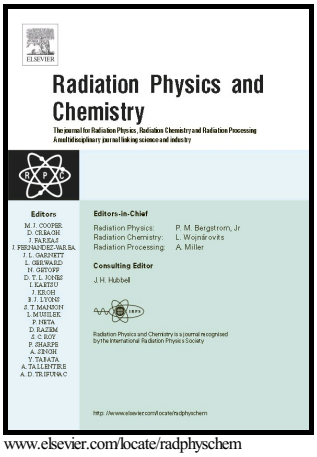

www.elsevier.com/locate/radphyschem

Does the gelation temperature or the sulfuric acid concentration influence the dosimetric properties of radiochromic PVA-GTA Xylenol Orange Fricke gels?

Salvatore Gallo, Grazia Gambarini, Ivan Veronese, Simona Argentiere, Marco Gargano, Luca Ianni, Cristina Lenardi, Nicola Ludwig, Emanuele Pignoli, Francesco d'Errico

PII: S0969-806X(18)31516-0
DOI: https://doi.org/10.1016/j.radphyschem.2019.03.014
Reference: RPC8210

To appear in: *Radiation Physics and Chemistry*

Received date: 31 December 2018
Revised date: 18 February 2019
Accepted date: 13 March 2019

Cite this article as: Salvatore Gallo, Grazia Gambarini, Ivan Veronese, Simona Argentiere, Marco Gargano, Luca Ianni, Cristina Lenardi, Nicola Ludwig, Emanuele Pignoli and Francesco d'Errico, Does the gelation temperature or the sulfuric acid concentration influence the dosimetric properties of radiochromic PVA-GTA Xylenol Orange Fricke gels?, *Radiation Physics and Chemistry,* https://doi.org/10.1016/j.radphyschem.2019.03.014

Does the gelation temperature or the sulfuric acid concentration influence the dosimetric properties of radiochromic PVA-GTA Xylenol Orange Fricke gels?

Salvatore Gallo[1,2,*], Grazia Gambarini[1,2], Ivan Veronese[1,2], Simona Argentiere[1], Marco Gargano[1], Luca Ianni[1], Cristina Lenardi[1,3], Nicola Ludwig[1], Emanuele Pignoli[4], Francesco d'Errico[5,6]

(1) Dipartimento di Fisica, Università degli Studi di Milano, Milano (Italy)

(2) Istituto Nazionale di Fisica Nucleare (INFN), sezione di Milano, Milano (Italy)

(3) Interdisciplinary Centre for Nanostructured Materials and Interfaces (CIMaINa), Milano (Italy)

(4) Fondazione IRCCS "Istituto Nazionale dei Tumori", Milano (Italy)

(5) Scuola di Ingegneria, Università degli Studi di Pisa, Pisa (Italy)

(6) School of Medicine, Yale University, New Haven, CT (USA)

Corresponding author:

**Salvatore Gallo*

Università degli Studi di Milano and INFN

via Giovanni Celoria 16 - 20133 Milano, Italy

e-mail: salvatore.gallo@unimi.it

Abstract

Purpose of this study is to test if possible effects of gelation temperature and pH on the cross-linking process between poly(vinyl alcohol) (PVA) and glutaraldehyde (GTA), have consequences on the dosimetric properties of PVA-GTA Xylenol Orange Fricke gel dosimeters. Therefore, dose-response curves and Fe^{3+} diffusion rate of PVA-GTA Fricke gel dosimeters prepared using different sulfuric acid concentrations and different gelation temperature were investigated by optical absorbance measurements.

The results demonstrated that the sulfuric acid concentration determines both the dose sensitivity of the PVA-GTA Xylenol Orange Fricke gel dosimeters and the interval of linearity of the dose-response curve.

Although the effects of gelation temperature and sulfuric acid concentration on the PVA-GTA cross-linking process may occur, no significant consequences on diffusion properties of PVA polymer network were observed. Indeed, Fe^{3+} diffusion rates in all investigated samples were very similar, and less than half of those achievable in Fricke gel dosimeters prepared with natural gel matrices like gelatin and agarose.

Keywords

Fricke gels; polyvinyl alcohol; glutaraldehyde; dosimetry.

1. Introduction

Quality assurance procedures required in modern radiation therapy would greatly benefit from the development of reliable and accurate dosimetric systems able to measure three-dimensional (3D) distributions of the radiation dose (Kron et al., 2016). Fricke gel (FG) dosimeters are promising tools for this purpose: they rely on the radiation-induced oxidation of Fe^{2+} ions to Fe^{3+} ions with a chemical yield proportional to the absorbed dose (Seco et al., 2014). The spatial distribution of Fe^{3+} is used to acquire a 3D image of the absorbed dose, by means of Magnetic Resonance Imaging (MRI) exploiting the different paramagnetic moments of Fe^{2+} and Fe^{3+} ions (Schulz et al., 1990; Marrale et al., 2014a, 2014b) or by means of optical imaging, using a suitable dye that produces a different optical absorbance when chelates Fe^{3+} ions, like Xylenol Orange sodium salt (XO) (Kelly et al., 1998; Babic et al., 2009; Abdelgawad et al., 2017) or Methylthymol blue (MTB) (Alves et al., 2018; Eyadeh et al., 2018a). Furthermore, due to the aqueous nature of the gel matrix, FGs are tissue equivalent and their response is largely independent of radiation quality and dose rate (Moussous et al, 2011; Soliman et al., 2017). Despite these advantages, FG dosimeters have not yet found routine application in the clinical environment. In fact, some drawbacks of FG dosimeters still represent challenges to overcome, making these systems an interesting topic of research. Firstly, irradiated FG dosimeters suffer from a gradual blurring over time of the spatial radiation dose patterns due to the diffusion of ferric ions, which eventually destroys the information on 3D dose distribution (Olsson et al.,

1992; Rae et al., 1996; Babu et al., 2019). Secondly, the dose-response of FG dosimeters is known to depend significantly on several elements that characterize their manufacture, including purity and composition of chemical reagents, as well as processing parameters during preparation and gelation (Del Lama et al., 2017). Consequently, the reproducibility level within the same laboratory and among different research groups is lower than that achievable for other dosimetric systems.

In an attempt to improve the dosimeter, poly(vinyl alcohol) (PVA) cross-linked by glutaraldehyde (GTA) was recently introduced as a matrix for the preparation of Fricke gels (Jin et al., 2012; Ruijia et al., 2010; d'Errico et al., 2017; Marini et al., 2017; Marrale et al., 2017; Boase et al., 2018; Smith et al., 2015; Gallo et al., 2019; Collura et al., 2018; Gallo et al., 2017; Eyadeh et al., 2018b; Rabaeh et al., 2018). PVA cross-linked with GTA is a hydrogel that, due to its crosslinks within the polymeric chains, absorb and retain large amount of water but do not dissolve in aqueous solutions (Hennink and van Nostrum, 2012).

When examining the PVA-GTA crosslinking reaction kinetics, possible effects of gelation temperature and pH on the cross-linking process and thus on the diffusion properties of the PVA polymer network cannot be excluded. Indeed, it is known that water molecules involved in the crosslinking of PVA with GTA may exist in different states, namely strongly bound, weakly bound or non-bound to the polymer network, depending on factors such as temperature, pH, and salinity (Gun'ko et al., 2017). In addition, environmental factors including temperature and pH affect the relative abundances of monomeric and polymeric species of glutaraldehyde in commercial aqueous solution that in turn may greatly influence the intra- and inter-molecular crosslinking reactions (Purss et al., 2005; Gohil et al., 2006; Hansen et al., 1997). Purpose of this study is to test if possible effects of gelation temperature and pH on the cross-linking process between poly(vinyl alcohol) and glutaraldehyde, have consequences on the dosimetric properties of PVA-GTA Xylenol Orange Fricke gel dosimeters. Therefore, dose-response curves and Fe^{3+} diffusion rate of PVA-GTA Xylenol Orange Fricke gel dosimeters prepared using different sulfuric acid concentrations and different gelation temperature were investigated by optical absorbance measurements.

2. Materials and methods

2.1. PVA-GTA Fricke gel dosimeters preparation

All batches of PVA-GTA-FG dosimeters were prepared using the following analytical grade compounds: 9.1 % w/w poly(vinyl alcohol) (PVA, Mowiol®18-88, Sigma Aldrich), 0.5 mM ferrous ammonium sulfate hexahydrate (FAS, $Fe(NH_4)_2(SO_4)_2*6H_2O$, Carlo Erba); 0.165 mM Xylenol Orange sodium salt (XO, $C_{31}H_{28}N_2Na_4O_{13}S$, Riedel-de Haën), 26.5 mM of glutaraldehyde (GTA, $C_5H_8O_2$, Sigma Aldrich), and various concentrations (18, 25, 50, and 100 mM) of sulfuric acid (SA, H_2SO_4, Suprapur®, Sigma Aldrich). The procedure for PVA-GTA Fricke gel dosimeters preparation, described in detail elsewhere (Gallo et al., 2019), is here briefly summarized.

The PVA solution (solution **1**) was prepared by dissolving dry PVA in 80% of the total ultrapure water (resistivity 18.2 MΩ·cm), obtained by a water purification system (Milli-Q® Direct, EMD Millipore, Germany) at 70 °C under moderate stirring (~150 rpm). After the complete dissolution, the PVA solution was allowed to cool down at room temperature (RT, *i.e.* 25°C). Afterwards, the Fricke-XO solution (solution **2**) was prepared by adding two-thirds of the total amount of sulfuric acid, ferrous ammonium sulfate hexahydrate, and Xylenol Orange sodium salt, in this order, into 10% of the total water volume. The GTA solution (solution **3**) was prepared by pouring the GTA and the remaining one-third of the total amount of sulfuric acid into the residual 10% of the water. Finally, the three solutions were mixed and poured into poly(methyl methacrylate) cuvettes with 10 mm optical path length, closed with polypropylene cuvette stoppers and sealed with Parafilm™.

In addition, a series of PVA-GTA-Fricke-Gel-Layer (FGL) dosimeters with 3 mm optical path and surface dimensions 11 cm x 5 cm were prepared. Details of FGLs geometry and assembling can be found elsewhere (Gambarini et al., 2004).

Different sets of PVA-GTA Xylenol Orange Fricke gel dosimeters were prepared to evaluate the dependence of their response on the sulfuric acid concentration. For these dosimeters, the gelation process occurred at the controlled temperature of 25°C, *i.e.* the temperature at which the solutions of PVA, of Fricke-XO, and of GTA were melted.

Another group of PVA-GTA Xylenol Orange Fricke gel dosimeters was prepared with the purpose of assessing the dependence of their response on the gelation temperature. Therefore, for the FG prepared with a sulfuric acid concentration equal to 25 mM, two other different gelation temperatures were considered: after the final melting at 25°C, some dosimeters were placed inside a refrigerator at 6°C and some others inside a thermostatic bath at 42°C. Details and characteristics of the various sets of PVA-GTA Xylenol Orange FG dosimeters prepared and the analyses performed are summarized in Table 1.

After the complete gelation, all the PVA-GTA Xylenol Orange Fricke gel dosimeters were kept refrigerated at a temperature of 6°C for one day and brought back to RT 1 hour before the irradiations.

Table 1 - Sets of PVA-GTA Xylenol Orange FG dosimeters prepared and used for the analyses of the dose-response and diffusion rate. Each set of dosimeters comprised at least 3 samples.

Set of dosimeters	Shape	Sulfuric acid concentration [mM]	Gelation temperature [°C]	Type of analysis
1	Cuvette	25	6	Influence of gelation temperature on the dose-response
2	Cuvette	25	25	
3	Cuvette	25	42	
4	Layer	25	6	Influence of gelation temperature on the diffusion rate
5	Layer	25	25	
6	Layer	25	42	
7	Layer	18	25	Influence of sulfuric acid concentration on the diffusion rate
8	Cuvette	18	25	Influence of sulfuric acid concentration on the dose-response
9	Cuvette	25	25	
10	Cuvette	50	25	
11	Cuvette	100	25	

2.2. Dose-response measurements

PVA-GTA Xylenol Orange FG dosimeters inside cuvettes were uniformly irradiated with an IBL 437C ^{137}Cs blood irradiator at the "Fondazione IRCCS Istituto Nazionale dei Tumori" of Milano (Italy). For the sets of dosimeters 1-3 (see table 1) the investigated dose interval was 6.4-24.0 Gy. For the sets of dosimeters 8-11 (see table 1) the interval was extended to 4.8-36.0 Gy. For each dose value, at least triplicates of samples were irradiated.

An UV-Vis spectrophotometer (Cary 100 UV-Vis, Agilent Technologies, Santa Clara, CA, USA) was employed for optical absorbance measurements of the irradiated samples in the wavelength range 350-750 nm. Optical absorbance spectra were acquired using as reference one cuvette filled with ultrapure water. Furthermore, since in the conventional gel dosimetry the absorbed dose is correlated to optical absorbance variation of the dosimeters following irradiation, also one un-irradiated sample for each batch was used as reference. According to the indications in the literature (d'Errico et al., 2017; Marini et al., 2017), the measurements were performed about one hour after the irradiation and the maximum optical absorbance values at 585 nm were used for reconstructing the dose-response curves.

2.3. Diffusion rate measurements

Diffusion rate measurements were performed using FGLs prepared using different gelation temperatures and different sulfuric acid concentration (see Table 1). It is worth noting that at RT the final melted solution prepared with sulfuric acid concentration higher than 25 mM was excessively viscous and could not be poured into the layer structures.

The same procedure recently adopted to study the diffusion rate in gelatin Fricke-Xylenol-Orange gel dosimeters loaded with laponite was used. Details of the experimental set-up and data analyses can be found elsewhere (Gallo et al., 2018). Briefly, two FGLs for each set of dosimeters were irradiated simultaneously to a dose of 8 Gy with X-rays generated by an X-rays tube (Gilardoni Radiolight, Italy) operating at 80 kV and 5 mA. During the irradiation, half of the area of each FGLs was partially covered with a 2 mm thick layer of lead in order to attenuate the beam (attenuation > 99.5 % at the maximum X-rays energy of 80 keV) thus to produce a steep dose gradient.

Light transmittance images of each FGL were acquired just before irradiation and at regular intervals up to 6 hours post-irradiation, using a laboratory-made equipment consisting of a planar white-light illuminator (model LLUB, by PHLOX®) and a charge coupled device (CCD, model uEye, by IDS®) with a narrow band-pass filter centered at 585 nm (FWHM of 10 nm).

It must be pointed out that for the purpose of this study, *i.e.* to investigate possible differences in the Fe^{3+} diffusion rate in FG prepared under different conditions, neither the radiation dose value, nor the quality of the radiation beam are elements expecting to influence the results. Therefore, for sake of experimental

convenience, the FGLs were irradiated using an X-rays tube located in the same department of the optical detector used for acquiring the light transmittance images, thus to optimize the scheduling of the experiments. Similarly, the delivered dose was chosen for originating optical density (OD) values in the FGLs clearly distinguishable from background values. For each FGL, the differences of optical density Δ(OD) were calculated on a pixel by pixel basis and the profile of Δ(OD) across the steep dose gradient was derived, together with its temporal variation due to diffusion phenomena. Then, each Δ(OD) profile was fitted using an inverse square root function (ISQR) (Kron et al., 1997) of the form:

$$A(x) = A_2 + \frac{1}{2}(A_1 - A_2)\left[1 + \frac{x-C}{\sqrt{(x-C)^2+n}}\right] \qquad (1)$$

where *A(x)* is the Δ(OD) as a function of position *x* along the layer axis, A_1 and A_2 are the maximum and minimum Δ(OD) values, *n* is the curvature parameter that varies with time while the initial step distribution diffuses, and *C* is a parameter used to account for possible lateral shifts of the inflection point. According to the procedure described in the same paper (Kron et al., 1997), from the analysis of the change of the curvature parameter *n* with time *t*, the diffusion rate *D* can be obtained as:

$$D = \frac{(\sqrt[3]{4}-1)}{4ln2}\frac{n}{t} \approx 0.212\frac{n}{t} \qquad (2)$$

3. Results and discussion

3.1. Optical absorbance spectra

Fig. 1 shows typical optical absorbance spectra of PVA-GTA Xylenol Orange FG dosimeters prepared at the gelation temperature of 25°C, using a sulfuric acid concentration of 25 mM, and irradiated at increasing doses. Spectra of panels (a) and (b) were measured using an un-irradiated sample and ultrapure water as reference, respectively.

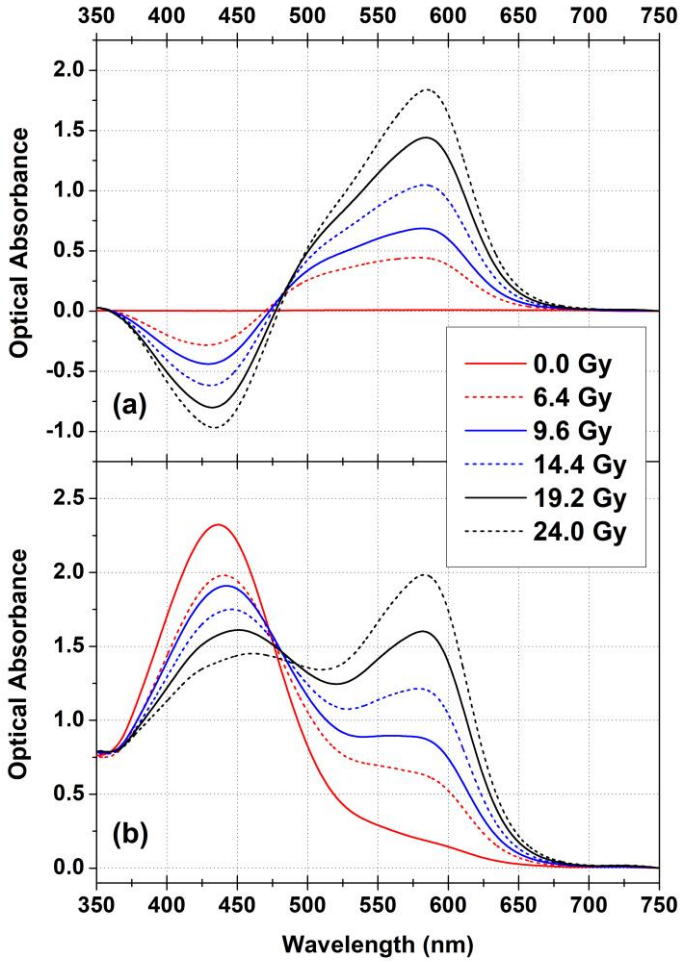

Figure 1 – Typical optical absorbance spectra of PVA-GTA Xylenol Orange Fricke gel dosimeters irradiated to increasing doses. (a) An un-irradiated sample was used as reference. (b) Ultrapure water was used as reference.

The optical absorbance spectra of the irradiated FG dosimeters showed the broad absorption band centered around 585 nm, due to the formation of XO-Fe^{3+} complexes. The intensity of this signal increased while increasing radiation dose, with a consequent reduction of the absorption band at 430 nm, due to the XO molecules not bound with ferrous ions. Although it is known that the XO optical properties are influenced by pH and chemical features of the medium (Gay et al., 1999; Liosi et al., 2017), the shapes of the optical absorbance spectra of PVA-GTA Xylenol Orange FG dosimeters were very similar to those of FG dosimeters prepared with natural gelation matrices (Gallo et al., 2018; Davies and Baldock, 2008; Gambarini et al., 2017). This suggested that the tested different gel matrices have comparable effects on the formation and properties of the XO-Fe^{3+} complexes.

3.2. Influence of gelation temperature on the dose-response curves

The dose-response curves of the PVA-GTA Xylenol Orange Fricke gel dosimeters prepared using different gelation temperatures and irradiated to different doses were obtained from the optical absorbance values at the wavelength of 585 nm. The experimental data are shown in Fig.2, together with straight lines fitted to each dataset. The values of the fitting parameters are summarized in Table 2.

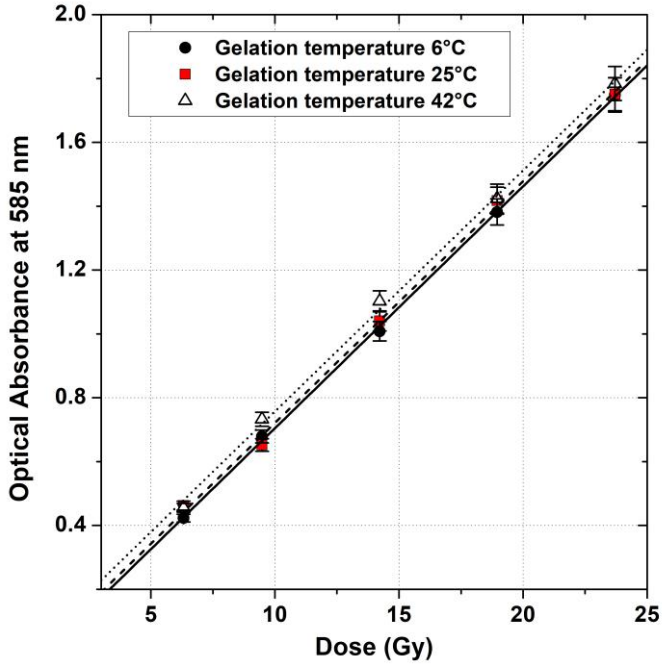

Figure 2 - Optical absorbance at 585 nm of PVA-GTA Xylenol Orange FG dosimeters irradiated at increasing doses and prepared using the different gelation temperatures of 6°C (black dots), 25°C (red squares) and 42°C (white triangles). The error bars correspond to one standard deviation (1 SD). The lines are the weighed-linear fits to the experimental data.

Table 2 - Sensitivity to absorbed dose of PVA-GTA Xylenol Orange FG dosimeters prepared using different gelation temperatures.

Set of dosimeters	**Sulfuric acid concentration [mM]**	**Gelation temperature [°C]**	**Sensitivity [Gy^{-1}]**	**R^2**
1	25	6	0.077±0.001	0.9997
2	25	25	0.077±0.002	0.9993

3	25	42	0.076±0.002	0.9993

The slope values of the fitted straight lines, which indicate the sensitivity of the FG dosimeters to the radiation dose, agreed within experimental errors and they were similar to the values reported in the literature about PVA-GTA Xylenol Orange FG dosimetry (d'Errico et al., 2017; Marini et al., 2017; Eyadeh et al., 2018b). It is worth noting that a sensitivity of the order of 0.077 Gy^{-1} was also obtained in previous studies performed with FG dosimeters based on natural gel matrices (Marini et al., 2017; Gallo et al., 2018).

Generally, the preparation of FGs using traditional natural matrices involves the dissolution of the gelation agent in water at temperatures above 90 °C and 50 °C for agarose and gelatine, respectively. Subsequently, the Fricke solution is added at a lower mixing temperature, *i.e.* before the gel solution starts to set. Accordingly, gelation is achieved by cooling. It was observed that both the mixing temperature and the cooling rate influenced the radiation dose sensitivity of these FG dosimeters (Olsson et al., 1991; Tarte et al., 1996). The dependence of gel sensitivity on cooling rate might have important consequences in case of production of large gel dosimeters acting also as phantoms (*e.g.* with volume of one liter or more). Indeed, for such volumes the cooling rate at the edge of the dosimeter might be much faster than at its center, causing a non-uniform performance across the volume (De Deene et al., 2007; Welch et al., 2017). PVA-GTA matrix has the advantage of not requiring temperature gradients for gelation. Furthermore, the sensitivity to radiation dose of PVA-GTA Xylenol Orange FG was found to be independent of the gelation temperature. Such evidence paved the way to the production of PVA-GTA Xylenol Orange FG phantoms free from heterogeneities over large volumes.

3.3. Influence of gelation temperature on Fe^{3+} diffusion rate

Fig. 3 shows examples of Δ(OD) profiles measured approximately 1 hour and 6 hours post-irradiations, related to FGL samples of sets 4, 5, and 6 (see Table 1). The steep dose gradient is evident in all the curves, as well as its progressive smoothing as a consequence of the gradual diffusion of ferric ions.

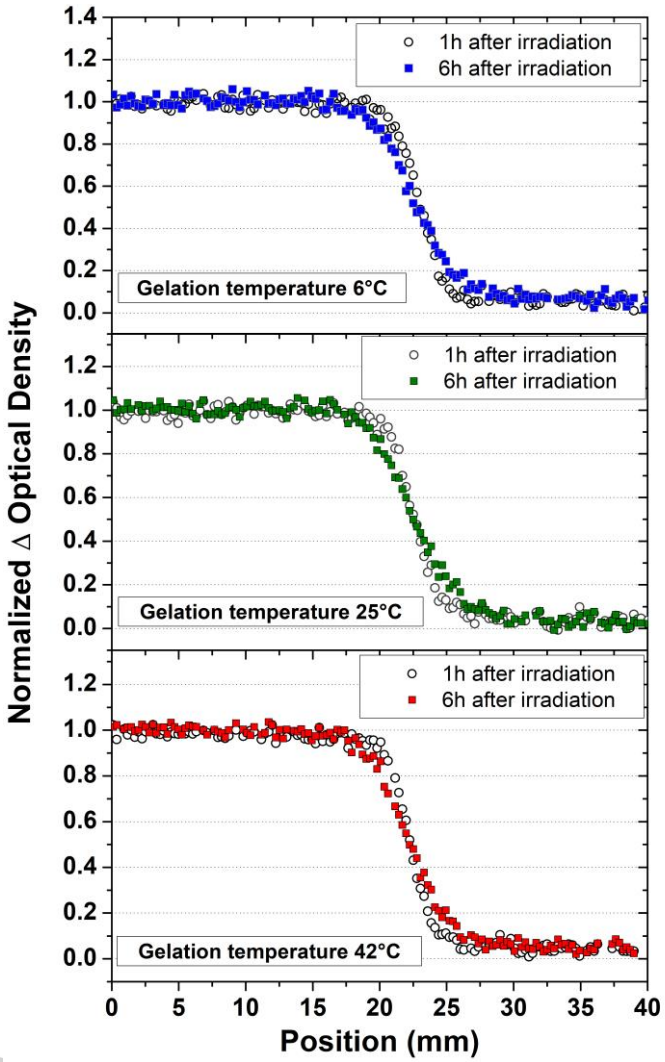

Figure 3 - Examples of normalized Δ(OD) profiles of PVA-GTA Fricke gels prepared using different gelation temperatures, measured at different post-irradiation times. Normalized profiles were obtained by considering the mean values of Δ(OD) measured between 0 and 10 mm.

The rate of variation of the profile shape was independent of the gelation temperature, as demonstrated by the temporal dependence of the curvature parameter (*n*) observed for the three gel samples (Fig. 4).

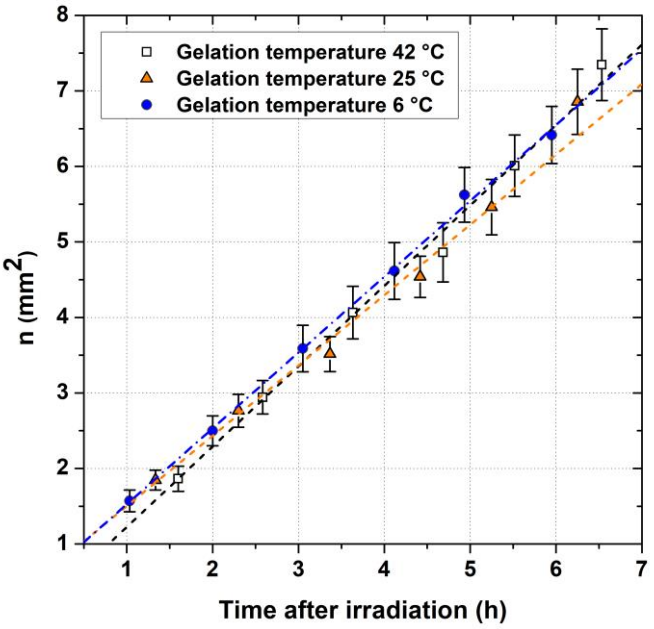

Figure 4 - Curvature parameter *n* vs post-irradiation time obtained by fitting Δ(OD) profiles of PVA-GTA Xylenol Orange FG prepared using different gelation temperatures. The error bars correspond to one standard deviation (1 SD).

A summary of the results about diffusion phenomena is given in Table 3.

Table 3 – Diffusion rates in the different FGLs studied.

Set of dosimeters	Sulfuric acid concentration [mM]	Gelation temperature [°C]	Diffusion rate D (mm^2/h)
4	25	6	0.25±0.04
5	25	25	0.23±0.02
6	25	42	0.23±0.03

No significant differences were observed between the diffusion rates of the gel dosimeters prepared using different gelation temperatures, indicating that the use of different gelation temperatures did not affect the Fe^{3+} diffusion rates in PVA-GTA FGL dosimeters. The obtained values are less than half the diffusion rates measured in gelatine-based FG dosimeters using the same experimental approach (Gallo et al., 2018), and also available in the literature (Rae et al., 1996). These results confirm the improved dosimetric performance of the PVA-GTA gel matrix over natural gel matrices.

3.4. Influence of sulfuric acid concentration

The diffusion rates measured in PVA-GTA FGL dosimeters prepared at 25°C with the sulfuric acid concentrations of 18 and 25 mM (sets 7 and 5 in Table 1) has resulted to be equal to 0.24±0.02 and 0.23±0.02 mm^2/h, respectively. Therefore, Fe^{3+} diffusion phenomena proved not to be influenced by sulfuric acid concentration in the investigated interval, suggesting no significant changes in the overall crosslinking mechanism of PVA with GTA. This agrees with previous analyses of the reaction mechanism of crosslinking of PVA with GTA, in the presence of sulfuric acid as catalyst (Kim et al., 1994), where the rate-determining step is considered to be the nucleophilic attachment of hydroxyl groups onto protonated aldehydic groups. Since the sulfuric acid molecules protonate the aldehydic groups, the higher the sulfuric acid concentrations, the lower the gelation temperature. Further evidence of the dependence of the gelation reaction kinetics on proton concentration were reported by *Hansen et al*. (Hansen et al., 1997), considering the decay rate of aldehyde proton peak in NMR studies. Moreover, since all samples were prepared under acidic conditions, it may be excluded that pH has a significant influence on de-acetylation reaction and in turn on the crosslinking process. In fact, poly(vinyl alcohol) is produced by polymerization of Vinyl acetate to Poly(vinyl acetate) and subsequent hydrolysis to PVA. The de-acetylation reaction is incomplete and results in PVA polymers with different degrees of hydrolysis and therefore different solubility and chemical properties. At basic pH values, hydrolization of remaining acetate groups occurred and the increased availability of hydroxyl groups may affect the crosslinking of PVA with GTA (Mansur et al., 2008).

On the other hand, changes in sulfuric acid concentration proved to greatly influence the dosimetric properties of the PVA-GTA FG dosimeters in terms of dose-response. In Fig. 5, optical absorbance values measured at 585 nm in dosimeters prepared with different sulfuric acid concentrations (sets 8-11 in Table 1) are plotted versus the absorbed dose. The linear fits of each dataset in the 4.8-30.0 Gy dose range are also shown in Fig. 5. The corresponding slope values are given in Table 4. PVA-GTA FG dosimeters prepared with 100 mM sulfuric acid exhibited a linear dose-response curve up to 36.0 Gy, *i.e*. the whole investigated range. Conversely, the dose-response curves of dosimeters prepared with lower sulfuric acid concentrations seem to approach saturation just above 30.0 Gy. A wider range of linearity is seen to correspond to a lower sensitivity: a progressive decrease of sensitivity from approximately 0.082 Gy^{-1} down to 0.025 Gy^{-1} was

obtained by increasing the sulfuric acid concentration from 18 to 100 mM. Such findings were previously observed in FG dosimeters prepared with natural gel matrices (Schulz et al., 1990; Davies and Baldock, 2008; Bero et al., 2001; Gohary et al., 2016; Del Lama et al., 2017).

The agreement of our data with previous studies demonstrates that proton concentration has a strong influence in PVA-GTA gel matrices in regulating the redox equilibria and thus the total amount of Fe^{3+}, as well as the equilibrium of XO-Fe^{3+} complexes with different stoichiometry (Gay et al., 1999; 2002, Liosi et al., 2017). Therefore, a strict control of the sulfuric acid concentration in PVA-GTA Xylenol Orange FG dosimeters appears to be essential not so much for regulating the crosslinking density between PVA and GTA, as for achieving the desired radiation dose sensitivity and linearity.

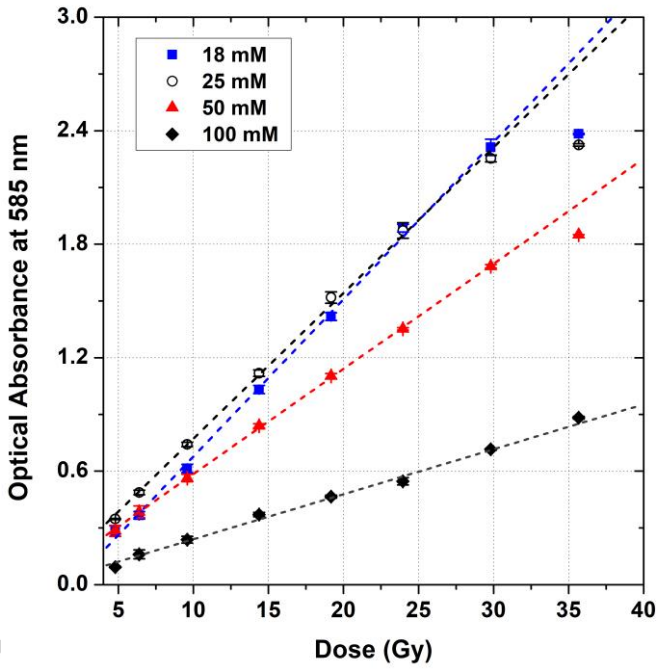

Figure 5 - Optical absorbance at 585 nm of PVA-GTA Xylenol Orange FG dosimeters prepared using different sulfuric acid concentrations and irradiated at increasing doses. The error bars correspond to one standard deviation (1 SD). The lines are the linear fits to the experimental data in the dose interval 4.8-30.0 Gy.

Table 4 - Sensitivity to absorbed dose of PVA-GTA Xylenol Orange FG dosimeters prepared using different sulfuric acid concentrations.

Set of dosimeters	Sulfuric acid concentration [mM]	Gelation temperature [°C]	Sensitivity [Gy^{-1}]	R^2
8	18	25	0.082±0.002	0.9998
9	25	25	0.078±0.002	0.9993
10	50	25	0.057±0.001	0.9996
11	100	25	0.025±0.002	0.9993

4. Conclusions

A study was carried out on the influence of the gelation temperature and the sulfuric acid concentration used to produce Xylenol Orange Fricke gel dosimeters based on PVA-GTA matrices. Similarly, to traditional Fricke gel dosimeters, also in PVA-GTA Xylenol Orange Fricke gel dosimeters the sulfuric acid concentration determines both the sensitivity of the dosimeters to absorbed dose, and the interval of linearity of the dose-response curve.

Although effects of gelation temperature and pH on the PVA-GTA cross-linking process may occur, no significant consequences on the Fe^{3+} diffusion properties within a PVA polymer network were observed. In fact, Fe^{3+} diffusion rates measured in all investigated samples were found to be very similar and less than half of those achievable in traditional Fricke gel dosimeters prepared with gelatin and agarose, confirming the higher stability of PVA over natural gel matrices. This characteristic, together with the independence of the dose-response curve of the PVA-GTA Xylenol Orange FG dosimeters of the gelation temperature over a wide temperature range, supports the potential of these gels for the manufacture of large phantoms for 3D dose mapping.

Acknowledgments

The authors wish to thank Daniela Bettega, Paola Calzolari, Andrea Marini, and Luigi Lazzeri for their useful comments and suggestions. The authors are also grateful to Luca Marrone for the irradiation of the samples at the "Fondazione IRCCS Istituto Nazionale dei Tumori".

References

Abdelgawad, M.H., Soliman, Y.S., ElGohry, M.I., Eldib, A.A., Ma C.C., Desouky, O.S., 2017. Measurements of radiotherapy dosimetric parameters using Fricke gel dosimeter. Biomed. Phys. Eng. Express 3, 025021.

Alves A., de Almeida S., Sussuchi M., Lazzeri L., d'Errico F., Souza S., 2018. Investigation of chelating agents/ligands for Fricke gel dosimeters Radiation Physics and Chemistry 150 151-156.

Babic, S., McNiven, A., Battista, J., Jordan, K., 2009. Three-dimensional dosimetry of small megavoltage radiation fields using radiochromic gels and optical CT scanning. Physics in medicine and biology 54(8), 2463–2481.

Babu S., Peace S., Rafic K., Raj E., Christopher S., Ravindran P., 2019. Escalation of optical transmittance and determination of diffusion co-efficient in low-bloom strength gelatin-based Fricke gel dosimeters Radiation Physics and Chemistry 156, 300-306.

Bero, M., Gilboy, W., Glover P., 2001. Radiochromic gel dosemeter for three-dimensional dosimetry. Radiation Physics and Chemistry 61, 433–435.

Boase, N., Smith, S., Masters, K., Hosokawa, K., Crowe, S., Trapp J., 2018. Xylenol orange functionalised polymers to overcome diffusion in Fricke gel radiation dosimeters. Reactive and Functional Polymers 132, 81-88.

Collura, G., Gallo, S., Tranchina, L., Abbate, B., Bartolotta, A., d'Errico, F., Marrale, M., 2018. Analysis of response of PVA-GTA Fricke-gel dosimeters through clinical magnetic resonance imaging. Nucl. Instr. Meth. B 414, 146-153.

d'Errico, F., Lazzeri, L., Dondi, D., Mariani, M., Marrale, M., Souza, S., Gambarini G., 2017. Novel GTA-PVA Fricke gels for three-dimensional dose mapping in radiotherapy. Radiat. Meas. 106, 612-617.

Davies, J. and Baldock, C., 2008. Sensitivity and stability of the Fricke-gelatin-xylenol orange gel dosimeter. Radiation Physics and Chemistry 77(6), 690–696.

De Deene, Y., Pittomvils, G., Visalatchi S., 2007. The influence of cooling rate on the accuracy of normoxic polymer gel dosimeters. Phys. Med. Biol. 52, 2719–2728.

Del Lama, L., Petchevist, P., de Almeida, A., 2017. Fricke Xylenol Gel characterization at megavoltage radiation energy. Nucl. Instr. Meth. B 394, 89-96.

Eyadeh M., Rabaeh K., Hailat T., Aldweri F., 2018a. Evaluation of ferrous Methylthymol blue gelatin gel dosimeters using nuclear magnetic resonance and optical techniques Radiation Measurements 108 26-33.

Eyadeh, M., Rabaeh, K., Hailat, T., Al-Shorman, M., Aldweri, F., Kanan, H., Awad S., 2018b. Investigation of a novel chemically cross-linked fricke-Methylthymol bluesynthetic polymer gel dosimeter with glutaraldehyde cross-linker. Radiation Measurements 118, 77–85.

Gallo, S., Collura, G., Longo, A., Bartolotta, A., Tranchina, L., Iacoviello, G., d'Errico, F., Marrale, M., 2017. Preliminary MR relaxometric analysis of Fricke-gel dosimeters produced with Poly-vinyl alcohol and glutaraldehyde. Nuclear Technology & Radiation Protection 32(3), 242-249.

Gallo, S., Cremonese, L., Gambarini, G., Ianni, L., Lenardi, C., Argentiere, S., Bettega, D., Gargano, M., Ludwig, N., Veronese, I., 2018. Study of the effect of laponite on Fricke xylenol orange gel dosimeter by optical techniques. Sensors and Actuators B: Chemical 272, 618-625.

Gallo, S., Artuso, E., Brambilla, M., Gambarini, G., Lenardi, C., Monti, A., Torresin, A., Pignoli, E., Veronese, I., 2019. Characterization of radiochromic PVA-GTA Fricke gels for dosimetry in X-rays external radiation therapy. Journal of Physics D: Applied Physics (Provisionally Accepted).

Gambarini, G., Birattari, C., Mariani, M., Marchesini, R., Pirola, L., Prestini, P., Sella, M., Tomatis S., 2004. Study of light transmittance from layers of Fricke-xylenol-orange-gel dosimeters. Nucl. Instr. Meth. B 213, 321–324.

Gambarini, G., Veronese, I., Bettinelli, L., Felisi, M., Gargano, M., Ludwig, N., Lenardi, C., Carrara, M., Collura, G., Gallo, S., et al., 2017. Study of optical absorbance and MR relaxation of Fricke xylenol orange gel dosimeters. Radiat, Meas. 106, 622-627.

Gay, C., Collins, J., Gebiki J., 1999. Determination of Iron in Solutions with the Ferric–Xylenol Orange Complex. Anal. Biochem. 273(2), 143-148.

Gay, C. and Gebicki, J., 2002. Perchloric Acid Enhances Sensitivity and Reproducibility of the Ferric–Xylenol Orange Peroxide Assay. Anal. Biochem. 304(1), 42-46.

Gohary, M., Solimam, Y., Amin, E., Abdel Gawad, M., Desouky, O., 2016. Effect of perchloric acid on the performance of the Fricke xylenol gel dosimeter. Appl. Radiat. Isot. 113, 66-69.

Gohil, J., Bhattacharya, A., Ray P., 2006. Studies on the crosslinking of Poly(VinylAlcohol). Journal of Polymer Research, 13(2), 161–169.

Gun'ko, V., Savina, I., Mikhalovsky S., 2017. Properties of Water Bound in Hydrogels. Gels 3(4), 37.

Hansen, E., Holm, K., Jahr, D., Olafsen, K., Stori A., 1997. Reaction of poly(vinyl alcohol) and dialdehydes during gel formation probed by 1H n.m.r.—a kinetic study. Polymer 38(19), 4863-4871.

W.E. Hennink, W.E., van Nostrum, C.F., 2012. Novel crosslinking methods to design hydrogels. Advanced Drug Delivery Reviews 64, 223–236.

Jin, C., Chen, J., Yang, L., Luo, W., Wu, G., Zha Y., 2012. Effect of DMSO on the sensitivity and diffusion of FPGX gel dosimeter. Radiation Physics and Chemistry 81, 879–883.

Kelly, R.U., Jordan, K. J., Battista J., 1998. Optical CT reconstruction of 3D dose distributions using the ferrous benzoic-xylenol (FBX) gel dosimeter. Med. Phys. 25, 1741–1750.

Kim, K., Lee, S., N.W., 1994. Han, Kinetics of crosslinking reaction of PVA membrane with glutaraldehyde. Korean J. Chem. Eng. 11(1), 41-47.

Kron, T., Jonas, D., Pope, J., 1997. Dual gel samples for diffusion measurements in gels. Magn. Reson. Imaging 15, 211-221.

Kron, T., Lehmann, J., Greer, P.B., 2016. Dosimetry of ionising radiation in modern radiation oncology. Phys. Med. Biol. 61(14), 167-205.

Liosi, G., Dondi, D., Vander Griend, G., Lazzaroni, S., d'Agostino, Mariani, M., 2017. Fricke-gel dosimeter: overview of Xylenol Orange chemical behavior. Radiation Physics and Chemistry 140, 74-77.

Mansur, H., Sadahira, C., Souza, A., Mansur A., 2008. FTIR spectroscopy characterization of poly(vinyl alcohol) hydrogel with different hydrolysis degree and chemically crosslinked with glutaraldehyde. Materials Science and Engineering: C, 28(4), 539-548.

Marini, A., Lazzeri, L., Cascone, M., Ciolini, R., Tana, L., d'Errico F., 2017. Fricke gel dosimeters with low-diffusion and high-sensitivity based on a chemically cross-linked PVA matrix. Radiat. Meas. 106, 618-621.

Marrale, M., Collura, G., Gallo, S., Nici, S., Tranchina, L., Abbate, B., Marineo, S., Caracappa, S., d'Errico F., 2017. Analysis of spatial diffusion of ferric ions in PVA-GTA gel dosimeters analyzed via magnetic resonance imaging. Nucl. Instr. Meth. B 396, 50–55.

Marrale, M., Brai, M., Longo, A., Gallo, S., Tomarchio, E., Tranchina, L., Gagliardo, C., d'Errico F., 2014a. NMR relaxometry measurements of Fricke gel dosimeters exposed to neutrons. Radiation Physics and Chemistry 104, 424-428.

Marrale, M., Brai, M., Gagliardo, C., Gallo, S., Longo, A., Tranchina, L, Abbate, B., Collura, G., Gallias, K., Caputo, V., Lo Casto, A., Midiri, M., d'Errico F., 2014b. Correlation between ferrous ammonium sulfate concentration, sensitivity and stability of Fricke gel dosimeters exposed to clinical X-ray beams. Nucl. Instr. Meth. B 335, 54–60.

Moussous, O., Khoudri, S., Benguerba M., 2011. Characterization of a Fricke dosimeter at high energy photon and electron beams used in radiotherapy. Austr. Phys. Eng. Sci. Med. 34(4), 523-528.

Olsson, L., Appleby, A., Sommer J., 1991. A new dosimeter based on ferrous sulphate solution and agarose gel, Applied radiation and isotopes. 42(11), 1081-1086.

Olsson, L.E., Petersson, S., Westrin, B., Fransson, A., Nordell B., 1992. Diffusion of ferric ions in agarose dosimeter gels. Phys. Med. Biol. 37, 2243–2252.

Purss, H., Qiao, G., Solomon D., 2005. Effect of "glutaraldehyde" functionality on network formation in poly(vinyl alcohol) membranes. Journal of App. Polymer Science, 96, 780–792.

Rabaeh, K., Eyadeh, M., Hailat, T., Aldweri, F., Alheet, S., Eid R., 2018. Characterization of ferrous-methylthymol blue-polyvinyl alcohol gel dosimeters using nuclear magnetic resonance and optical techniques. Radiation Physics and Chemistry 148, 25–32.

Rae, W., Willemse, C., Lötter, M., Engelbrecht, J., Swarts J., 1996. Chelator effect on ion diffusion in ferrous-sulfate-doped gelatin gel dosimeters as analyzed by MRI. Med. Phys. 23(1), 15–23.

Ruijia, X., Liming, Y., Jie, C., Qiang, Q., Liang, R., Fangqi, C., Wenyun, L., Xiaoqing, D., Yuanzi, Z., Guohua W., 2010. Preparation and characterization of FPGX hydrogel dosimeters. Nuclear Science and Techniques 21, 60–62.

Schulz, R.J., deGuzman, A.F., Nguyen, D.B., Gore, J.C., 1990. Dose-response curves for Fricke-infused agarose gels as obtained by nuclear magnetic resonance. Phys. Med. Biol. 35(12), 1611-1622.

Seco, J., Clasie, B., Partridge, M., 2014. Review on the characteristics of radiation detectors for dosimetry and imaging. Phys. Med. Biol. 59(20), 303-347.

Smith, S., Masters, K., Hosokawa, K., Blinco, J., Crowe, S., Kairn, T., Trapp J., 2015. Technical Note: Preliminary investigations into the use of a functionalised polymer to reduce diffusion in Fricke gel dosimeters. Medical Physics. 42(12), 6798-6803.

Soliman, Y.S., Gohary, M.I.E., Gawad, M.H.A., Amin, E.A., Desouky, O.S., 2017. Fricke gel dosimeter as a tool in quality assurance of the radiotherapy treatment plans. Applied Radiation and Isotopes 120, 126-132.

Tarte, B., Jardine, P., Van Doorn T., 1996. Laser-scanned agarose gel sections for radiation field mapping. International Journal of Radiation Oncology Biology Physics, 36(1), 175-179.

Welch, M., and Jaffray, D., 2017. The correction of time and temperature effects in MR-based 3D Fricke xylenol orange dosimetry. Phys. Med. Biol. 62, 3221–3236.

Highlights

- Gelation temperature and sulfuric acid concentration do not affect the diffusion rate of Fe^{3+} in PVA-GTA XO Fricke gels.
- The dose response curve of the PVA-GTA XO Fricke gels are independent of the gelation temperature.
- Sulfuric acid concentration determines the sensitivity and the interval of linearity of the dose response in PVA-GTA XO Fricke gels.