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Influence of saccharides on the dosimetric properties of PVA-GTA Fricke gels

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Summary. — The Fricke gels (FG) composition has been modified over the years in order to improve their dosimetric characteristic for spatial dose evaluation in radiotherapy. Some problems have limited the clinical use of FG and still represent significant challenges for the scientific community working in the field of gel dosimetry. With this study, the effects of saccharides like sucrose and glucose on the dosimetric properties of Fricke gels based on poly(vinyl-alcohol) (PVA) as gelling agent and glutaraldehyde (GTA) as cross-linker have been tested. The dose-response curves of PVA-GTA Fricke gel dosimeters prepared using different sucrose and glucose concentrations were investigated by optical absorbance measurements. The shape of the optical absorbance spectra of the gel dosimeters in the wavelength interval 360–720 nm have shown a slight dependence on the saccharides concentration and varied with the absorbed dose. The results demonstrated that the use of different concentrations of sucrose and glucose does not produce significant dosimetric consequences in the interval of linearity (0–16 Gy) of the dose-response curve of the PVA-GTA Fricke gel dosimeters.

1. – Introduction

The Fricke gel (FG) dosimeters have been long studied thanks to the dosimetric potential of the ferrous sulphate solution [1] (for which the radiation-induced production of ferric ions from ferrous ions depends on the irradiation dose) and the rigidity of the gel matrix [2], which prevents the ferric ions from easily diffusing in the solution. This is an advantage with respect to an aqueous solution since this last does not preserve spatial information on the dose-dependent changes of the local magnetic properties related to the local ferric ions concentration. The two above-mentioned features have made the Fricke

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gel dosimeters ideal candidates for performing 3D reconstruction of dose distribution, particularly useful in the planning phase of radiation treatments [3].

A radiation-sensitive device able to map a 3D distribution of the dose delivered in a clinical setting must combine suitable dosimetric features with the ability of capturing and storing the information on local variations induced by the delivered dose [4]. Dosimetric materials of different nature have been studied over the decades allow to obtain 1D or 2D dose measurements [5-10]. Therefore, only gel dosimeters are the best candidates for 3D dosimetry [11].

The recent literature includes several experiments on Fricke gels aimed at optimizing the recipe to increase the sensitivity to dose and/or the local stability of the radiation-produced ferric ions and applications for clinical beam dosimetry, in particular, many experiments have pursued precisely the development of a recipe for Fricke gels that would optimize their performance as dosimeters for reading by magnetic resonance imaging (MRI) and/or optical spectrophotometers [12-16]. For this reason, optical indicators have been added to the Fricke gel.

The Xylenol Orange sodium salt (XO) is one of the metallic ions optical indicators most commonly used. The Fe^{3+} binds to XO forming the complex (XO-Fe^{3+}) that can be measured by the spectrophotometric technique. This complex absorbs most strongly in the green-yellow spectral region (500–600 nm) and so the effect of the radiation exposure to the gel is visible to naked eye and easy documentable [17, 18]. Additionally, the effect of the addition of glucose, sucrose, starch and locust bean on the response of Fricke gel dosimetry have been studied [19]. In this work, the authors have found that the addition of saccharides to Fricke gels (prepared using the agarose as a gelling agent and adding XO) eliminates the cooling rate dependence of their dose sensitivity. This has implications for uniform dose sensitivity throughout large gel volumes. Also, the presence of saccharides leads to higher dose sensitivity, which can be further enhanced with oxygenation. A disadvantage of the higher sensitivity gels however is increased rates of unwanted ferrous ion thermal oxidation.

The recent development and optimization of a synthetic gel matrix prepared with poly(vinyl-alcohol) (PVA) cross-linked by glutaraldehyde (GTA) contributed to enhance the interest toward Fricke gel dosimeters [20-22]. In fact, compared to natural gelling agents (such as agarose or gelatin), the use of PVA and GTA proved to guarantee higher levels of reproducibility in the manufactory process of the gel. Furthermore, the stability of the response of PVA-GTA-FG dosimeters is better than achievable with gelatin and agarose, thanks to the slower diffusion of the radiation-induced ferric ions within the synthetic matrix [23-31].

In this work, driven by the results reported in Healy *et al.* [19] and taking into account the recent improvements made to the hydrogel produced by PVA chemically cross-linked with GTA, we have studied the dosimetric optical response of the PVA-GTA Fricke gels loaded with glucose and sucrose. These two saccharides were chosen as representatives of the saccharides categories of monosaccharides and disaccharides. The samples were exposed to clinical photons in the dose range between 0 and 16 Gy and the analyses were conducted by optical absorbance (OA) 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 produced by Sigma-Aldrich: poly(vinyl-alcohol) (PVA, Mowiol® 18-88), ferrous ammonium sulphate

TABLE I. – *Final concentration of all reagents used to produce PVA-GTA Fricke gels.*

SET	Saccharides	Saccharides		SA	FAS	XO	PVA	GTA
		[g/l]	[mM]	[mM]	[mM]	[mM]	[%w/w]	[mM]
1	–	–	–	25	0.5	0.165	9.1	26.5
2	glucose	0.5	2.77	25	0.5	0.165	9.1	26.5
3	glucose	1.0	5.54	25	0.5	0.165	9.1	26.5
4	glucose	1.5	8.31	25	0.5	0.165	9.1	26.5
5	sucrose	0.5	1.46	25	0.5	0.165	9.1	26.5
6	sucrose	1.0	2.92	25	0.5	0.165	9.1	26.5
7	sucrose	1.5	4.38	25	0.5	0.165	9.1	26.5

hexahydrate (FAS); Xylenol Orange tetra-sodium salt (XO), glutaraldehyde (GTA), sulphuric acid (SA), glucose (GL) and sucrose (SU). The final concentration of all reagents used to produce the PVA-GTA Fricke gel is reported in table I. The procedure for PVA-GTA Fricke gel dosimeters preparation, described in detail somewhere else [30], is here briefly summarized.

The PVA solution was prepared by dissolving dry PVA in ultrapure water (80% of the total water volume) at 70 °C, under magnetic stirring. After the complete dissolution, the PVA solution was left to cool down at room temperature. Afterwards, the Fricke-XO solution was prepared by adding SA, FAS, XO and, where expected, SU or GL (fig. 1) into ultrapure water (20% of the total water volume) with moderate magnetic stirring.

Finally, Fricke gel dosimeters were obtained by incorporating the Fricke-XO solution into the PVA solution and subsequently by adding the GTA as a cross-linker. After one minute of stirring to achieve homogeneity, the final solution was poured into poly(methylmethacrylate) standard spectrophotometer cuvettes ($10\times10\times45$ mm) closed with cuvette stoppers and sealed with Parafilm®. After the complete gelation, all the Fricke gel dosimeters were maintained in a refrigerator at the temperature of 10 °C for one day and brought back to room temperature one hour before the irradiations and the OA measurements.

2˙2. *Dose-response measurements.* – To assess the dose-response of the PVA-GTA Fricke gel dosimeters were uniformly irradiated with an IBL ^{437}C ^{137}Cs blood irradiator

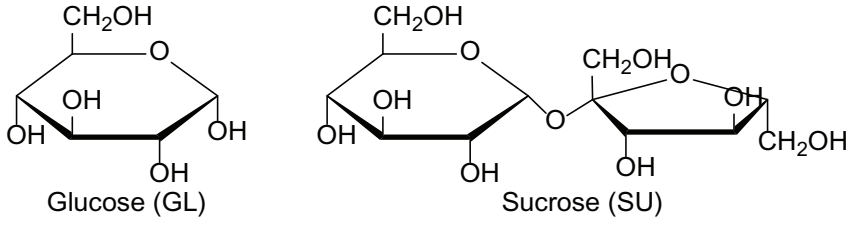

Fig. 1. – Chemical structures of glucose (GL) and sucrose (SU).

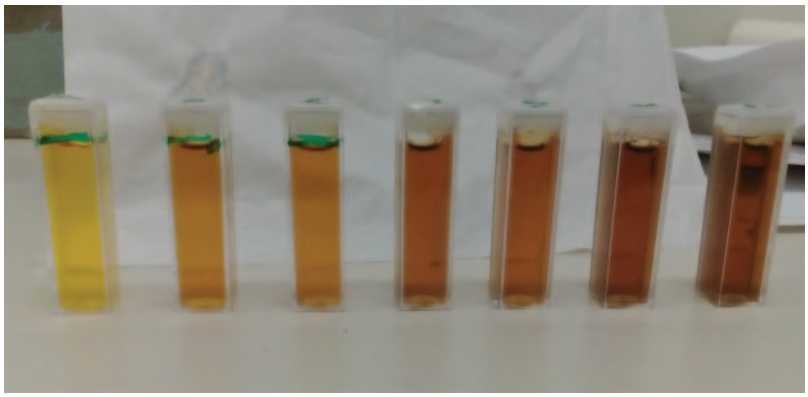

Fig. 2. – Photos of PVA-GTA-FG inside cuvettes for optical absorbance measurements irradiated at different doses in the range 0–16 Gy. The delivered dose increases from left to right.

at the "Fondazione IRCCS Istituto Nazionale dei Tumori" of Milano (Italy) at room temperature [15]. The dose range of 0–16 Gy was investigated. For each dose value, three samples were irradiated. In fig. 2, an example of the gel samples (SET 1), after the different irradiations, is shown. The figure highlights that the colour changes induced by gamma irradiation is visible at naked eye.

An UV-Vis spectrophotometer (Cary 100 UV-Vis) was employed for optical absorbance measurements of the irradiated samples in the wavelength range 360–720 nm. Optical absorbance spectra were acquired using one un-irradiated sample for each SET as reference. According to the indications with our previous studies, where the problem of low doses was solved [30], the optical absorbance values at 555 nm were used for reconstructing the dose-response curves and the measurements were performed about one hour after the irradiation [22, 30].

2˙3. *Radiological water- and tissue-equivalence.* – In order to verify the radiological water-equivalence of the PVA-GTA hydrogels loaded with the saccharides considered, mass energy absorption coefficients for photons and stopping power for electrons were assessed and compared with those of water (ICRU-44). The values of mass energy absorption coefficient and stopping power of PVA-GTA hydrogels loaded with and without the saccharides considered in this work and water were calculated as a weighted average of mass energy absorption coefficients and stopping powers of the chemical element constituents, respectively. The chemical formulas and elemental compositions of the media of interest were used for the calculations, together with the *National Institute of Standards and Technology* (NIST) physical reference data.

3. – Results

3˙1. *Radiological water-equivalence.* – Figure 3 shows the ratio between the mass energy absorption coefficients for photons of PVA-GTA hydrogels loaded with saccharides and the mass energy absorption coefficients for photons of water (fig. 3(a) for different concentrations of sucrose and fig. 3(b) for different concentrations of glucose). Similarly, fig. 4 shows the ratio between the mass collision stopping power for electrons related to PVA-GTA hydrogels loaded with saccharides and the mass collision stopping power for

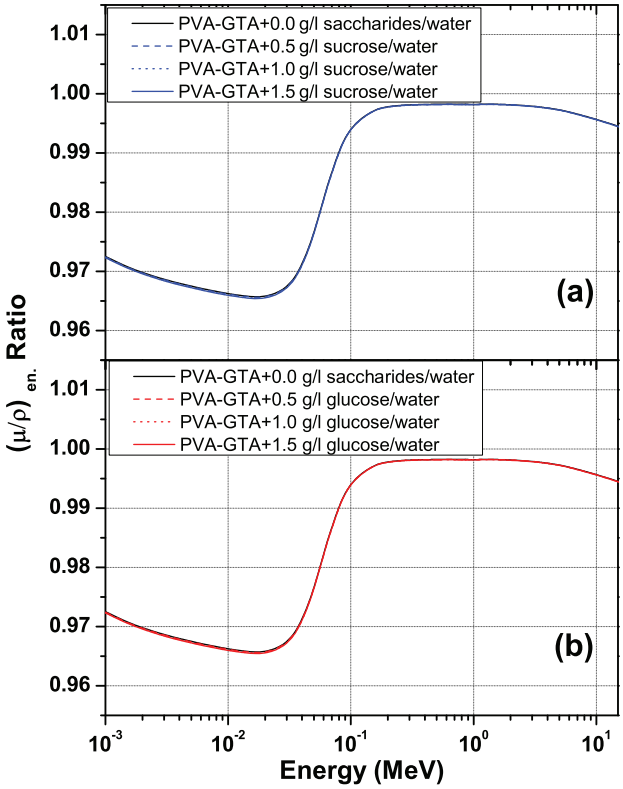

Fig. 3. – (a) Ratio between mass energy absorption coefficients for photons of PVA-GTA gels with different amount of sucrose and water as a function of energy. The black solid line refers to the PVA-GTA-FG sample without saccharides, the blue dashed, dotted and solid lines refer to PVA-GTA-FG loaded with 0.5 g/l, 1.0 g/l and 1.5 g/l, respectively. (b) Ratio between mass energy absorption coefficients for photons of PVA-GTA gels with different amount of glucose and water as a function of energy. The black solid line refers to the PVA-GTA-FG sample without saccharides, the red dashed, dotted and solid lines refer to PVA-GTA-FG loaded with 0.5 g/l, 1.0 g/l and 1.5 g/l, respectively.

electrons related to water (fig. 4(a) for different concentrations of sucrose and fig. 4(b) for different concentrations of glucose). Concerning saccharide-free PVA-GTA gels, more details are reported in Gallo *et al.* [30].

The data have been shown in the form of ratio in order to better highlight any variations. The differences between the mass energy absorption coefficients for photons of PVA-GTA with and without saccharides, and water are lower than 1.0% in the energy interval extending from 0.1 MeV to 15 MeV (fig. 3), *i.e.*, the energy interval of interest in X-rays external radiation therapy. At lower energies the differences increase, with a maximum deviation between gels and water of approximately 3.5% around 0.03 MeV.

In the energy interval 0.1–10 MeV, the differences between the mass collision stopping power for electrons of PVA-GTA gels, water are lower than 1.0% for the entire energy range considered.

Moreover, the addition of glucose or sucrose in the different quantities used in these experiments does not affect the radiological properties of the hydrogel matrix based on PVA-GTA.

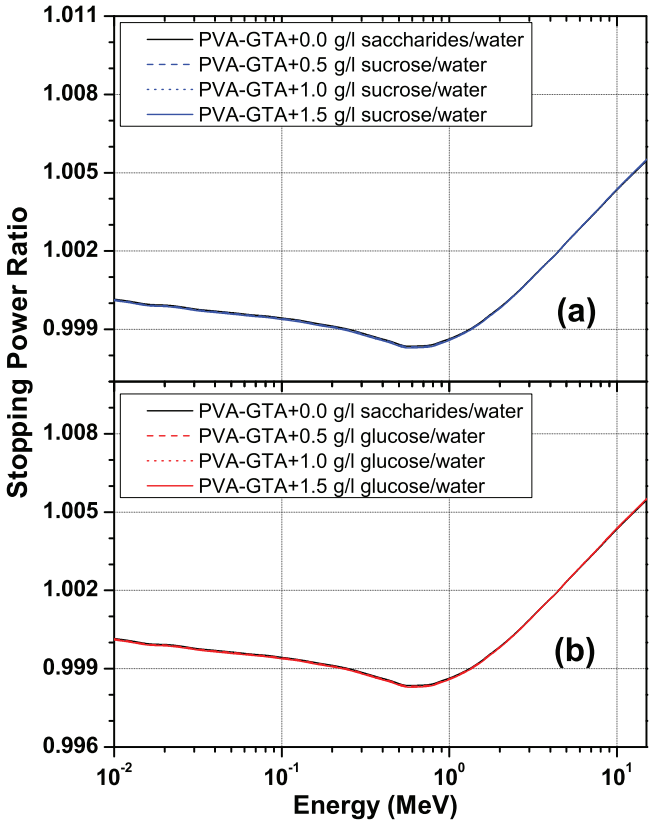

Fig. 4. – (a) Ratio between collisional stopping power of PVA-GTA gels and water with different amount of sucrose and water as a function of energy. The black solid line refers to the PVA-GTA-FG sample without saccharides, the blue dashed, dotted and solid lines refer to PVA-GTA-FG loaded with 0.5 g/l, 1.0 g/l and 1.5 g/l, respectively. (b) Ratio between collisional stopping power of PVA-GTA gels and water with different amount of glucose and water as a function of energy. The black solid line refers to the PVA-GTA-FG sample without saccharides, the red dashed, dotted and solid lines refer to PVA-GTA-FG loaded with 0.5 g/l, 1.0 g/l and 1.5 g/l, respectively.

As reasonably expected considering the chemical composition of PVA-GTA gels [30] and of sucrose ($C_{12}H_{22}O_{11}$) and glucose ($C_6H_{12}O_6$), the results of figs. 3 and 4 confirmed the nearly radiological water-equivalence of the gel matrix in the energy interval of interest in X-rays external radiation therapy.

3˙2. *Optical absorbance spectra.* – Typical optical absorbance spectra of Fricke-XO gel dosimeters prepared with sucrose in amount of 0.5, 1.0 and 1.5 g/l and irradiated at various doses are shown in fig. 5. Figure 6, on the other hand, shows the optical absorbance spectra for Fricke gel with increasing glucose concentrations (from 0.5 to 1.5 g/l) at different delivered dose values.

The optical absorbance spectra of all the studied gel dosimeters showed the broad absorption band centred around 585 nm, with a shoulder extending in the lower wavelength region (500–560 nm), due to the formation of XO-Fe^{3+} complexes. The intensity of this signal increased while increasing the radiation dose, with a consequent reduction

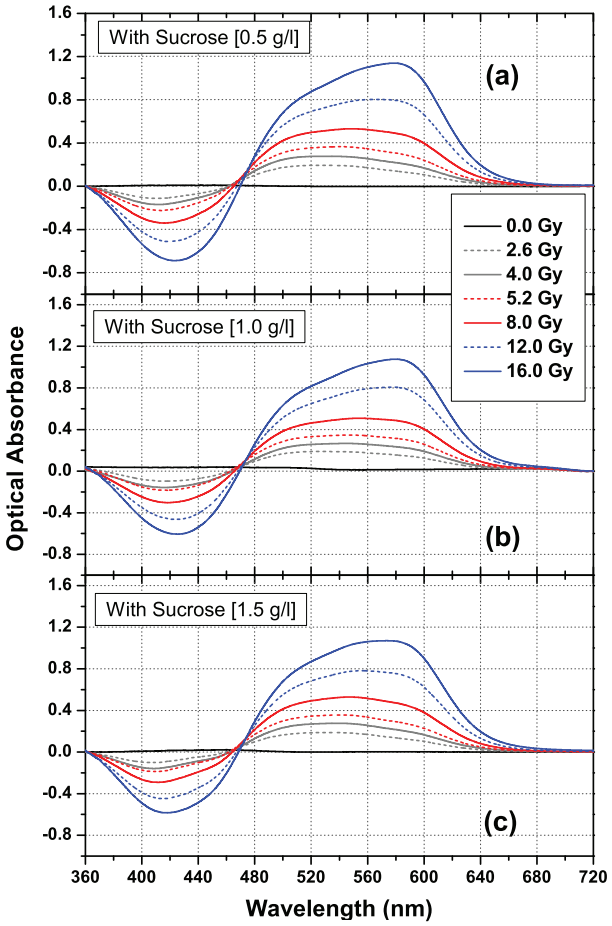

Fig. 5. – Optical absorbance spectra of the various types of gel dosimeters irradiated with increasing doses. An un-irradiated sample was used as reference. (a) Fricke gel with sucrose 0.5 g/l; (b) Fricke gel with sucrose 1.0 g/l and (c) Fricke gel with sucrose 1.5 g/l.

of the absorption band at 430 nm, due to the XO molecules not bound with ferrous ions. For a fixed dose, the relative intensity of the main peak at 585 nm with respect to the side shoulder slightly changed with the gel composition. Indeed, the optical absorbance at 585 nm proved to decrease with increasing the saccharides concentration in the gel matrix.

This behaviour is more evident for gels enriched with sucrose. These variations can be attributed to the solubility of the saccharides in solution.

As expected, the optical absorbance of Fricke gel dosimeters with saccharides (sucrose or glucose) increased with increasing the radiation dose in the interval 480–660 nm. This is totally in accordance with the results of PVA-GTA based gels without the addition of saccharides [22, 28]. Similarly, a decrease of the variation of optical absorbance around 430 nm with increasing the radiation dose occurred. Such features can be observed also for the Fricke gel dosimeters containing saccharides, suggesting that the addition of glucose

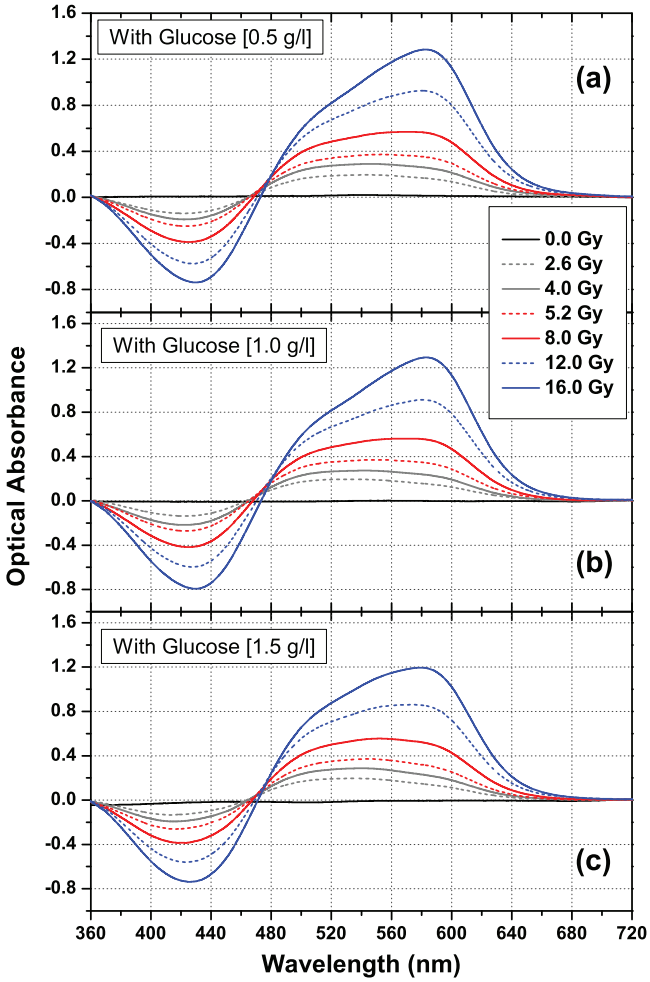

Fig. 6. – Optical absorbance spectra of the various types of gel dosimeters irradiated with increasing doses. An un-irradiated sample was used as reference. (a) Fricke gel with glucose 0.5 g/l; (b) Fricke gel with glucose 1.0 g/l and (c) Fricke gel with glucose 1.5 g/l.

or sucrose into the gel matrix does not impair the operating principle of the dosimeters and their optical analyses.

Furthermore, in all the investigated gels the shape of the absorbance spectra changed with changing the radiation dose, as is more visible in figs. 7 and 8 where the spectra of figs. 5 and 6 were divided by the absorbed dose, respectively. The normalized optical absorbance spectra of each dosimeter showed an isosbestic point around 555 nm, suggesting the presence of different XO-Fe^{3+} complexes in the gel matrices, as previously observed in Fricke solutions and in various gel dosimeters prepared with different types of XO and without saccharides [30, 32]. Moreover, an increase of the optical absorbance around 585 nm and a decrease around 520 nm are visible in the spectra of figs. 7 and 8. The addition of sucrose or glucose to the investigated concentrations does not change the position of the isosbestic point. This indicates that the presence of the saccharide does

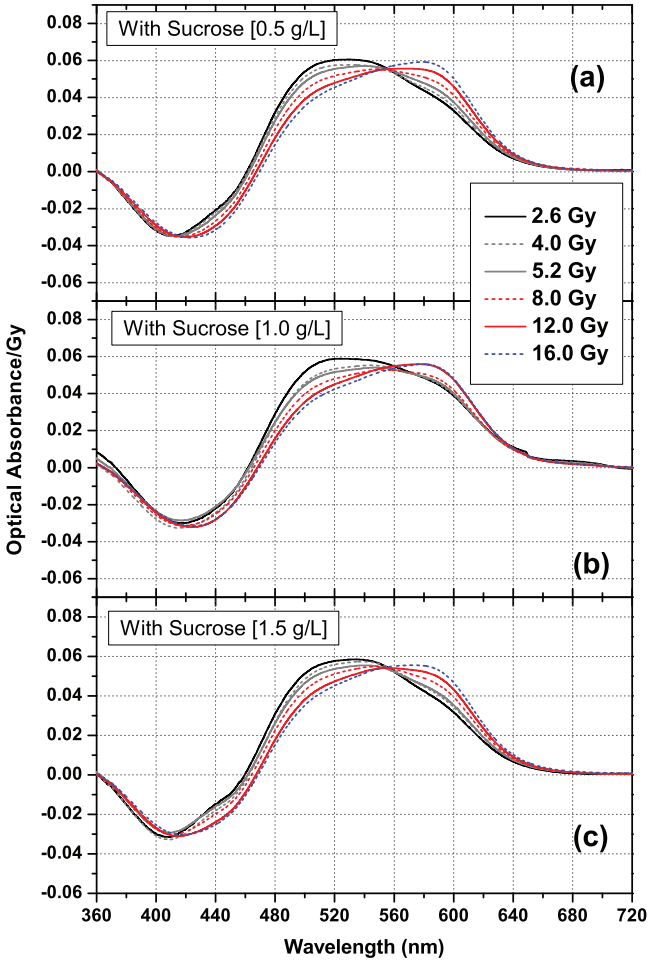

Fig. 7. – Optical absorbance spectra of the various types of gel dosimeters, divided by the absorbed dose. An un-irradiated sample was used as reference. (a) Fricke gel with sucrose 0.5 g/l; (b) Fricke gel with sucrose 1.0 g/l and (c) Fricke gel with sucrose 1.5 g/l.

not influence the complexation reaction of XO with radio-induced ferric ions.

The dose-response curves of the Fricke-XO gel dosimeters prepared with and without saccharides were evaluated from the optical absorbance spectra of figs. 5 and 6 at the wavelengths of 555 nm in agreement with the results shown in Gallo *et al.* [30]. The results obtained are shown in figs. 9 and 10.

Linear regression was applied to all data and the parameters are shown in table II. All the samples considered (with and without the addition of sucrose and glucose) show an excellent linear trend of the optical absorbance at 555 nm in response to the delivered dose. All fits have a linear correlation coefficient (R^2) greater than 0.999, demonstrating the correctness of the fit used. No problems are noted for doses below 5 Gy.

All the results are strongly in agreement with each other. All intercept values are close to zero. This is in line with what was found in our previous work [30] and suggests that the addition of saccharides does not introduce problems for the estimation of low

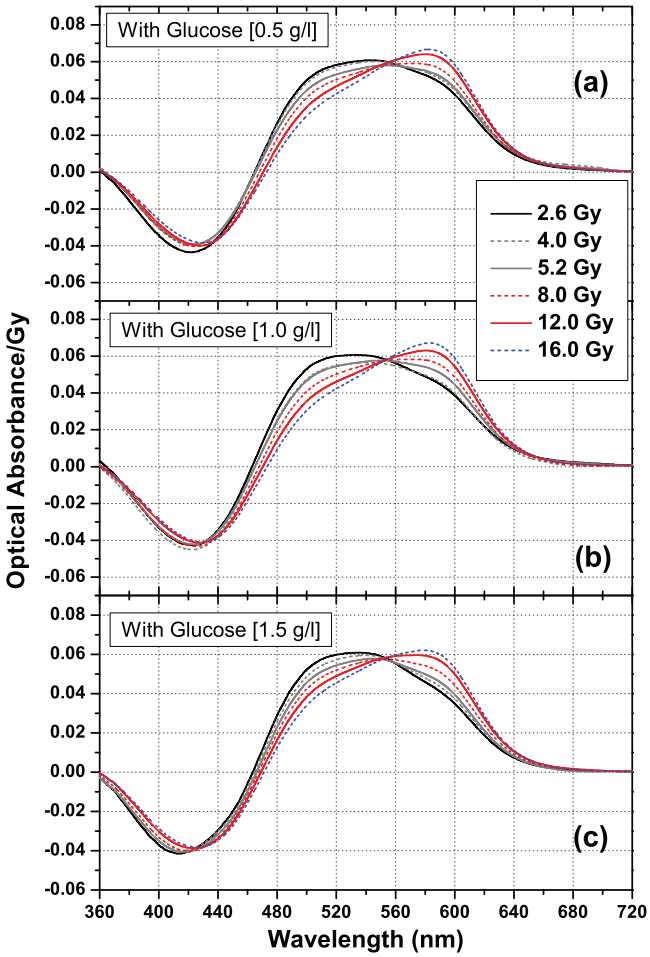

Fig. 8. – Optical absorbance spectra of the various types of gel dosimeters, divided by the absorbed dose. An un-irradiated sample was used as reference. (a) Fricke gel with glucose 0.5 g/l; (b) Fricke gel with glucose 1.0 g/l and (c) Fricke gel with glucose 1.5 g/l.

doses [18] or dummy thresholds [33]. Regarding the slopes of the fits, which are related to the optical dosimetric sensitivity, all values are comparable within the experimental errors. Afterwards, using the unpaired *t-test*, we estimated the confidence levels 55–85%, between sensuosity of PVA-GTA gel without saccharide and PVA-GTA gel with various saccharides concentrations. The only couple that showed a confidence level lower than 15% is that relating to gels without sucrose and with sucrose in amount of 1.5 g/l. However, such little difference in the sensitivity does not appear to be significant from a dosimetric point of view and could be due to possible remaining small differences in the pH values among the types of gels [30, 34, 35].

This allows us to state that the addition of saccharides in Fricke gel made with synthetic PVA matrices chemically cross-linked with GTA does not bring about significant improvements in the dosimetric sensitivity of the gels. This seems to disagree with what was found by [19] where the effect is studied on agarose-based Fricke gel and with both optical and MRI techniques.

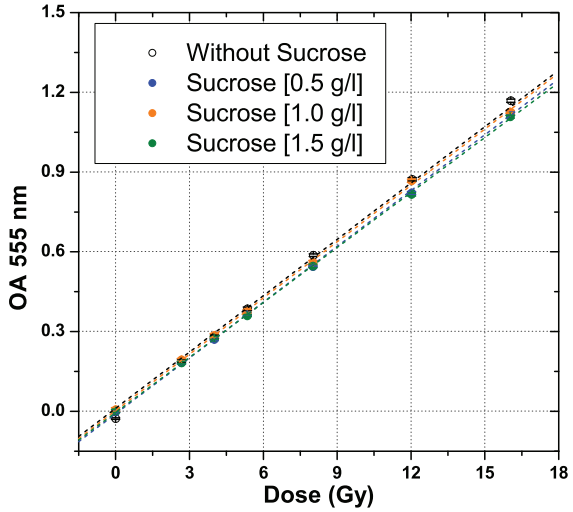

Fig. 9. – Optical absorbance at 555 nm of PVA-GTA FG dosimeters prepared using different sucrose amounts and irradiated at increasing doses. The error bars correspond to one standard deviation (1 SD). Blue dots: 0.5 g/l of sucrose; orange dots: 1.0 g/l of sucrose; green dots: 1.5 g/l of sucrose. The lines are the linear fits to the experimental data in the whole dose interval.

A possible interaction between the matrices of organic origin and the saccharides is not excluded with the consequential improvement of the dosimetric properties of these gels.

The effect of saccharides on PVA-GTA matrix was also studied by Yang *et al.* [36]. The authors tested the dosimetric properties with optical techniques on PVA-GTA gels

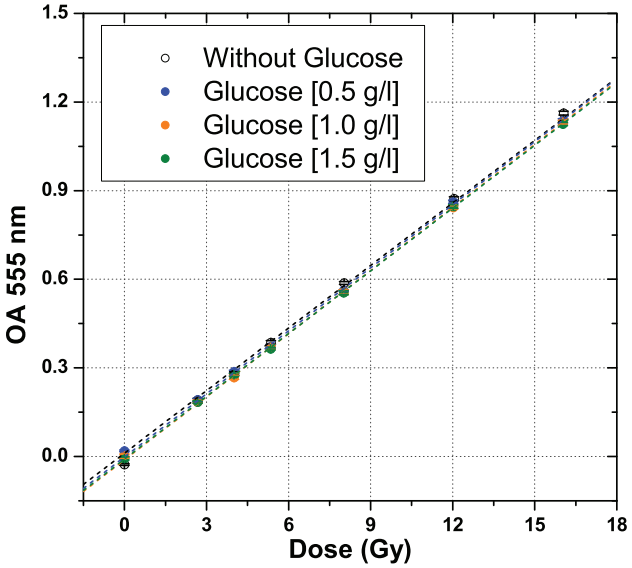

Fig. 10. – Optical absorbance at 555 nm of PVA-GTA FG dosimeters prepared using different glucose amounts and irradiated at increasing doses. The error bars correspond to one standard deviation (1 SD). Blue dots: 0.5 g/l of glucose; orange dots: 1.0 g/l of glucose; green dots: 1.5 g/l of glucose. The lines are the linear fits to the experimental data in the whole dose interval.

TABLE II. – *Sensitivity to absorbed dose of PVA-GTA-FG dosimeters prepared using different saccharides amounts.*

Sample	Saccharides	Intercept	Sensitivity [Gy^{-1}]	R^2
1	–	0.011 ± 0.013	0.0706 ± 0.0009	0.999
2	glucose 0.5 g/l	-0.001 ± 0.006	0.0711 ± 0.0006	0.999
3	glucose 1.0 g/l	0.010 ± 0.004	0.0712 ± 0.0004	0.999
4	glucose 1.5 g/l	-0.009 ± 0.005	0.0708 ± 0.0004	0.999
5	sucrose 0.5 g/l	-0.009 ± 0.007	0.0700 ± 0.0004	0.999
6	sucrose 1.0 g/l	0.003 ± 0.008	0.0706 ± 0.0008	0.999
7	sucrose 1.5 g/l	-0.004 ± 0.005	0.0690 ± 0.0006	0.999

enriched with glucose but at lower concentrations (up to 1.5 mM) than those reported in this work. In that work it was found that the glucose enhanced the stability but decreased the sensitivity with increasing concentration. Moreover, the authors also used different concentrations of the constituents of the Fricke solution and they focused attention on optical absorbance at 585 nm in a dose range below 5 Gy. It is known that, from 0 to 5 Gy, the optical absorbance of FG at 585 nm has an anomalous behaviour. Because the experimental conditions are different, a direct comparison of the data is not possible, but since the results are not completely in agreement, more insights are needed in order to understand better the role of the saccharides in PVA-GTA gels.

4. – Conclusions

Different types of PVA-GTA Fricke gel dosimeters loaded with sucrose and glucose have been studied and compared to recent formulations. The analysis of the OA spectra has shown behaviours that associate all the different types of gels and are not affected by the type of matrix or by the presence of additives such as saccharides.

The presence of the saccharides does not bring significant improvements in terms of optical dose-response curve. The addition of sucrose or glucose does not affect the water-radiological equivalence.

The use of PVA leads to an improvement of the gel manufacturing procedures, guarantees greater gel purity, without altering the dosimetric properties. Studies are currently underway that plan to add other stabilizers such as ascorbic acid, EDTA or organic acids to the matrix with the aim of improving the dosimetric properties of these gels both in terms of spatial and temporal stability. Measurements are also ongoing via magnetic resonance to be combined with optical analyses.

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