitro-phenylpyridine homologue[2]. Moreover was study the degradation - free radicals induced by illumination and UV irradiation - of nifedipine by EPR spectroscopy, to explore the possibility of using this technique in study of stability and damage in the microcrystalline powder form. Electron Paramagnetic Spectroscopy (EPR) spectroscopy is a very useful method for the detection of the irradiated biological systems and now it plays a significant role in the characterization of free radicals obtained by illumination and by UV irradiation of commercial tablet and active form of nifedipine. When an unpaired electron in a magnetic field interacts with a nuclear

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spin, the spectrum splits into two or more lines, which produce hyperfine structure in the spectrum. The hyperfine structure of the EPR spectra, when it is well resolved, proved more important information about the free radicals, because most detected free radicals are nitrogen- and carbon-centered radicals and the spectra positions are almost in the same magnetic field. The aim of the present work is to study by EPR spectroscopy the behavior of the illumination- and UV irradiation-induced free radicals in the nifedipine, to characterize the specific features of these radicals and stability of molecular compounds, on the exposed time.

2. Method and samples

Nifedipine [$C_{17}H_{18}N_2O_6$, 3,5-pyridine dicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitro-phenyl)- dimethyl ester] was exposed to the daylight and UV radiation at different exposure time, from 10 to 60 minutes. Nifedipine is decomposed under natural daylight to give nitroso-phenylpyridine homologue; witch is presented in Figure 1.

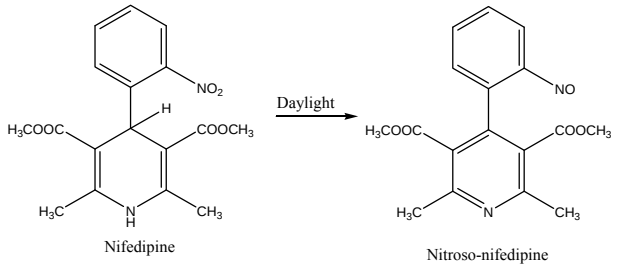

Fig. 1. Degradation of nifedipine by daylight

EPR spectra were recorded with an "ADANI Portable EPR Spectrometer PS8400", operating in the X-band (9.1GHz – 9.6GHz) equipped with a computer acquisition system.

The computer simulation analysis of the spectra was made by using a program that is available to the public through the Internet (http://alfred.neihs.nih/LMB) for obtaining the magnetic characteristic parameters.

3. Results and Discussions

By EPR spectroscopy were analyzed non-irradiated and irradiated samples of commercial tablet of nifedipine. EPR measurements proved that nifedipine contained various stable paramagnetic species after illumination and the relative yielding of the free radicals depends on the exposure time. By increasing the exposure time the intensity of the EPR signal increased too, shown that the number of free radicals formed depending on the exposure time (Fig. 2).

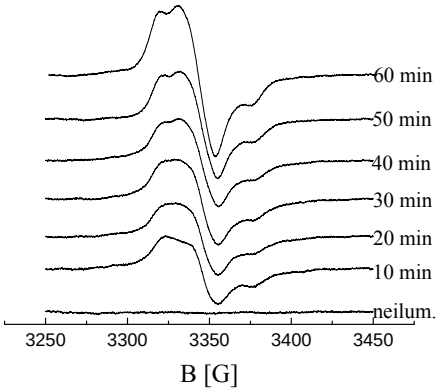

Fig. 2. EPR spectra of illuminated commercial tablet of nifedipine

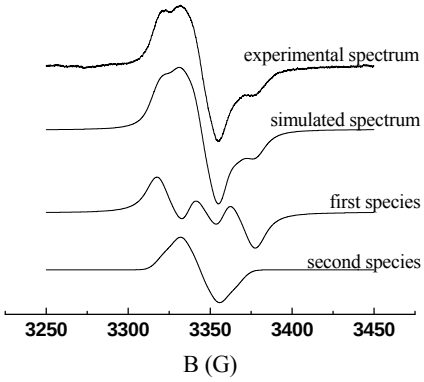

Fig. 3. Experimental and simulated spectrum of 50 min. illuminated nifedipine

By computer simulation of EPR spectra, some spectroscopic properties and suggestions concerning possible structure of the radicals are discussed. A good agreement between experimental and simulated spectrum was obtained adopting the existence of two radical species (Fig. 3).

The first free radical supposed to be a radical centered on nitrogen; witch gives a triplet with a line width of 7.39G. This species is due to the interaction of the unpaired electron with nitrogen, a(N)=21.24G. But also the unpaired electron interact with four protons with hyperfine coupling a_1(H)=8.43G and a_2(H)= a_3(H)= a_4(H)=3.65G. The second free radical gives a singlet with line width of 5.46G due to the interaction of unpaired electron with four protons: a_1(H)=5.95G and a_2(H)= a_3(H)= a_4(H)=10.26G.

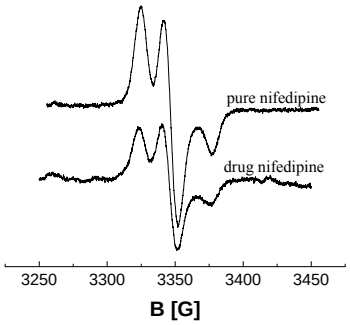

Fig. 4. EPR spectra of 15 minutes UV irradiated commercial tablet and active substance of nifedipine

The measurements for the UV irradiated commercial tablet of nifedipine prove that, at higher energy the splitting of the spectrum is resolved better. It was observed a difference in the rate of increasing free radical species, because the intensity of the first line increases more quickly at UV light, than at visible light.

The main difference is between irradiated commercial tablet and active substance. At the same exposure time to UV light, the spectrum intensity of the active substance is higher than in case of the commercial tablet. This proves that the inclusion compounds, witch are in the commercial tablet alongside the active substance, have a sluggish effect in the free radical formation process (Fig 4). The effect of

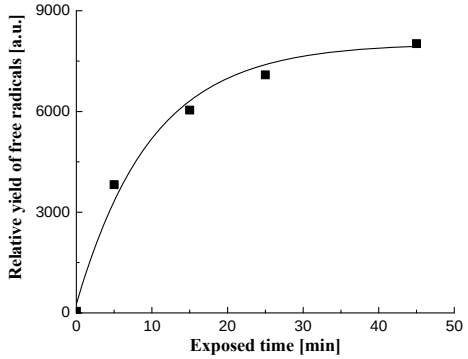

Fig. 5. The relative yields of radicals in UV irradiated pure nifedipin as function of exposure time.

exposure time on radical yield in UV irradiated active substance of nifedipine is shown in Figure 5. The relative yield in the irradiated samples at each exposure time (from 5 to 60 minutes) was determined by double integrated of corresponding EPR spectrum. Experimental data were fitted by an exponential function, describing a first order kinetic of formation of the free radicals: $I(D) = I_{sat}\left[1 - \exp(-k \cdot D)\right]$ in which I_{sat} is the limiting value corresponding to the steady state concentration of the radicals and k is the rate constant of destroying the radicals by the radiation. It can be concluded that nifedipine is a very instable drug, because the kinetics saturation is at low value of exposed time.

4. Conclusions

EPR spectroscopy may be used in order to analyze the effect of day- and UV light in commercial tablet and active substance of nifedipne. By computer simulation was obtained the possible two radical species generated by daylight, the difference and the similarity between the commercial tablet and active substance of nifedipine, and between the type of irradiation (UV and sunlihgt). The EPR spectroscopy method was applied to study the kinetics of nifedipine decomposition under UV light. The spectra of the nifedipine, collected at different exposure time, were subjected to analysis and results that the degradation may be described with a first order kinetics pathway.

Acknowledgements

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