IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
June 2019 Vol.:15, Issue:3

Influence of Ionizing Radiation on Moxifloxacin by Means of EPR Spectroscopy

IJPPR
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ISSN 2349-7203
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Submission: 23 May 2019
Accepted: 29 May 2019
Published: 30 June 2019

Keywords: EPR, gamma irradiation, moxifloxacin, Decay kinetic

ABSTRACT

In this paper, the effect of gamma radiation on moxifloxacin evaluated using Electron Paramagnetic Resonance (EPR) spectroscopy through the analysis of changes in signal intensity as a function of absorbed dose and time. The results indicate that the signal intensity of the EPR line appearing after irradiation an increases dependently absorbed dose. Distinguishing irradiated moxifloxacin from non-irradiated one is possible from the time-dependent changes in the EPR spectra within 600 days after gamma irradiation.

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INTRODUCTION

Moxifloxacin is a synthetic antibiotic used diabetic foot infections, perinecrotic wound tissue healing, penetration of into bone obtained during hip replacement in Plastic Surgery[1-2]. There is currently much interest in the use of ionizing radiation to the sterilization of pharmaceutical products [3-7]. Sterilization with ionizing radiation (gamma-rays, X-rays, electron beam) is a process with the advantage such as environmentally safe, thorough material penetration even for high-density products, applicable any temperature, applicable to drugs in any pharmaceutical formulations. Additionally, products in a heat-sensitive container such as soft gelatin capsules and plastic tubes can only be terminally sterilized by gamma radiation. Besides all these advantages, the effects of ionizing radiation generally the existing of free radicals which can be only evaluated by EPR techniques. Therefore, the irradiation and post-irradiation effects of gamma radiation pharmaceutical materials must be investigated in detail study. Studies on radiation sterilization of drugs are gain interest in the literature. The samples on which radiation sterilization studies have been reported include vitamins, antibiotics, steroids, bronchodilators, anti-hypertensive, anticancer agents, antiprotozoals [8-16]. The main purpose of this study is to examine the feasibility of gamma-radiation sterilization for moxifloxacin from based on EPR technique.

MATERIALS AND METHODS

Moxifloxacin was obtained from Neutec Drug Company in Turkey. Chemical structure of moxifloxacin is depicted in Figure no.1. Almost the same weight of the sample (≈ 30 mg) for each irradiation dose was placed in EPR quartz tubes. Powder of moxifloxacin was irradiated at different doses up to 20 kGy at room temperature. After the irradiation, the sample was kept in plastic bags, and left in the dark at room temperature. EPR measurements of this sample were taken 2 days after irradiation to avoid any short-lived paramagnetic species. The EPR spectra of both irradiated and non-irradiated powder samples moxifloxacin of were recorded at room temperature with a Bruker EMX model spectrometer operating at microwave power 0.499 mW, microwave frequency of 9.8 GHz, modulation amplitude 0.104 mT, magnetic field modulation frequency 86 kHz. The g factors were calibrated by comparison with a DPPH sample (g=2.0036).

RESULTS AND DİSCUSSİON

EPR spectra of unirradiated and irradiated powder samples

EPR measurements were carried out for unirradiated and irradiated moxifloxacin. While unirradiated moxifloxacin exhibit no EPR signal, irradiated powder spectra of moxifloxacin has very intense EPR resonance peaks. The intensity of these signal increases with absorbed doses and may be saturated and/or decreases afterward. No pattern change occurred with increasing absorbed dose in room temperature.

Spectra Simulation

Figure no. 2 presents the EPR spectrum of the powder moxifloxacin, ɣ-irradiated at room temperature. Gamma irradiated moxifloxacin was observed to exhibit an EPR spectrum of the singlet type at the room temperature, having g-value 2.0028. Gamma irradiated moxifloxacin at room temperature was observed to exhibit an EPR spectrum consisting of many unresolved strong and weak resonance lines. The main strong resonance line seems to be a singlet and dominating the EPR spectrum of irradiated moxifloxacin. The hyperfine coupling constants, a^{1}_{α} = 1.56 mT, a^{2}_{α} = 2.79 mT, a_N = 0.4 mT which were used to determine the simulated spectrum. The hyperfine splitting of nitrogen atom is not observed in the spectrum, because these are the close value to the line width of the spectrum. The $\dot{C}H_2$ radical gave rise to a singlet centered at g= 2.0028 with 0.68 mT width. These considerations all lead to the conclusion that $\dot{C}H_2$ radical was a formed by abstraction of one of the H atoms bonded to α-carbon atom. The radical structure of moxifloxacin was estimated by comparison of the Mc Kelvey simulation program results [17].

Dose-Response Curve

We observed no change in the area under the EPR spectra absorption curve, therefore, we follow signal intensity as a function of absorbed dose and time. After gamma irradiation of the moxifloxacin, there is only an increase in the intensity of the EPR signal. Evaluations were done to determine the dosimetric potential of moxifloxacin. The free radicals number (per g at 20 kGy) was estimated by comparison of the second integral from radiosterilized moxifloxacin and DPPH standard. Therefore, the G value 0.13 (the number of radicals per 100 eV) is estimated [16]. This value is 1 for alanine [19]. From the obtained result of G value, we can say moxifloxacin is fairly resistant to gamma radiation. The dependency of the

central line on the irradiation dose is presented in Fig. 3. As shown in Fig. 3, up to irradiation doses nearly 20kGy the number of free radicals produced by gamma radiation is linear with the absorbed dose.

As concluded from Fig.3, the signal intensities of moxifloxacin have a linear behavior in the dose range 2-20 kGy, it's high radiation yields and the results clearly revealed that EPR technique easily enables us to distinguish irradiated samples from nonirradiated ones long after irradiation make the moxifloxacin potential candidate to dosimetric material.

Study of EPR signal decay kinetics

The decay kinetics of the radiation-induced EPR signal is a very important parameter. This may give information about radiation treatment since the concentration of the radiation-induced free radicals significantly decreases in time. The powder samples of moxifloxacin irradiated at a dose of 15 kGy were studied to determine the effect of storage on the signal intensity of radiation-induced free radicals. Samples were kept in the dark at room temperature over a period of 600 days. The EPR spectra were recorded periodically during this storage time and results are shown in Figure 4. Decay kinetics of signal intensities calculated separately. The decay kinetics of free radicals simulated with using $I(t) = I_0 + A.e^{-kt}$ function in which A and k represent the relative weights and decay constants of the proposed radical species and t was the storage time in days. The limits of detection of free radicals after irradiation at 15 kGy and storage at ambient temperature is 55 days for primidone.

CONCLUSİONS

The obtained results for gamma irradiated moxifloxacin are reported. From these results, we can say that EPR measurements could be safely used to get both qualitative information whether moxifloxacin irradiated or not irradiated up to 600 days after irradiation and quantitative results; dependence of absorbed dose. The signal intensities of moxifloxacin a have a linear behavior in the dose range 2-20 kGy, this high radiation yields and distinguishing irradiated moxifloxacin from nonirradiated ones long after irradiation make primidone potential candidate to dosimetric material. From the EPR experimental data, one can see that for doses up to 20 kGy there is a linear behavior for moxifloxacin drug sample, after which a saturation process starts. This value is lower than the dose of 25kGy

corresponding to the radiosterilized drug. Therefore, radiosterilization of moxifloxacin in the solid dry state could be technically feasible.

REFERENCES

[1] Sebastian G. Wicha, Thomas Haak, Karl Zink, Frieder Kees, Charlotte Kloft, and Martin G. Kees, Pharmacokinetics and target attainment Analysis of Moxifloxacin inPatients With Diabetic Foot Infections, The Journal of Clinical Pharmacology 2015, 55(6) 639–646.
[2] Landersdorfer CB, Kinzig M, Hennig FF, et al. Penetration of moxifloxacin into bone evaluated by Monte Carlo simulation.Antimicrob Agents Chemother. 2009;53(5):2074–2081.
[3] Wilczyński S, Pilawa B, Koprowski R, Wróbel Z, Ptaszkiewicz M, Swakoń J, Olko P. EPR studies of free radicals decay and survival in gamma-irradiated aminoglycoside antibiotics: sisomicin, tobramycin, and paromomycin. European Journal of Pharmaceutical Science, 2012;45:251–262.
[4] G. Damian, G. Schmutzer, D. Petrisor. Investigation of light-induced free radicals in nifedipine. Journal of Optoelectronics and Advanced Materials, 2007 9(3), 680-683.
[5] Gibella, M., Tilquin, B., Detection of the radiolysis of solid state ampicillin by UV-spectroscopy. 1999. Analysis, 27, 657–662.
[6] Marciniec, B., Stawny, M., Kozak, M., Naskrent, M., The effect of ionizing radiation of 1,4-dihydropyridine derivatives in the solid state, 2008. Spectrochimica Acta Part A 69(3), 865–870.
[7] Basly, J.P., Longly I., Bernard M., Radiation effects on dopamine and norepinephrine.1997. Pharmaceutical Research. 14,810-814
[8] Engalytcheff, A., Kolberg, M., Barra, A-L, Andersson K.K., Tilquin B., The use of multi-frequency EPR techniques to identify the radicals produced in irradiated beta-blockers
[9] Basly, J.P., Basly, I., Bernard, M., Radiosterilization dosimetry of vitamins: an ESR study. Int. J. Radiat. Biol., 1998, 74, 521–528.
[10] Engalytcheff, A., Kolberg, M., Barra, A.L., Andersson, K.K., Tilquin, B., The use of multi-frequencyEPRtechniquestoidentifytheradicalsproducedin irradiated b-blockers. FreeRadicalRes. 2004, 38,59–66.
[11] Marciniec, B., Plotkowiak, Z., Wachowski, L., Kozak, M., Popielarz-Brzezinski, M.,
Analytical study of b-irradiated antibiotics in the solid state.J.Therm. Anal. Calorim., 2002. 68,423–436.
[12] Jacobs, G.P., A review of the effects of gamma radiation on pharmaceutical materials. J. Biomater. Appl. 1995, 10, 59–96.
[13] Basly, J.P., Longly I., Bernard M., Radiation Sterilization of formoterol, Pharmaceutical Research, 1997, 14,810-814
[14] Basly, J.P., Basly, I., Bernard, M., Influence of radiation treatment on two antibacterial agents and four antiprotozoal agents: ESR dosimetry. Int. J. Pharm., 1997a, 154, 109–113.
[15] Varshney, L., Dodke, P.B., Radiation effect studies on anticancer drugs; cyclophosphamide and doxorubicin for radiation sterilization. Radiat. Phys. Chem., 2004, 71, 1103–1111
[16] Onori, S., Pantaloni, M., Fattibene, P., Ciranni Signoretti, E., Valvo, L., Santucci, M., ESR identification of irradiated antibiotics: cephalosporins. Appl. Radiat. Isot., 1996. 47, 1569–1572. 2004, Free. Radical Research, 38,1, 59,66.
[17] McKelvey, R.D.,1987, J.Chem.Educ.64,497.
[18] Slifkin, M. A., Suleiman, Y. M. The use of DPPH as a standard for the measurement of G-values,1975, Radiation Effects, 27, 111-112.
[19] Miyazaki, T., Kaneko, T., Yoshimura, T., Crugq, A-S., Tilquin, B., Electron spin resonance study of radiosterilization of antibiotics: ceftazidime, 1994, Journal of Pharmaceutical Science, 83,68-71.

Figure and Table Captions

Figure no. 1: Chemical structure of moxifloxacin

Figure no. 2: The EPR experimental spectrum of γ-irradiated (a) moxifloxacin and (b) simulated form of the spectrum

Figure no. 3: Dependence of the number of free radicals with the absorbed dose of irradiated moxifloxacin

Figure no. 4: EPR signal intensity of irradiated moxifloxacin as a function of time after irradiation.

FIGURES

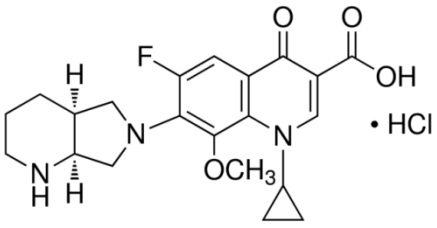

Figure 1

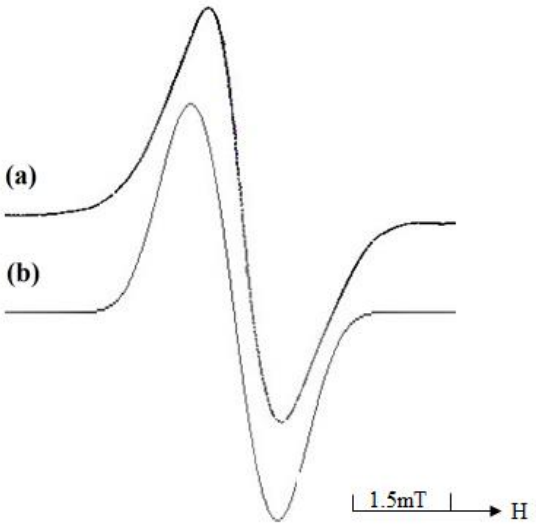

Figure 2

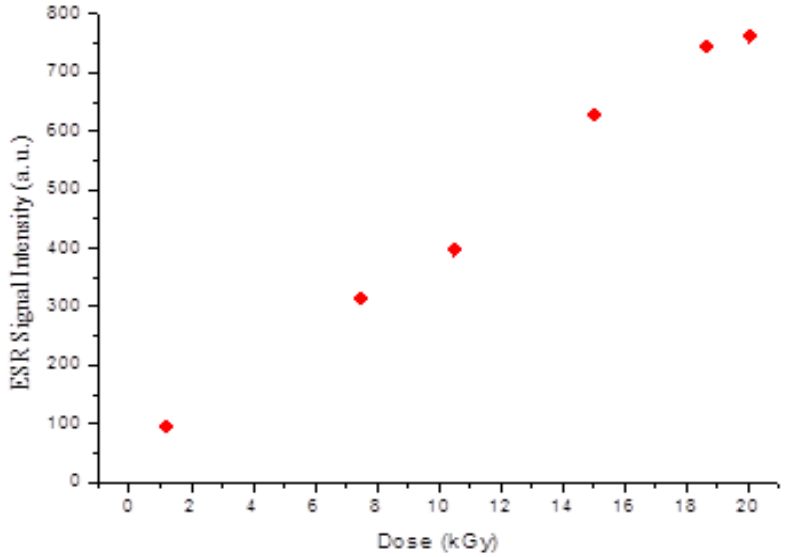

Figure 3

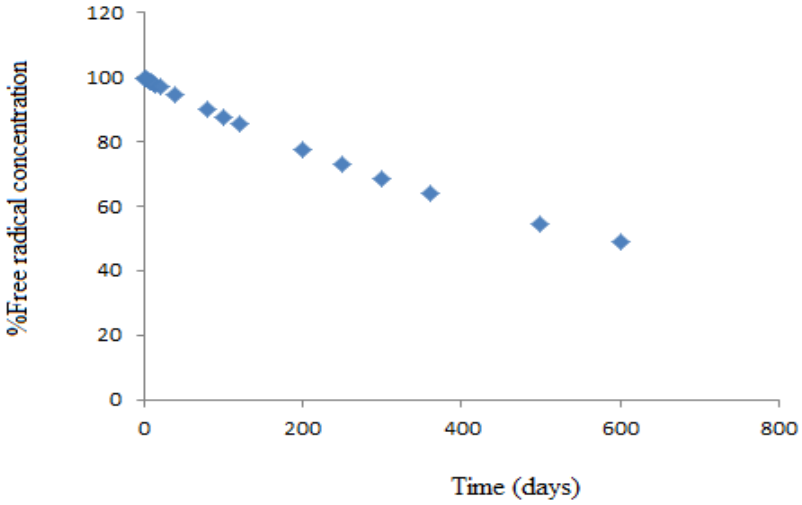

Figure 4