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Dose response of gluconic acid doped Fricke gels irradiated with X-rays

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ABSTRACT

Adjusting the dose of radiation which is received by a cancer patient during radiotherapy is very important. The use of dosimetric gels to calculate the applied dose distribution three-dimensionally is a current research topic in radiotherapy. In this study, 16 different Fricke gels including gluconic acid (GA) were produced. These gels were irradiated from 0 to 250 cGy with increments of 50 cGy. MR intensity values and images, UV absorbance values and FT-IR spectra of gels were obtained before and after the irradiation process. The UV absorbance and MR intensity values showed a linear increase in relation to the increase in the applied dose and the amount of ferrous sulfate and GA content in the gels. The oxidation of iron increases as a result of the interaction with hydrogen peroxide which is the product of the irradiation process and GA, and thus the response of the gel to the irradiation process becomes more effective.

1. Introduction

The use of radiation in the treatment of cancerous cells is called radiotherapy. It is important to know the dose amount applied to cancer patients. A number of systems were developed to measure the dose of radiation, such as control dosimetry, small area dosimetry, out-of-field low dose dosimetry, in vivo dosimetry, brachytherapy, and auditing of radiotherapy applications [1]. Dosimetric gels can be used for the determination of the dose distribution three dimensionally before the planned treatment. As a result of the interaction of the gel dosimeters with radiation, there are changes in various properties such as optical, magnetic, color, ultrasonic permeability and scattering. Fricke gels are useful as three-dimensional dosimeters because of their ease of production and tissue equivalence [2,3]. The basic change in Fricke gels, which are produced by dissolving iron sulfate solution containing very low amounts of acid and salt in a gel structure, is conversion of Fe^{2+} to Fe^{3+} by irradiation. Fricke gels are generally examined by magnetic resonance imaging (MRI) technique utilizing the different behaviors of ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron in the magnetic field [4-8]. The main disadvantage of Fricke gel dosimeters is that the ferric ions undergo diffusion after irradiation and this gradually causes the dose pattern to blur. In dosimeters containing xylenol orange (XO), diffusion is slightly reduced and it is used for NMR (nuclear magnetic resonance) analysis especially [9].

There are several studies that analyzed Fricke gels with optical techniques. Gambarini et al. [10] investigated the optical absorbance and magnetic resonance of Fricke XO gel dosimeters prepared with different XO and gelling agents. Gallo et al. [9] examined the optical absorbance spectra (350-750 nm interval) of Fricke XO gel dosimeters loaded with laponite. Optically-enhanced gel dosimeters produced by adding Ethylene diamine tetra acetic acid (EDTA) to the ammonium ferrous sulfate solutions including XO were studied [11]. Fricke XO-gelatin (FXG) and its application as a gel dosimeter in radiotherapy were determined with some parameters such as beam uniformity, optical absorbance and output factor [12]. More recently, Lazzaroni et.al used a ligand having the iminodiacetic and phenol moieties instead of XO in Fricke gels for more accurate and feasible dose evaluation by

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optical and MRI analysis [13]. In our study, the dose distribution of X-ray irradiated Fricke gels, including gluconic acid (GA) were examined. Ultra violet (UV) absorbance values and Fourier transform infrared (FT-IR) spectra of gels were obtained before and after the irradiation process. GA, which is found in some fruits and in iron-containing tablets taken as food supplements, was added to Fricke gels in this and a previous [7] study for the first time as a biocompatible material. In this way, the aim was to increase the oxidation of Fe^{2+} to Fe^{3+}, which is the basis for the usage of Fricke gel as dosimeter, by adding reactions of GA. Results of the UV and FT-IR analysis proved these expected chemical reactions occurred.

2. Material and Method

2.1. Materials

Gelatin bovine medical grade (CAS 9000-70-8), D-Gluconic acid (CAS 526-95-4) and Iron(II) sulfate hydrate (CAS 7782-63-0) were purchased from Sigma-Aldrich for production of gels.

2.2. Preparation of Fricke Gels

In this study, firstly 4 different groups of gels were prepared. These groups contained 0, 0.5, 1.0 and 2.0 mM GA ($HOCH_2(CHOH)_4COOH$), respectively. Then, $Fe(NH_4)_2(SO_4)_2.7H_2O$ solutions containing 50 mM H_2SO_4 were added to gels to provide the desired concentrations (0.125, 0.25, 0.5 and 1.0 mM) of Fe^{2+}. Thus, firstly, 16 different types of Fricke gel were prepared. The preparation of gels is given in detail as follows. Deionized water of 100 ml was heated to 85 °C and then 1 g bovine gelatin was added and mixed at 400 rpm for 5 minutes with a magnetic stirrer under air flow at 20 Lh^{-1}. The solution was left to boil at saturation for 20 min and then cooled down to 70 °C. GA was added with the required amount and stirred for one minute. The solution was then removed from the magnetic stirrer and $FeSO_4$ solutions containing H_2SO_4 were added. After 10-15 seconds of manual mixing, they were poured into spectrophotometry cuvettes with a 1 cm optical path. Each type of gel was poured into 6 cuvettes for 6 different irradiation doses. Thus, finally, 96 different Fricke gel samples were prepared. Prepared gels were kept in a refrigerator at +4 °C until the irradiation process and analyses were carried out. The contents and names of the gels according to the applied dose (0 and a 250 cGy) are given in Table 1. As can be seen from the table, when the gels are named, they were first grouped as A, B, C, D according to their gluconic acid content, then 1, 2, 3, 4 numbers were added according to the amount of iron sulphate and finally applied radiation dose values were written. Other names of 64 samples (irradiated at 50, 100, 150 and 200 cGy) were not shown in the table to avoid taking up much space.

Table 1. Names and contents of the gels

Name of group	FeSO4 (mM)	Name of gel before irradiation	Name of gel after 250 cGy irradiation
A (Gluconic acid 0 mM)	0.125	A10	A1250
	0.25	A20	A2250
	0.5	A30	A3250
	1.0	A40	A4250
B (Gluconic acid 0.5 mM)	0.125	B10	B1250
	0.25	B20	B2250
	0.5	B30	B3250
	1.0	B40	B4250
C (Gluconic acid 1.0 mM)	0.125	C10	C1250
	0.25	C20	C2250
	0.5	C30	C3250
	1.0	C40	C4250
D (Gluconic acid 2.0 mM)	0.125	D10	D1250
	0.25	D20	D2250
	0.5	D30	D3250
	1.0	D40	D4250

2.3. Irradiation Process, MR Imaging, UV and FT-IR Analyses

After 24 hours, the prepared gels were removed from the refrigerator, allowed to reach room temperature and irradiated with linear accelerator X-rays from 0 to 250 cGy with increments of 50 cGy. The linear accelerator (Siemens, Primus, Erlangen, Germany) generated X-rays at 6 MV and was calibrated using a traceable ionization chamber complying with IAEA TRS-398 standard. The irradiation of gel dosimeters was done with a similar setup to the calibration of the linac system. 6 MV X-rays were used with a dose rate of 600 MU/min at 100 cm SSD and 10 x 10 cm field size under a 0.5 cm water phantom. Total uncertainty was ±2% of dose delivered. Irradiated gel dosimeters were scanned with a 3T MR system (Siemens, Skyra, Germany). Quadrature brain coil was used with standard turbo spin echo protocol with TR = 367 ms and TE = 14 ms. T1 weighted MR images were obtained and MR intensities were acquired from ROIs (region of interest) with software (Siemens, Syngo Via, Germany).

Absorbance values for the Fricke gels were obtained using a Metash 5100 UV / VIS Spectrophotometer at 300 nm wavelength before and after the irradiation process.

FT-IR analysis was performed to monitor changes in the chemical structures of the generated gels. Transmission data were obtained using the Vertex 70 FT-IR device in ATR mode for A40, B40, C40, D40, A4250, B4250, C4250 and D4250 samples.

3. Results and Discussion

Before discussing the results of the UV and FT-IR analyses, it is useful to examine the reactions previously described in the literature [14, 15] which are caused by the

irradiation of the gel samples. Since a large part of the solution is composed of water, it is necessary to look at the reactions related to radiolysis of water primarily. Although many reactions take place, the main reactions that occur when water and aqueous solutions are exposed to X-rays are as follows:

$H_2O \rightsquigarrow e^- + H_2O^+$ (Ionization of water molecule) (1)

$e^- + n\ H_2O \rightarrow e^-_{aq}$ (Secondary electrons are hydrated by giving their energy to water) (2)

$e^-_{aq} + H_3O^+ \rightarrow H + H_2O$ (Production of hydrogen atom) (3)

$H_2O^+ + H_2O \rightarrow H_3O^+ + OH\cdot$ (Formation of hydronium ion and hydroxyl radical) (4)

$e^-_{aq} + e^-_{aq} + 2H_2O \rightarrow H_2 + 2OH^-$ (Formation of hydrogen and hydroxyl ion) (5)

$e^-_{aq} + H + H_2O \rightarrow H_2 + OH^-$ (Formation of hydrogen and hydroxyl ion) (6)

$OH\cdot + OH\cdot \rightarrow H_2O_2$ (Production of hydrogen peroxide) (7)

The possible reactions that occur with the irradiation of the Fricke gel systems are as follows. The initial reactions use the products of water radiolysis reactions:

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$ (8)

$Fe^{2+} + OH\cdot \rightarrow Fe^{+3} + OH^-$ (9)

$OH + Fe^{2+} + H^+ \rightarrow H_2O + Fe^{3+}$ (10)

$H + Fe^{2+} \rightarrow H^+ + Fe^{3+}$ (11)

Then, gelatin (RH) which is a macromolecule in the gel system enters reactions with the formed radicals to form new products:

$e^-_{aq} + H^+ \rightarrow H\cdot$ (12)

$OH\cdot + RH \rightarrow R\cdot + H_2O$ (13)

$H\cdot + RH \rightarrow R\cdot + H_2$ (14)

$R\cdot + O_2 \rightarrow RO_2\cdot$ (15)

New chain reactions begin with this new radical in the system:

$Fe^{2+} + RO_2\cdot + H^+ \rightarrow Fe^{3+} + RO_2H$ (16)

$RO_2H + Fe^{2+} \rightarrow Fe^{3+} + RO\cdot + OH^-$ (17)

$RO\cdot + RH \rightarrow R\cdot + ROH$ (18)

When all these reactions are examined, it appears that many new products are formed in the irradiated gel. The effects of these new species on the results of UV and FT-IR analyses are examined in the following sections.

3.1 UV Measurement Results

The following graphs were obtained according to the results of absorbance at 300 nm before and after the irradiation process.

When Fig. 1 is examined, the absorbance intensities increased with the addition of GA as expected, but the increase in $FeSO_4$ concentration affected the increase in UV absorbance values more. In particular, gels containing high amounts of $FeSO_4$ have very high absorbance values. As the amount of applied radiation increases, the intensity of the absorbance increases. These increases in the UV absorbance values were caused by new products (such as) formed during the reactions described above.

3.2 FT-IR Analysis Results of Fricke Gels Non-Irradiated and Irradiated with 250 cgy Dose of X-rays

The wavenumbers of the specific peaks on the FT-IR spectrum for Fricke gels produced in this work and the related bond structures are given in Table 2. If the spectrum obtained in this study is compared with the FT-IR profile of pure gelatin given by Hermanto et. al. [16] and Hossan et.al. [17], the peak values given in Table 2 at 3294, 3078, 2941, 1635, 1539 and 868 cm^{-1} belong to gelatin. These values are very similar to the 3222, 3100, 2947, 1637 and 1542 cm^{-1} peaks, respectively, given by Hossan et al. [17]. In the literature, Fe-O and Fe-OH peaks occur in the fingerprint region of 400 - 1500 cm^{-1}.

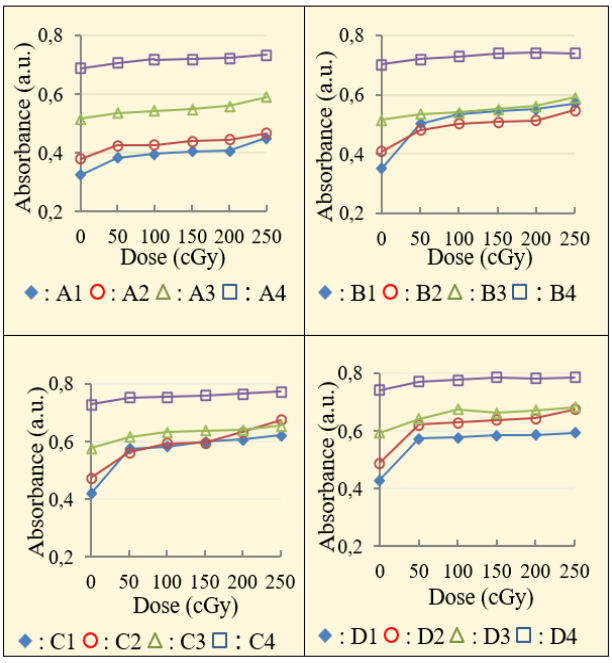

Figure1. Dose (cGy) and absorbance graph of the gels before and after the irradiation process.

Table 2. The bond structures and wavenumbers for the main peaks in the FT-IR graphs presented in Figure 2 and Figure 3

Wavenumber (cm^{-1})	**3294**	**3078**	**2941**	**1635**	**1539**	**1167**	**1045**	**868**	**577**
Bond structure	N-H stretching, -OH stretching	C-H stretching	C-H stretching	C=O stretching	C-N-H bending	C-O stretching	C-O	N-H out of plane bending	Fe-O stretching

Table 3. Slope of dose response lines and R^2 values for each gel

	Name of gels							
	A10-A1250	**A20-A2250**	**A30-A3250**	**A40-A4250**	**B10-B1250**	**B20-B2250**	**B30-B3250**	**B40-B4250**
Slope	0.663	0.977	1.227	1.958	0.864	2.250	2.034	2.486
R^2	0.948	0.968	0.963	0.876	0.861	0.967	0.987	0.962
	C10-C1250	**C20-C2250**	**C30-C3250**	**C40-C4250**	**D10-D4250**	**D20-D2250**	**D30-D3250**	**D40-D4250**
Slope	2.217	2.585	2.044	2.051	1.138	1.811	2.138	1.845
R^2	0.992	0.902	0883	0.885	0.804	0.941	0.930	0.934

Sun et al. [18] studied the structure of nano-magnetite in the presence of GA and Gündüz and Bayrak [19] used nanoscale iron for an adsorption process. They indicated that the peaks showing the Fe-O bond formed at 579 cm^{-1}. Xiao et al. [20] found that magnetite (Fe_3O_4) has strong absorbance at 570 cm^{-1}. Similarly, Ercan et.al. showed the absorption bands for their synthesized iron oxide nanoparticles at 599.83 and 475 cm^{-1} as related for Fe-O stretches of Fe_3O_4 and Fe_2O_3 [21]. So, the peak at 577 cm^{-1} shows the presence of Fe-O bond and Fe_3O_4 structure in Figures 2 and 3. According to Chen et al. [22], FT-IR/ATR analysis of glucose solutions showed absorbance peaks around 3300 and 1650 cm^{-1}. C-O bands of the spectrum at 1167 and 1045 cm^{-1} are evidence of the presence of acid. When all these data are examined, the following reactions can be suggested as causing the changes in the spectrum:

$$GA + H_2O_2 \rightarrow \text{glucose} + O_2 + H_2O \quad (19)$$

$$Fe(OH)_3 + \text{glucose} \xrightarrow[h\nu]{} Fe_3O_4 + GA \quad (20)$$

$$Fe^{3+} + 3H_2O \rightarrow Fe(OH)_3 + 3H^+ \quad (21)$$

Considering these suggested reactions; it can be said that the oxidation of iron increases as a result of the interaction of hydrogen peroxide, which is the product of the irradiation process, and GA and thus the response of the gel to the irradiation process becomes more effective. The increases in the UV and MR intensity values according to the GA amount confirm this prediction.

As the amount of Fe^{2+} concentration increases, the MR intensity values increase linearly. Similarly, the gels with high GA content have a better dose response trend. In general, the dose response relationship of gels containing 0.5 and 1 mM GA appears to be better.

3.3. MR Intensity Values and Images of the Gels

The MR intensity values were plotted against the irradiation dose. The slope of the straight lines (proportional to the radiation sensitivity of gels) and R^2 values are shown in Table 3. Figure 4 shows the MR images of the gels using an MR sequence with TR 367 ms and TE 14 ms. As can be seen in this figure, as the amount of iron and GA in the gels increases, brighter areas appear on MR images.

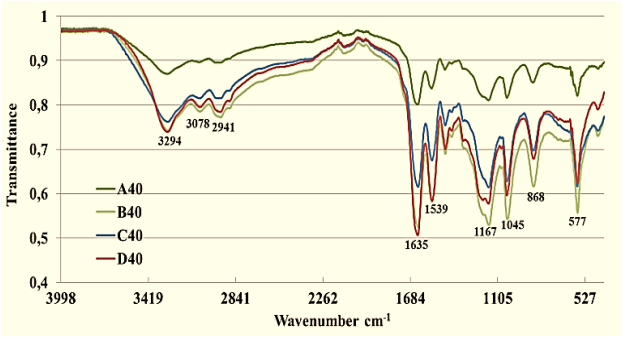

Figure 2. FT-IR graphs of Fricke gels including 1.0 mM $FeSO_4$ and different amounts of GA before the irradiation process

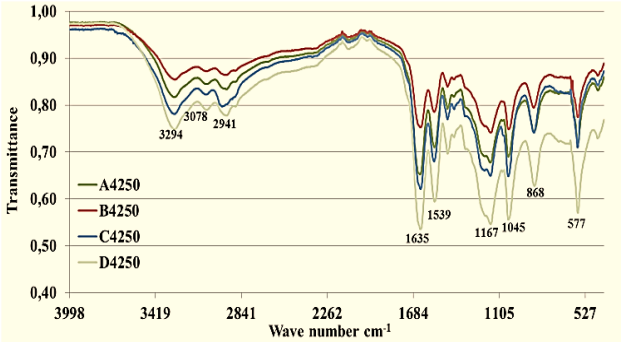

Figure 3. FT-IR graphs of Fricke gels including 1.0 mM $FeSO_4$ and different amounts of GA after the irradiation process with 250 cGy dose of X-rays

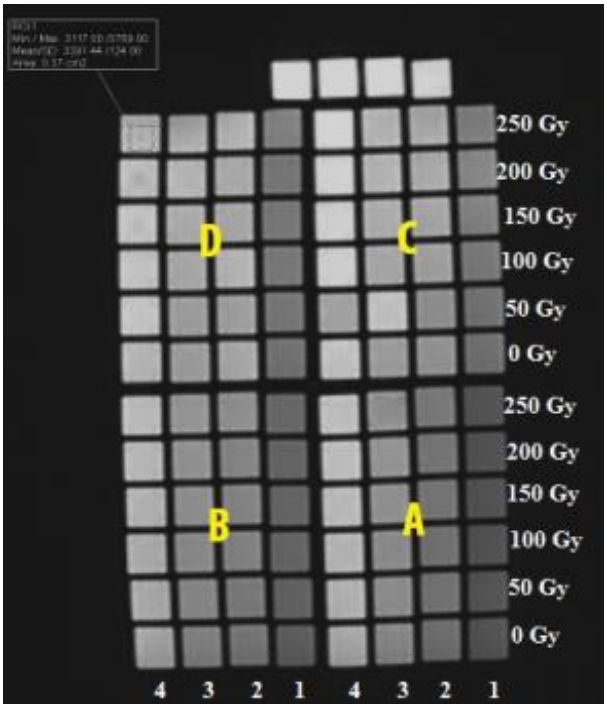

Figure 4. MR Images of the gels containing GA (A: 0 mM, B: 0.5 mM, C: 1 mM, D: 2 mM) and $FeSO_4$ solutions (1: 0.125 mM, 2: 0.25 mM, 3: 0.5 mM, 4: 1.0 mM)

4. Conclusions

In this study, Fricke gels containing $FeSO_4$ and GA with different concentrations were produced and then irradiated up to 250 cGy with increments of 50 cGy. UV and FT-IR analyses were performed on the samples before and after irradiation. The UV absorbance values of the gels containing GA increased linearly with the applied radiation dose. Similarly, the MR intensity values showed a linear increase in correlation to the increase in the applied dose and the amount of ferrous sulfate and GA content of the gels. These increases are related to the oxidation of iron depending on chemical reactions where reactants are GA and products of irradiation process.

Declaration

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors also declared that this article is original, was prepared in accordance with international publication and research ethics, and ethical committee permission or any special permission is not required.

Author Contributions

All authors conceived the study together. Ö. Korkut developed methodology and analysis, S. Aktaş performed experiments and M.E. Sağsöz supervised and improved the study.

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