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A comparison of three Fe^{3+} chelating agents used in Fricke gel dosimetry

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Summary. — "Fricke solutions" have been used for ionizing radiation dosimetry since 1927. The system consists of an acidic solution of Fe^{2+} ions, which oxidize to Fe^{3+} upon irradiation. The addition of the Fricke solution to a tissue-equivalent hydrogel matrix allows 3D dose-mapping, that is the basis of Fricke gel dosimetry. Fricke gel dosimeters still have some drawbacks that hinder its practical usage for 3D mapping, namely signal diffusion effects and spontaneous color changes due to auto-oxidation. To limit these effects, the use of ferric ion ligands has been introduced. In this study, we compared the dosimetric optical response of Fricke gels made with xylenol orange and two alternative ligands suck us methylthymol blue and 5-sulfosalicylic acid.

1. – Introduction

The Fricke solution is an absolute dosimeter which can be combined with some metal-binding organic ligands that allow the assessment of the absorbed dose through visible light absorption measurements.

Gore and Kang (1984) suggested infusing the Fricke solution in a tissue-equivalent hydrogel matrix to obtain spatial dose maps by means of magnetic resonance imaging (MRI) [1, 2]. FGs have been amply investigated and they are considered promising 3D dosimeters, however, they suffer from two main drawbacks: the relatively fast diffusion of radiation-induced Fe^{3+} ions and auto-oxidation of Fe^{2+} ions during storage [3].

Ligands play a major role in this respect, and xylenol orange (XO) has been used extensively [4-6]. The intensity of the MRI signal of hydrogel in the presence of XO is lower than without XO, probably because XO either reduces the effect of oxidation of Fe^{2+}

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ions or, otherwise, hinders the exchange of energy between the spin and lattice slowing longitudinal relaxation [2]. This means that XO reduces the sensitivity of the dosimetric gels to X-rays and makes the images much noisier. As a consequence, other metallic indicators have been studied in order to improve the sensitivity of the gel dosimeters and further reduce ions diffusion [5].

In this study, ligands alternative to XO and their interactions with Fricke hydrogels were investigated. Among these ligands, methylthymol blue (MTB) [7], and 5-sulfosalicylic acid (SSA) [8] showed the required differentiation between optical absorbance of ferrous vs ferric ions. XO, MTB and SSA metal ions indicators were selected with the aim to compare their optical and dose-response profiles for dosimetric applications.

In the formulations under investigation, the free radical scavenger DMSO was added to minimize the auto-oxidation effect and improve the stability of the dose response [9]. Tissue-equivalent hydrogels based on poly(vinyl-alcohol) (PVA) chemical cross-linked with glutaraldehyde (GTA) were chosen for their remarkable dosimetric properties [10-12].

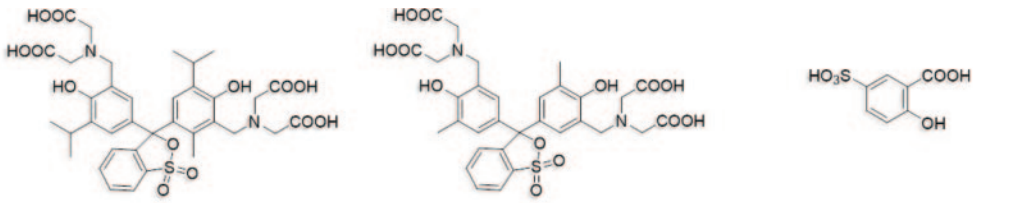
2. – Materials and methods

The PVA-GTA-FG dosimeters were prepared using these analytical grade compounds: 9.1% w/w PVA, 1.4% w/w DMSO, 2.0 mM ferrous ammonium sulfate; 26.6 mM of GTA, and 10 mM of sulfuric acid. The procedure for dosimeters preparation is described in detail elsewhere [13-15]. Figure 1 shows the structural formula and the concentration of the 3 studied ligands.

The PVA-GTA Fricke gel dosimeters were uniformly irradiated with 6 MV X–rays produced by a linear accelerator Varian Clinac-2100. The PVA-GTA Fricke gel dosimeters were exposed to different dose values up to 12 Gy. A UV-Vis spectrophotometer (Cary 100 UV-Vis, Agilent Technologies, Santa Clara, CA, USA) was used for Optical Absorbance (OA) measurements of the irradiated samples in the wavelength range 400–700 nm. OA spectra were acquired using ultrapure water as reference.

3. – Results and discussion

The XO–Fe^{2+} complex produces a well-known visible yellow color in the green-yellow spectral region of 500–600 nm (with a main absorbance peak around 585 nm) which can be measured spectrophotometrically. Upon irradiation, Fe^{2+} gets oxidized into Fe^{3+} as



(a)	(b)	(c)
Xylenol Orange (XO) - 0.2 mM	Methylthymol blue (MTB) - 0.2 mM	5-sulfosalicylic acid (SSA) - 3.5 mM

Fig. 1. – Chemical structures and concentration of used XO, MTB and SSA.

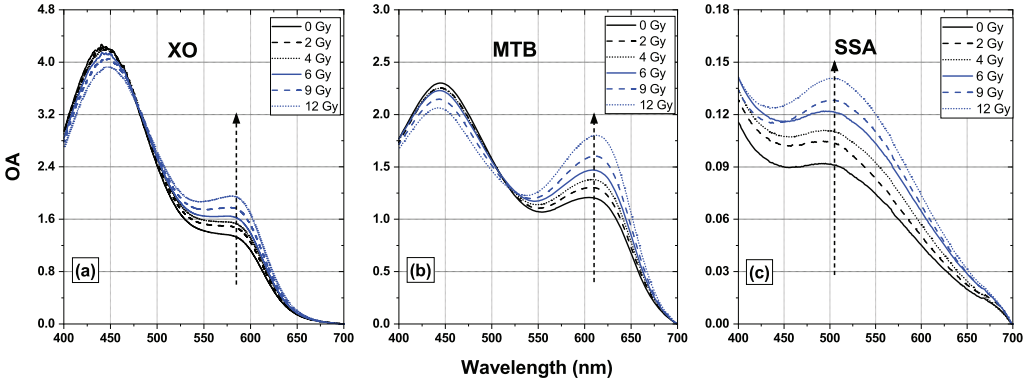


Fig. 2. – OA spectra of PVA-GTA Fricke gel dosimeters with (a) XO, (b) MTB and (c) SSA, irradiated up to 12 Gy using. Ultrapure water was used as reference.

a function of dose, turning the color of the gel from yellow to purple (absorbance peak around 430 nm), typical of the XO-Fe^{3+} complex (fig. 2(a)). The most representative XO–Fe^{3+} complexes present three different stoichiometric ratios between XO and ferric ions [13], sometimes making the dose evaluation complicated, especially at low doses, due to the overlapping of the absorption peaks of the different complexes.

In 2015, Penev and co-workers proposed the use of MTB dye [16], which is a structural analogue of conventional XO. As shown in fig. 1(b), the maximum absorbance of Fe^{3+}-MTB complex shifts at higher wavelength compared to Fe^{3+}–XO (610 nm *vs.* 585 nm). This means that the gel can be imaged with a red-light source enhancing the quality of optical images since the optical scattering in MTB system should be lower than in XO system. The last chelating agent taken into consideration is SSA [8].

SSA is a color agent able to chelate Fe^{2+} ions and producing a colorless hydrogel with transparent background. After irradiation, the Fe^{3+}–SSA complex is generated, and a visible color change from colorless to pink (optical absorbance peak at 505 nm) occurs as a function of the absorbed dose (fig. 2(c)). An interesting advantage in using SSA is the formation of a single Fe^{2+}-ligand complex with 1:1 stechiometry, reducing, consequentially, the optical artefacts of XO.

In order to evaluate the effect of the radiation on the optical absorbance, the dose-response curves of the dosimeters irradiated at various doses (from 0 to 12 Gy) at the specific absorption wavelengths of the three molecules are plotted in fig. 3. The Fricke dosimeter with MTB shows a similar linear dose response compared to the XO-containing gel with an R^2 of 0.9937 and of 0.9941 for MTB and XO samples respectively. However, PVA-GTA hydrogel with MTB possesses slightly higher sensitivity than PVA-GTA hydrogel with XO. On the other hand, SSA shows a good linearity in the dose-response curve ($R^2 = 0.9464$) but a lower sensitivity compared to both XO and MTB. Despite this result, SSA seems an interesting metallic indicator due to its simple chemical structure that opens the possibility of easily modifying the molecule and, consequently, finding alternative solutions for increasing optical sensitivity and reducing Fe^{3+} ions diffusion in the matrix.

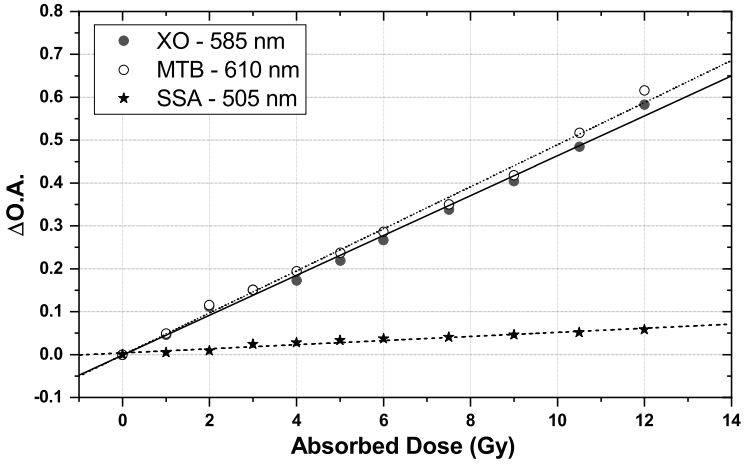


Fig. 3. – Dose-response curves of PVA-GTA hydrogel samples containing XO, MTB or SSA. Each point is the mean of absorbance data from at least three samples. Error bars (1 standard deviation) are smaller than the plot symbols. The dashed lines are the linear fit to the experimental data.

4. – Conclusions

This study compares three different Fe^{3+} chelating agents and the results show that XO and MTB have similar dose-response profiles, while SSA has lower sensitivity. While our study confirmed the overall advantages of using XO, it also suggests that SSA offers potential worthy of advance study. The future perspective is to chemically modify the SSA structure to improve its dosimetric response from both sensitivity and ions diffusion point of view and, afterwards, evaluate efficacy in clinical applications.

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