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Radiation Effects on Lamotrigine and Flourbiprofen: an EPR study

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Abstract: In this study, Electron paramagnetic resonance (EPR) spectroscopy was used to determine the gamma radiation damages in Lamotrigine and Flurbiprofen.The free radicals produced in the samples were interpreted in terms of some type of alkyl and amine radical fragments. The g values and hyperfine structure constants of the radicals were determined and the spectra were computer simulated. The free radicals were appeared to be stable at room temperature for more than two months.

Keywords: EPR, drugs, free radicals, gamma irradiation

Radyasyonun Lamotrijin ve Flurbiprofen Üzerine Etkisinin EPR Çalışması

Özet: Bu çalışmada gama radyasyonun Lamotrijin ve Flurbiprofen'de oluşturduğu hasarları belirlemek için Elektron Paramanyetik Rezonans Spektroskopisi kullanıldı. Örneklerde oluşan serbest radikallerin bazı alkil ve amin türü radikaller olabileceği şeklinde yorumlandı. Radikallerin g değerleri ve aşırı ince yapı sabitleri belirlendi. Örneklerin spektrum simülasyonları bilgisayar kullanılarak gerçekleştirildi. Örneklerde oluşan serbest radikallerin oda sıcaklığında iki aydan daha fazla kararlı olduğu ortaya çıktı.

Anahtar kelimeler: EPR, ilaç, serbest radikal, gama radyasyonu

1. Introduction

Ionizing radiation treatment is a useful method to sterilize and measure radiation doses of drugs and medical devices, cleaning the disinfection of foodstuffs and cosmetics [1-8]. EPR spectroscopy is used for the detection of free radicals formed in biological and chemical systems, or in irradiated drugs [9]. Also, EPR can be a tool for controlling the quality of products [10] especially stable in

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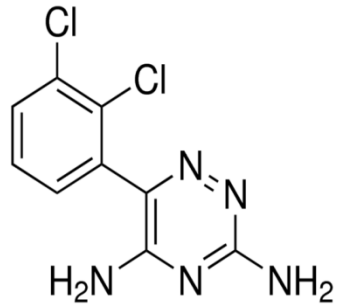
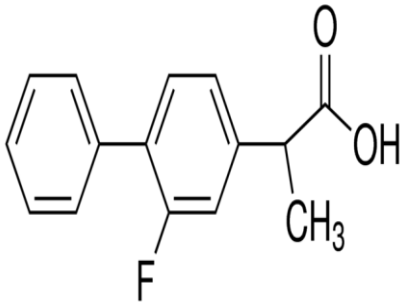
solid state material. The aim of this work is to report spectroscopic parameters, stability and structures of the radicals formed in two samples.The EPR investigation of Lamotrigine and Flurbiprofen has not been studied so far, and we have undertaken a study of these drugs.

2. Experimental

The drugs used in this study were provided by commercial sources.Their chemical formulas and commercial names are presented in Table1.

Table 1.List of the drugs studied with their commercial names, chemical formulas, molecular weights (g/mol) and chemical structures.

1.Lamotrigine, $C_9H_7N_5Cl_2$, 256.09	2.Flurbiprofen, $C_{15}H_{13}FO_2$, 244.26
	

The powders of drugs were irradiated with ^{60}Co γ-ray source of 2.00 kGy for about 10 hours at room temperature. The spectra were recorded with a Bruker EMX 081 model EPR spectrometer, using 2 mW microwave power. The magnetic field modulation frequency was 100 kHz, scan width 10 mT and modulation amplitude 0.2 mT. The g value calculated by comparison with a DPPH sample (g= 2.0036). The gamma-irradiated samples were stored at room temperature before recording the EPR spectra. The measurements were checked for two months to follow the stability of the formed radicals. The simulations of spectra, using the computer program [11], are shown in Fig.1b, 2b.

3. Result and discussion

Lamotrigine (LTG) is a broad-spectrum anti-epileptic drug (AED) used to treat various types of epilepsy and psychiatric disorders [12]. Lamotrigine appears to act by inhibiting the release of glutamate from presynaptic membranes, primarily by inhibiting voltage-dependent sodium currents to block high-frequency repetitive spike firing, which is believed to occur during the spread of seizure activity, without affecting ongoing physiological neural activity [13].

The EPR spectrum of Lamotrigine (LA) is a singlet with the g= 2.0002 ± 0.0005. The linewidth is on the order of 0.5 mT. The many-lined spectrum superimposed on the amino alkyl radical is shown in Fig.1a.

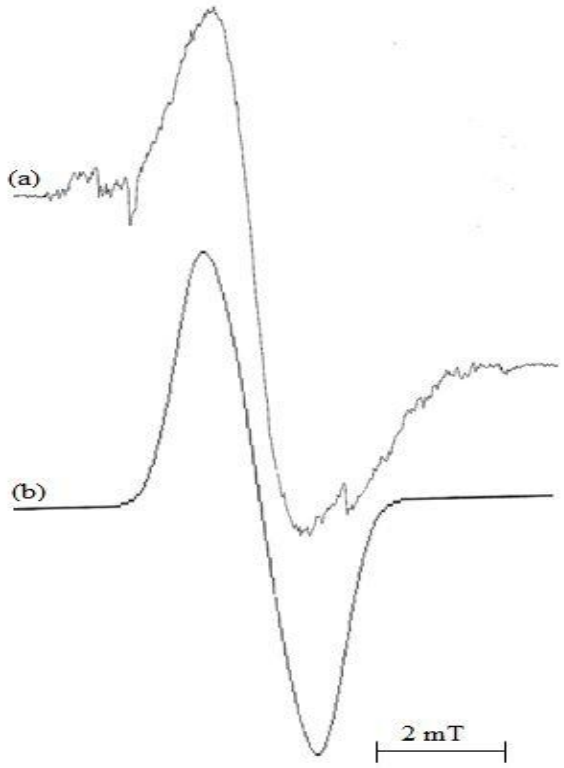


Figure 1. (a)Theoretical EPR of (Lamotrigine), (b) Experimental EPR of the (Lamotrigine)

This spectrum can be attributed to the radical presented in Table 2, with the hyperfine parameters a^1_{CH}= 1.7 mT, a^2_{CH}=1.3 mT, a^3_{CH} = 0.83 mT, a^2_{NH}= 0.72 mT, a^1_{NH}= 0.43 mT and a_N= 0.7 mT. The magnitude of β proton splitting on the dihedral angle (θ), the theory of β hyperfine interactions,

$$a^{\beta}_{H} = B_o + B_1 \cos^2 \theta$$

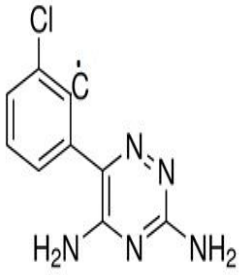
The constants B_o and B_1 have been experimentally determined as (0-0.32 mT) and (3.26-5 mT) [14], respectively.

$$a^{\beta}_{H} = 0 + 3.2 \times 1/2 = 1.6 \text{ mT}$$

This value is in good agreement with the observed spectrum. The hyperfine splittings of Lamotrigine are not observable due to line broadening, and therefore it is difficult to interpret the spectrum. The EPR spectrum of LA consists of an intense broad singlet due to five protons of hyperfine splitting and one nitrogen atom. Simulation spectrum of gamma irradiated LA was determined. The hyperfine constants of protons and g values of the radical species observed in the undamage molecule are in agreement with the previously obtained values for this species in the literature [15]. The values of the g-factors and hyperfine constants are suitable for carbon or nitrogen-centered radicals. Due to the largeness of line-width it is very difficult to obtain hyperfine parameters from the experimental spectrum. Therefore, hyperfine parameters corresponding to each species were obtained by simulation method (Fig. 1b). The g value, hyperfine constants and linewidths obtained as a result of simulation are given in Table2. The g-factor of free radical in the studied drugs is determined in the range of 2.0000- 2.0025.

Table 2. EPR parameters and proposed structure of paramagnetic species produced from LA

1. g= 2.0002 ± 0.0005;
a^1_{CH}= 1.7 mT, a^2_{CH}=1.3 mT, a^3_{CH} = 0.83 mT, a^2_{NH}= 0.72 mT, a^1_{NH}= 0.43 mT, a_N= 0.7 mT, ΔH= 0.5 mT



The EPR spectrum of gamma irradiated Flurbiprofen (FB) is shown in Fig.2a. The spectrum consists of a single line, and the radical for this spectrum is thought to result from the abstraction of hydrogen from the C-H (Table2).

The hyperfine interactions of the unpaired electron with the three methyl protons and other protons of nearly equal magnitude can be taken as a^1_{CH3}= 2.3 mT, a^2_{CH3}= 2.2 mT, a^3_{CH3}= 2.1 mT, a^1_{CH}= 1.6 mT, a^2_{OH}= 0.72 mT. This interaction can be understood from hyperfine coupling constant of the β protons

$$a^{\beta}_{H} = B_o + B_1 \cos^2 \theta$$

B_o is the spin polarization contribution (B_o= 0-0.354 mT), B_1 is the hyperfine conjugative contribution (4.6 mT) [14].

$$a_{\beta} = 0 + 4.6.1/2 = 2.3 \text{ mT}$$

A simulation of the flurbiprofen spectrum is obtained in Fig.2 (b), using the hyperfine coupling constants. The experimental and simulated EPR spectra are found to agree well with each other Fig.2a, 2b.

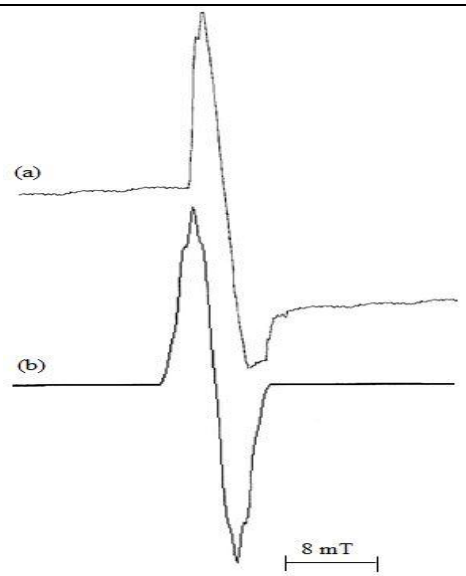


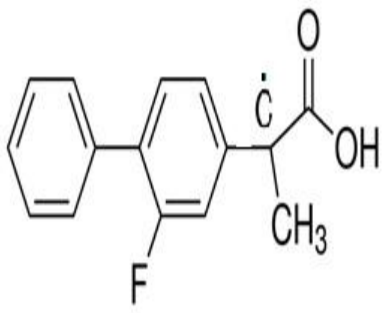
Figure 4.2 a) Theoretical EPR of (flurbiprofen) , **b)** Experimental EPR of the (flurbiprofen)

The measured g value is g= 2.0003± 0.0005. The hyperfine constants are similar to those carboxyl and alkyl radicals [16].

Flurbiprofen is a phenyl alkanoic acid derivative and a family of non-steroidal anti-inflammatory drug. It is widely used in the treatment of arthritis since its first appearance on the market in 1977 in Europe [17]. Flurbiprofen, a non-steroidal anti-inflammatory agent, is also used to treat rheumatoid arthritis and sore throat [18].

Table 3. EPR parameters and proposed structure of paramagnetic species produced from FB.

2. g= 2.0001± 0.0005;
a^1_{CH3}= 2.3 mT, a^2_{CH3}= 2.2 mT, a^3_{CH3}= 2.1 mT, a^1_{CH}= 1.6 mT, a^2_{OH}= 0.72 mT, ΔH= 0.5 mT



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