Journal of Radiation Research and Applied Sciences xxx (2017) 1–7

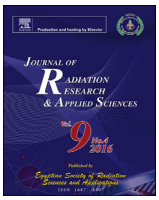
HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

Journal of Radiation Research and Applied Sciences

journal homepage: http://www.elsevier.com/locate/jrras



Potential effects of gamma irradiation on the stability and therapeutic activity of anticancer drug, doxorubicin

Fatmah M. Alshammari [a], Sonia M. Reda [a, b, *], Magdy M. Ghannam [c]

[a] Department of Physics, Faculty of Science, Hail University, KSA
[b] Department of Physics, Faculty of Science, Zagazig University, Egypt
[c] Department of Biophysics, Faculty of Science, Cairo University, Egypt

ARTICLE INFO

Article history:
Received 14 November 2016
Received in revised form
27 January 2017
Accepted 28 January 2017
Available online xxx

Keywords:
Radiotherapy
Chemotherapy
Gamma radiation
Doxorubicin
Overlapping
Stability of anticancer drug

ABSTRACT

Cancer therapy has progressed dramatically in recent years. In order to decrease the dose and side effects of the anticancer drug, the therapeutic options for patients with cancer include increasingly complex combinations of chemotherapy and radiotherapy. This combination may cause overlapping interaction between the two types of treatment and affect the stability of the anticancer drug. In this study, the effect of gamma irradiation on the stability and therapeutic activity of one anticancer drug (Doxorubicin) was studied. For this purpose, doxorubicin drug characterized by two methods, at first, *in-vitro* study, before and after drug irradiation with different doses of gamma rays (2, 5, 20, 100 GY) which achieved through measuring the dielectric relaxation and absorption spectrum of drug solution. Secondly, *in-vivo* studies, where the unirradiated and the drug, which later exposed to gamma rays, were injected respectively into 6 groups of mice (3 mice in each group). The dielectric relaxation and absorption spectrum were studded for hemoglobin of the injected mice. The results for the *in-vitro* study indicate that the values of dielectric parameters show unnoticeable change for drug molecules before and after irradiation as compared with the control. The results for *in-vivo* study indicated an increase in the values of relaxation time and Cole-Cole parameter, that may as a result of changes in the conformational structure in hemoglobin molecules which may affect their properties and hence RBC's physiological functions. The absorption spectra of hemoglobin molecules show an increase in the amplitude of the characteristic bands with irradiation dose indicate an increase of the oxygen binding capacity with hemoglobin. It was concluded that combination between the drugs and gamma irradiation can be used as a powerful conjunction that may give us the benefit chemo and radiotherapy treatment.

1. Introduction

Cancer therapy has progressed dramatically in recent years, and tremendous progress has been made in reducing the morbidity and mortality from many forms of cancer. The therapeutic options for patients with cancer include increasingly complex combinations of chemotherapy, radiotherapy and surgical intervention. (Chantal, Waston, Drake, Fenton, & Mcloughlin, 2008; Edward et al., 2004; Schultz, Beck, Stava, et al., 2003).

Radiotherapy is a crucial component of anticancer treatment; up to 50% of cancer patients receive radiotherapy. Apart from surgery, radiotherapy is the major method applied with curative intent for cancer patients. Radiotherapy plays a major part in the palliation of symptoms. (Stephen, 2009). On the other hand, cancer chemotherapy refers to the administration of cytotoxic chemicals, with the aim to, eradicate the tumour or reduce the tumour-related symptoms. Most chemotherapeutic drugs cause damage to DNA, which leads to programmed cell death (apoptosis) (Peter, 2001; Jaishree and Geoff, 2009). Doxorubicin is an anti-cancer drugs widely used in the treatment of various types of cancers. It belongs to antitumor antibiotics. The cytotoxicity of the drug is due to its ability to interact with DNA and plasma membrane and to participate in various oxidation reduction reactions. (Varshney & Dodke, 2004). It is intrinsically fluorescent which makes it convenient for

* Corresponding author. Department of Physics, Faculty of Science, Zagazig University, Egypt
E-mail address: sonreda@yahoo.com (S.M. Reda).

Peer review under responsibility of The Egyptian Society of Radiation Sciences and Applications.

http://dx.doi.org/10.1016/j.jrras.2017.01.001

Please cite this article in press as: Alshammari, F. M., et al., Potential effects of gamma irradiation on the stability and therapeutic activity of anticancer drug, doxorubicin, Journal of Radiation Research and Applied Sciences (2017), http://dx.doi.org/10.1016/j.jrras.2017.01.001

probing and visualization with various microscopic imaging technologies (Dai et al., 2008).

Combined modality treatment with radiotherapy and chemotherapy is used increasingly for the primary management of a variety of human tumors, with the aim of improving both local and distant control, decreasing distant metastasis, and improving survival without excessively increasing normal tissue injury. (Franco, Cortes-Funes, & Wasserman, 1978; Phillips & Karen, 1978; Ian, 1989; Karen, 1985; Maurice, Arriagada, & Cosset, 1985). In this combined treatment, radiation interacts with drugs and may effect on their quality. It was concluded that combination between the drugs and gamma irradiation can be used as a powerful conjunction that may give us the benefit chemo and radiotherapy treatment. This highly versatile system can be used in the testing of drug – organ disease interaction and so will aid in improving the clinical treatment protocol and fights against serious diseases.

This work is aimed to evaluate the effects of gamma irradiation on the stability of anticancer drugs. Moreover, study the overlapping interaction between radiotherapy and chemotherapy during cancer fitting is the main target of the presented work. For this purpose, doxorubicin, one of the most widely used anticancer drugs was chosen. The stability of the drug upon application of gamma irradiation will be achieved through measurements of electrical properties. Dielectric measurements can provide valuable significant information about the molecular arrangement of the drugs as well as the electrical conduction mechanism (Grant, Sheppard, & South, 1978). Furthermore, using UV–Visible spectroscopy can derive useful information on the biological molecules. This information can lead to valuable structural proposals (Pavia, Lampman, Kriz, & Vyvyan, 2009). The overlapping interaction between radiotherapy and the used drug will be achieved by studying the effect of irradiation on the therapeutic activity of the used chemotherapeutic drug.

2. Materials and methods

In this work, the study of the interaction between gamma radiations with anti-cancer drugs was divided into two main parts:

2.1. In-Vitro studies

2.1.1. Drug

Doxorubicin is an anthraxcycline antibiotic with antineoplastic activity. The molecular stucture of the drug is shown in Fig. 1. Doxorubicin, isolated from the bacterium *Streptomyces peucetius* var. caesius, is the hydroxylated congener of daunorubicin. Doxorubicin intercalates between base pairs in the DNA helix, thereby preventing DNA replication and ultimately inhibiting protein synthesis. Additionally, doxorubicin inhibits topoisomerase II which results in an increased and stabilized cleavable enzyme-DNA linked complex during DNA replication and subsequently prevents the ligation of the nucleotide strand after double-strand breakage. Doxorubicin also forms oxygen free radicals resulting in cytotoxicity secondary to lipid peroxidation of cell membrane lipids; the formation of oxygen free radicals also contributes to the toxicity of the anthracycline antibiotics, namely the cardiac and cutaneous vascular effects.

Doxorubicin hydrochloride drug (Adriblastina), was purchased from Pharmacia Italia S.P.A. (Italy). The drug concentration (2 mg/ml) was diluted to 0.1 mg/ml, and divided into five test tubes, the first is used as control and the others is exposed to 2Gy, 5Gy, 20Gy, and 100Gy respectively. The samples were diluted to a five different concentrations.

The studied samples were irradiated by ^{60}Co gamma rays presented at King Saud University, College of Science, Riyadh, Kingdom of Saudi Arabia with activity of 0.44 Gy/sec using gamma cell 220 manufactured by NORDION (Canada).

Physical methods were taken to characterize the drugs include dielectric relaxation and absorption spectrum of samples.

2.1.2. Dielectric relaxation

Electric measurements were investigated in the frequency range from 20 Hz up to 3 MHz (α & β dispersions of biological materials) using a WAYNE KERR precision component analyzer model 6440B (UK). The sample cell has two squared platinum black electrodes with cell constant k = 1 cm^{-1}. The measurements were performed at room temperature. For a dielectric material placed between two parallel plates capacitor, the measured values of the capacitance, C and resistance R were used to calculate the conductivity σ, as well as the real, ε', and imaginary, ε'', parts of the complex permittivity and the relaxation τ time through the following equations:

i) $\varepsilon' = \frac{C}{C_o} = \frac{C}{\varepsilon_o} k = \frac{C}{\varepsilon_o}\left(\frac{d}{A}\right) = \frac{C}{8.85\times10^{-12}} \times 100 = 1.13 \times 10^{13} C$

ε_o is the permittivity of free space (Foster & Schwan, 1996).

ii) Loss tangent factor $D = \frac{\varepsilon''}{\varepsilon'} = \frac{1}{2\pi RCf}$

iii) The conductivity $\sigma = \frac{1}{\left(R\frac{A}{d}\right)} = \frac{k}{R} = \frac{100}{R}(\Omega^{-1}m^{-1})$

iv) The dielectric loss $\varepsilon'' = D\varepsilon'$

v) The dielectric increment $\Delta\varepsilon = \varepsilon_1 - \varepsilon_o$

vi) Relaxation time $\tau = \frac{1}{2\pi f_c}$, f_c is the critical frequency corresponding to the midpoint of the dispersion curve.

vii) The plot ε' Vs ε'' (Cole-Cole plot) will produced a semi-circle.

It was shown by Cole and Cole that the angle traced between the circle radius and ε' axis is $\theta = \alpha\pi/2$. This in turn enable to estimate the Cole-Cole parameter α, experimentally, so $\alpha = 2\theta/\pi$ (Koji Asami, 2002).

2.1.3. The absorption spectrum

The absorption spectrum of the samples were measured using UV/Visible double beam spectrophotometer type 1650 PC manufactured by Shimatzu (Japan), in the wavelength range from 200 to 800 nm.

2.2. In-Vivo studies

2.2.1. Experimental design

Normal SWR/J male mouse, 8–10 weeks old and weighing 28±3g were used throughout the study. Animals were maintained under standard laboratory at a temperature of 24 ± 1 °C, a relative humidity of 45 ± 5% and photoperiod cycle of 12/12 h. Mice food (commercially available in Saudi Arabia) and water were offered *ad libitum*. Male mice were grouped into six groups each group

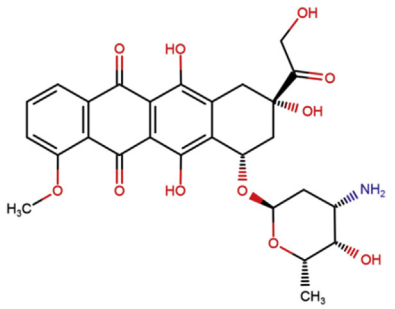


Fig. 1. Structure of doxorubicin.

Please cite this article in press as: Alshammari, F. M., et al., Potential effects of gamma irradiation on the stability and therapeutic activity of anticancer drug, doxorubicin, Journal of Radiation Research and Applied Sciences (2017), http://dx.doi.org/10.1016/j.jrras.2017.01.001