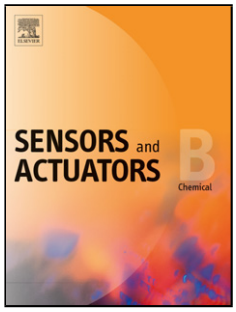

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Study of the effect of laponite on Fricke xylenol orange gel dosimeter by optical techniques

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Highlights

- Nano-sized clay particles can be incorporated into Fricke Xylenol Orange gel dosimeters
- The addition of nanoparticles does not impair the dosimetric properties of Fricke gels
- The dose-response curve of Fricke gels depends on the wavelength used for the optical analysis
- The addition of laponite in Fricke Xylenol Orange gel dosimeters does not improve the ferric ions diffusion rate

Abstract

Optical absorbance and dynamic light scattering studies of Fricke xylenol orange gel dosimeters loaded with laponite were carried out with the aim to investigate possible effects of nanoparticles on the dosimetric properties and diffusion phenomena of ferric ions. A procedure for incorporating laponite nano-sized clay particles into the gel dosimeters, prepared using porcine gelatine as gelling agent, was successfully developed. The shape of the optical absorbance spectra of the gel dosimeters in the wavelength interval 350-750 nm have shown a slight dependence on the nanoparticles concentration and varied with the absorbed dose. All investigated gel exhibited a linear dose response in the interval 0-22 Gy. Neither the sensitivity to the radiation dose nor the diffusion coefficient were significantly altered by the addition of laponite into the Fricke xylenol orange gel formulation employed.

Keywords: Fricke gel dosimeter; optical absorbance spectra; diffusion coefficient; laponite, Dynamic Light Scattering

1. Introduction

The most advanced delivery techniques in radiotherapy (RT) allow high conformal radiation dose distributions to the tumor targets with good sparing of the surrounding healthy tissues. Prerequisite for the success of these techniques is the establishment of effective quality assurance and treatment plan verification systems. In this contest, instruments and methods able to provide accurate dose distributions are crucial [1]. Various instruments and procedures for point dosimetry and two dimensions (2D) dosimetry in the modern RT are available and, in most of cases, quite well established. By contrast, the development of a standard method for accurate measurement of the radiation dose distribution in three dimensions (3D) is still highly desirable [2].

Together with polymer gel dosimeters, which rely on the radiation-induced polymerization of their co-monomer components [3,4], Fricke gel (FG) dosimeters are good candidates for 3D dose assessment in biological materials because of their tissue equivalence [5]. Indeed, their effective atomic number and density are similar to those of water and soft tissue [6]. Moreover, in view of their chemical and morphological characteristics, FGs serve as dosimeters and as phantoms at the same time [7].

FG dosimeters are obtained by incorporating an aqueous Fricke solution (*i.e.* an acidic oxygenated aqueous solution of ferrous ions Fe^{2+}) into a gel matrix. The two most widely used matrices for Fricke gels are gelatine, a hydrolyzed form of collagen extracted from animal tissues, and agarose, a polysaccharide polymer extracted from seaweed [5]. Upon irradiation, a dose-dependent transformation of ferrous (Fe^{2+}) to ferric (Fe^{3+}) ions occurs with oxidation yield proportional to the absorbed dose. This variation is detectable by Nuclear Magnetic Resonance (NMR) and Magnetic Resonance Imaging (MRI) [8]. Furthermore, the addition of the metallic-ion indicator Xylenol Orange (XO) to the FG dosimeters makes these systems capable of being analyzed by optical techniques [5]. In fact, the Xylenol Orange molecule shows a broad light absorbance band around 430 nm. After irradiation, the generated Fe^{3+} ions are chelated by XO and the resulting complex gives a broad optical absorbance peak around 585 nm [9]. Therefore, by means of suitable optical absorbance analysis of irradiated samples, it is possible to quantify the absorbed dose.

Currently, the main drawback of Fricke gel dosimeters is the diffusion of ferric ions, which leads to a gradual blurring of the dose pattern with time after irradiation [10,11]. In dosimeters that contain XO ions diffusion is slightly reduced [5] and therefore XO is used also when NMR analyses are performed.

Various approaches are being developed with the aim to overcome the diffusion limitation. For instance, novel gel formulations based on poly-vinyl alcohol (PVA) coupled with glutaraldehyde (GTA) acting as cross-linking agent, enabled to achieve diffusion rates significantly lower than those observed in agarose and gelatine matrices [12-16].

Alternatively, the introduction of nanoparticles in FG dosimeters appeared to reduce the diffusion phenomena. In particular, *Maeyama et al.* [17,18] showed by MRI analyses that the addition of nano-sized clay particles (NCP), namely laponite, into gel matrices, under de-aerated conditions and without the use of XO, succeeded in strong reduction of diffusion. Moreover, nano-composite Fricke gel dosimeter prepared using only Fricke solution and nano-clay in water, without any organic gelling agents, showed interesting dosimetric properties [19]. Laponite is a layered silicate manufactured from naturally occurring inorganic mineral sources. It is used to improve the performance and properties of a wide range of industrial and consumer products making. [20]. As far as the authors know, no studies about the addition of NCP in XO-FG dosimeters and the characterization of their optical properties are available in the literature, in spite of the increasing interest towards the use of optical methods for FG dosimeters analysis. In fact, optical tomographic scanners have been specifically designed for reading the FG dosimeters and are in continuous development [13]. These instruments have the advantage that they can be located on-site in the hospitals, removing the reliance on MRI scanners, generally overburdened by diagnostic clinical demands [7,8].

Driven by these needs, in this work we investigated the possible advantage of incorporating NCP into Fricke-XO gel dosimeters routinely prepared in our laboratory and widely used for various dosimetric studies by optical analyses [21]. The effects of the NCP on the Fricke gel dosimeters in terms of optical absorbance (OA) properties and diffusion coefficient are accordingly studied.

2. Materials and Methods

2.1 Fricke gel preparation

FG dosimeters were prepared using ultrapure water (resistivity 18.6 MΩ⁄cm) with the addition of the following

compounds: gelatine (from porcine skin Type A - 300 bloom, Sigma-Aldrich) in the amount of 3.0 % in weight of final volume (w/w); 0.5 mM ferrous ammonium sulphate hexahydrate (Mohr salt) $Fe(NH_4)_2(SO_4)_26H_2O$ (Carlo Erba); 0.165 mM Xylenol Orange sodium salt $C_{31}H_{28}N_2Na_4O_{13}S$ (Riedel-de Haën); NCP (laponite XLG, Rockwood Additives) in the amounts of 0.0, 0.5, and 1.0% w/w. Laponite crystals are disk-shaped with thickness 0.9 nm and average diameter 25 nm. [20].

Due to the technical data of laponite (pH of 9.8 for concentration of 2% w/w - [22,23]), different quantities of sulphuric acid H_2SO_4 (Suprapure 96% Carlo Erba), ranging from 25 mM and 97 mM, were added with the aim to achieve similar pH values in all the types of gel FG dosimeters (equal to approximately 1.8), independently of their NCP concentration.

In a preliminary step, some experiments have been carried out in order to investigate the modalities of gel preparation. Different percentages of laponite have attempted, but above 1% w/w a complete gelification was not attained and samples resulted to be greatly opaque. Therefore, the maximum laponite concentration of the investigated dosimeters was 1% w/w.

Since laponite must be added to water with mixing and allowed to disperse and hydrate fully before any other components are added [20], the following process for the Fricke gels preparation was followed. First, the porcine skin gelatine was dissolved in water (50% of the total water) at 50°C under stirring. After approximately 20 minutes, the complete gelatine dissolution was achieved and the solution was left to cool down.

Next, aqueous suspension of laponite was prepared by slowly adding NCP into water (the remaining 50% of the total water) at room temperature (about 25 °C) with rapid agitation. The solution was stirred for 15 min until turbidity vanished and a uniform dispersion was obtained. Afterwards, sulphuric acid, ferrous ammonium sulphate and xylenol orange sodium-salt were added in this order, obtaining nanocomposite Fricke-XO solution. Finally, this solution was mixed to the gelatine one at the temperature of 35°C. After 5 min of gentle stirring to achieve homogeneity, the solution was poured in standard spectrophotometry cuvettes (10 mm optical path) closed with plastic stoppers and sealed with Parafilm™.

These samples were used to investigate the optical absorbance properties of the gel dosimeters. Furthermore, Fricke-Gel-Layer-Dosimeters (FGLDs) with a 3 mm optical path and internal dimensions 11 cm x 5 cm were

prepared and used to study the diffusion phenomena. Details of the FGLDs preparation can be found elsewhere [24].

After the preparation, FG dosimeters were kept refrigerated at the temperature of 6°C for one day and brought back to room temperature 1 hour before the irradiations.

2.2 Optical absorbance spectra measurements

FG dosimeters inside the cuvettes were uniformly irradiated with a biological irradiator based on a Cs-137 source at the Fondazione IRCCS Istituto Nazionale dei Tumori of Milano (Italy). The dose range 0-22 Gy was investigated using two samples for each dose value. Intra-batch reproducibility was initially tested using six samples irradiated and measured in the same experimental conditions. In the wavelength region of interest for the dosimetric analyses, a reproducibility lower than 1.5% was obtained. Details are given in the supporting information (SI) material.

An UV-VIS spectrophotometer (Cary 100 UV-Vis, Agilent Technologies, Santa Clara, CA, USA) was employed for OA measurements of the irradiated samples in the wavelength interval 350-750 nm. Since in the conventional gel dosimetry, the absorbed dose is correlated to OA variation of the dosimeters following irradiation, OA spectra were acquired using as reference one un-irradiated sample for each batch.

The reference sample was always kept near the samples to be analyzed in order to reproduce the same effect of auto-oxidation inside the dosimeters. The measurements were performed 40 minutes after the irradiation in order to achieve chemical equilibrium.

2.3 Diffusion coefficient measurements

FGLDs were irradiated to a dose of approximately 8 Gy with X-rays generated by a X-ray tube (Gilardoni Radiolight, Italy) operating at 80 kV and 5 mA, mounting a tungsten anode and a beryllium window. A field size of about 30 x 30 cm^2 at the sample position enabled the uniform irradiation of two FGLDs simultaneously. The FGLDs were partially covered with a 2 mm thick layer of lead in order to shield half of the area of each dosimeter. A picture of a FGLD dosimeter irradiated in these conditions is shown in Fig. 1.

Light transmittance images of the FGLDs were acquired 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®) mounting a band-pass filter centered at 585nm (FWHM of 10 nm). The FGLDs were placed on the

illuminator within tailored black masks to avoid possible artefacts due to the light coming from the illuminator around the dosimeter.

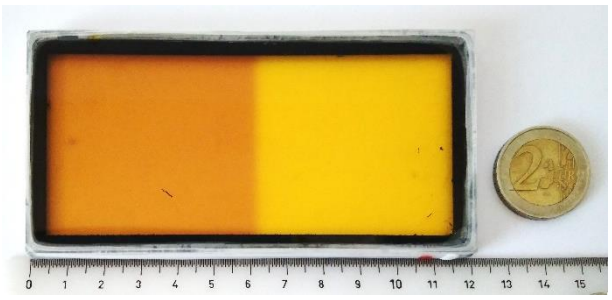

Fig. 1. Picture of an irradiated Fricke-Gel-Layer-Dosimeter. The sample was partially covered with a layer of lead during the X-rays irradiation, producing a steep dose gradient.

Light transmittance images of each FGLD were acquired in grey level (GL) before irradiation and at consecutive times up to 5 hours post-irradiation. Among subsequent measurements, the dosimeters were kept in the dark at the temperature of 6°C. The differences of optical density Δ(OD) were calculated pixel by pixel using an in–house software developed in C++ language.

The mean profile of Δ(OD) along the length of each FGLD (*i.e.* across the discontinuity of the GL values due to the steep dose gradient) was evaluated, as well as its temporal variation as effect of the diffusion phenomena. An inverse square root function (ISQR), as proposed by *Kron et al.,* [25] was fitted to each Δ(OD) profile:

$$A(x) = A_{MIN} + \frac{1}{2}(A_{MAX} - A_{MIN})\left[1 + \frac{x - x_C}{\sqrt{(x - x_C)^2 + n}}\right] \qquad (1)$$

where, *A(x)* is the Δ(OD) as a function of position x along the layer axis, A_{MIN} and A_{MAX} are the minimum and maximum measured Δ(OD) values, and *n* is a curvature parameter that varies with time while the initial step distribution diffuses. Possible lateral shifts of the inflection point are taken into account with the parameter x_C. The plot of *n* versus time is expected to be linear. From the slope α of the fitted straight line the diffusion coefficient *D* was calculated as [25]:

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

2.4 Dynamic Light Scattering characterization

Dynamic Light Scattering (DLS) measurements were performed in order to assess size and possible aggregation of laponite in acid aqueous medium as well as the laponite/gelatine interaction within the gel matrix. DLS is a technique based on the statistical analysis of the scattered light fluctuations in colloids due to the particle Brownian motion. The variation of scatter light intensity is related to the translational diffusion coefficient through the Stokes-Einstein equation [26].

Measurements were performed with a Malvern Zetasizer Nano ZS90 instrument operating with a light source wavelength of 532 nm and a fixed scattering angle of 90°.

The aqueous suspension of 1% w/w laponite after 97 mM sulphuric acid addition was characterized by DLS and electrophoretic mobility, to determine particle dimensions and the laponite surface charge in terms of zeta potential, respectively. The stability of the acidic laponite dispersion was monitored by repeating the DLS measurement after 7 days.

The laponite/gelatine interaction was studied on the gel containing 3% w/w gelatine, 1% w/w laponite and 97 mM sulphuric acid. The gel resuspension experiments were run by resuspending a small amount of the gelatin-laponite gel in 1 mL ultrapure water by mechanical stirring and subsequent sonication for 15 min in a water bath sonicator. Then the resuspended gel was centrifuged (1000 RCF, 5 min at room temperature) to remove micron-sized particles and analyzed by DLS. As a control, the same procedure was applied to gelatine gel without laponite. Experiments were run on triplicate and DLS data were the mean from three to five different measurements. The considered DLS parameters were maximum intensity peak and derived count rate (DCR) which is related to the number of nanoparticles present in a sample [27,28].

3. Results and discussion

3.1 Optical absorbance spectra measurements and dose-response curve analysis

Typical OA spectra of Fricke-XO gel dosimeters prepared with and without NCP in amount of 0.0, 0.5 and 1.0 % w/w and irradiated at various doses are shown in Fig. 2.

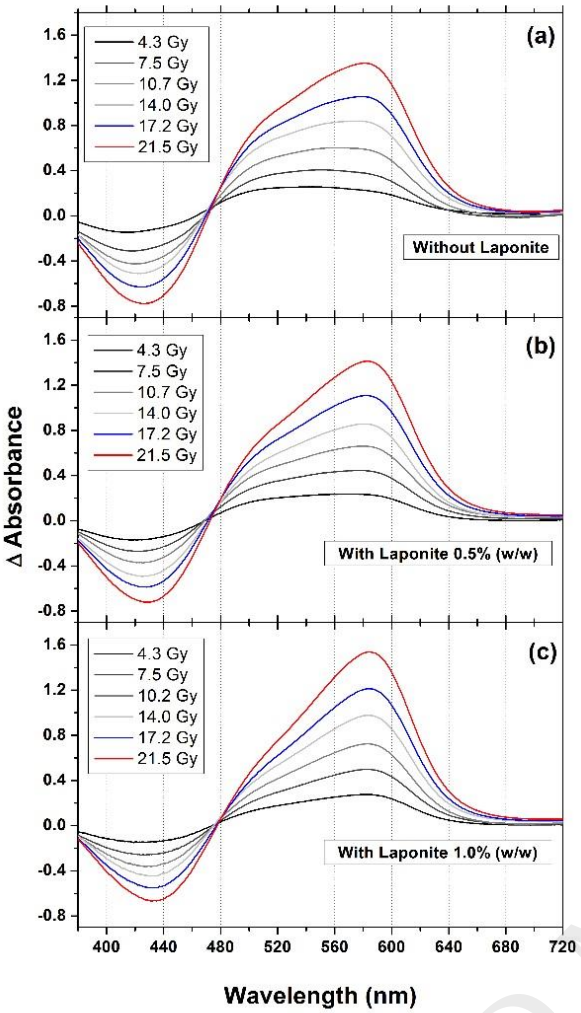

Fig. 2. Absorbance spectra of the various types of gel dosimeters irradiated to increasing doses. An un-irradiated sample was used as reference. (a) Fricke gel without laponite; (b) Fricke gel with laponite 0.5% w/w and (c) Fricke gel with laponite 1.0% w/w.

Absorbance spectra of all the studied gel dosimeters were characterized by a broad absorption peak in the wavelength region between 500 nm and 600 nm. The shapes of spectra show a main absorption around 585 nm, with a shoulder extending in the lower wavelength region (500-560 nm). For a fixed dose, the relative intensity of the main peak at 585 nm with respect to the side shoulder changed with the gel composition. Indeed, the optical absorbance at 585 nm proved to increase with increasing the NCP concentration in the gel matrix.

As expected, the OA of FG dosimeters without laponite increased with increasing the radiation dose in the wavelength region between 480 nm and 660 nm. Similarly, a decrease of the OA around 430 nm with increasing the radiation dose occurred. Such features can be observed also for the FG dosimeters containing NCP, suggesting that the addition of laponite 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 more visible in Fig. 3 where the spectra of Fig. 2 were normalized dividing each spectrum for the absorbed dose. The normalized OA 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 [29,30] and in various gel dosimeters prepared with different types of XO and gelling agents [21,31]. Moreover, an increase of the OA around 585 nm and a decrease around 500 nm are visible in the spectra of Fig. 3.

The dose-response curves of the Fricke-XO gel dosimeters prepared with and without NCP were evaluated from the OA spectra of Fig. 2 at various wavelengths in the interval 530-620 nm (in 10 nm steps). Example of the dose-response curves obtained for two selected wavelengths (555 and 585 nm) are shown in Fig. 4. The results of the linear fit parameters are reported in Table 1. At the wavelength of 555 nm (*i.e.* the isosbestic point of the spectra of Fig. 3) the dose-response curves of the three type of gel dosimeters are practically overlapping (Fig.4b) and the OA variation proved to be proportional to the absorbed dose (up to dosimeter saturation).

The dose-response curves reported in Fig. 4a (585 nm) show linearity, but exhibit different slopes and intercepts with respect to the 555 nm because of the observed differences in the OA spectra shapes.

At the wavelength usually utilized in dosimetry (585 nm) the sensitivity of the Fricke gel with NCP concentration of 1% was slightly higher than that of the other two gel samples (see slope values in Table 1). However, such increase 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 [6,11,32].

The dependence of the sensitivity of the FG dosimeter on the wavelength is shown in Fig. 5, where the slope values of the fitted dose-response straight lines versus wavelength are reported for all the types of gel. The maximum sensitivity occurred at 585 nm for all the FG dosimeters, making the band-pass filter used for the

optical density measurements of the FGLDs suitable also for the analysis of the samples containing NCP. The sensitivity of the FG dosimeters prepared with laponite proved to be slightly higher than that of samples without laponite for wavelengths above 550 nm. Such finding is consistent with the observed differences in the shape of the absorbance spectra among the various types of gel dosimeters (Fig. 2 and Fig. 3).

Furthermore, these results are consistent with those previously obtained in optical studies on FG without laponite [21,31].

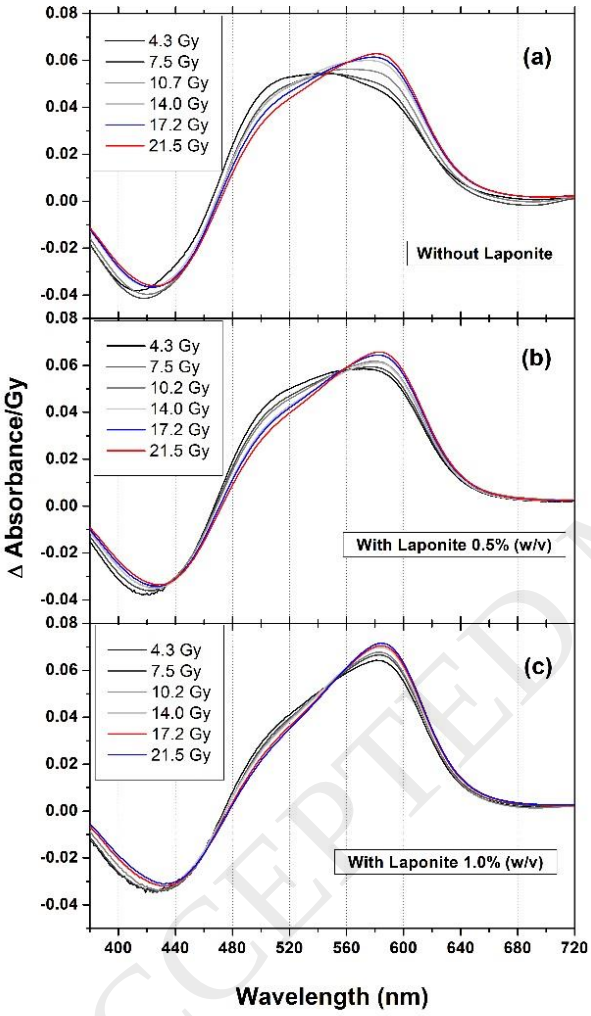

Fig. 3. Absorbance spectra of the various types of gel dosimeters, divided by the absorbed dose. An un-irradiated sample was used as reference. (a) Fricke gel without laponite; (b) Fricke gel with laponite 0.5% w/w and (c) Fricke gel with laponite 1.0% w/w.

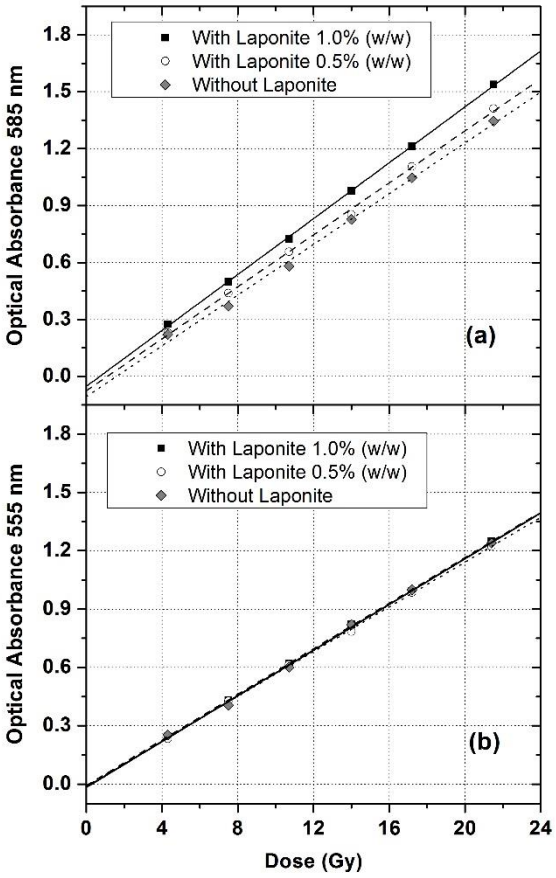

Fig. 4. Optical absorbance at 585 nm (a) and 555 nm (b) of the various types of Fricke gel in cuvettes irradiated at increasing doses in the 0-22 Gy interval. The error bars are shorter than the size of the symbols. The solid lines are the linear fits to the experimental data.

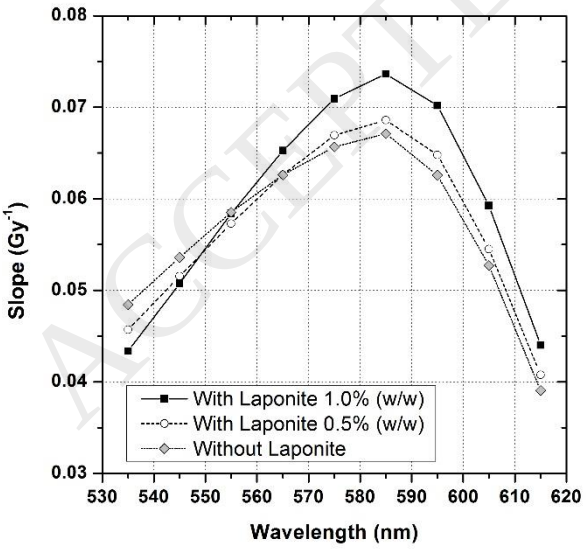

Fig. 5. Slope of the fitted dose-response straight lines versus wavelength, for all the studied types of gel.

Table 1 - Fit parameters of the linear fits shown in Fig. 4

	Wavelength 585 nm		**Wavelength 555 nm**	
Gel	Slope	intercept	Slope	intercept
FG without NCP	0.068±0.002	-0.106±0.028	0.058±0.001	-0.016±0.015
NCP-FG 0.5%	0.069±0.001	-0.075±0.017	0.058±0.001	-0.009±0.008
NCP-FG 1%	0.073±0.001	-0.052±0.009	0.059±0.001	-0.007±0.004

3.2 Diffusion coefficient measurements and DLS characterization

Fig. 6 shows the Δ(OD) profiles along the length of three different FGLD samples partially screened with the lead layer during the irradiation, measured at different post-irradiation times. A progressive flattering of the profile with the consequent blurring of the dose pattern was observed, as effect of the gradual diffusion of ferric ions. Such behavior is evident in the FGLD without laponite as well as in the samples prepared with laponite.

In order to quantify the diffusion coefficient in the three types of gel dosimeters, the curvature parameters (n) were derived by fitting each Δ(OD) profile with the ISQR function of equation (1). An example of the fit is shown in Fig. 7.

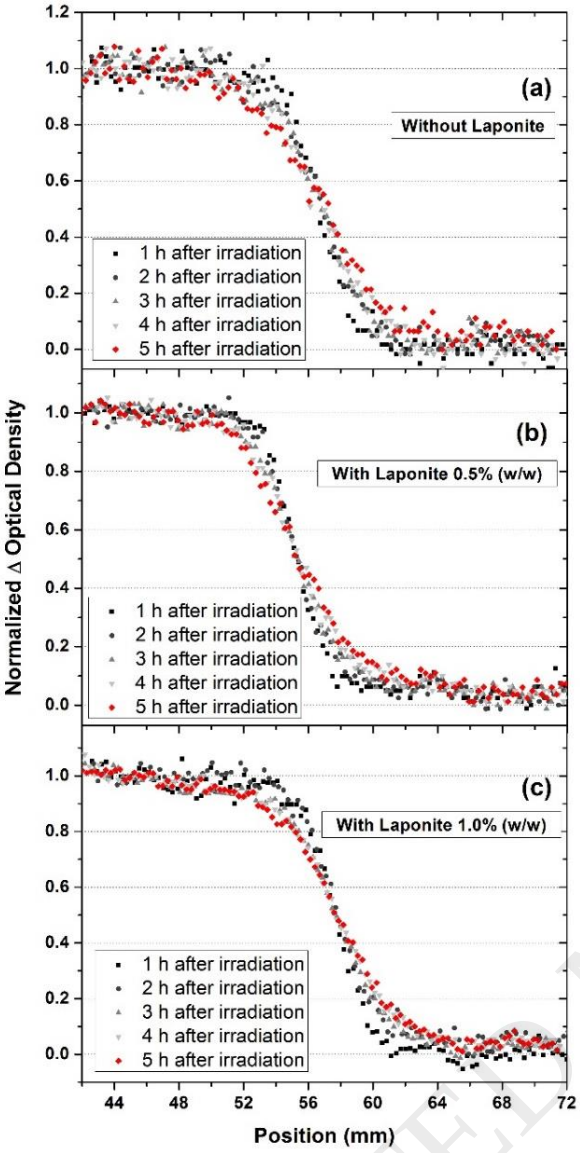

Fig. 6. Examples of Δ(OD) profiles measured at different post-irradiation times. (a) FGLD without laponite; (b) FGLD with laponite 0.5% w/w and (c) FGLD with laponite 1.0% w/w.

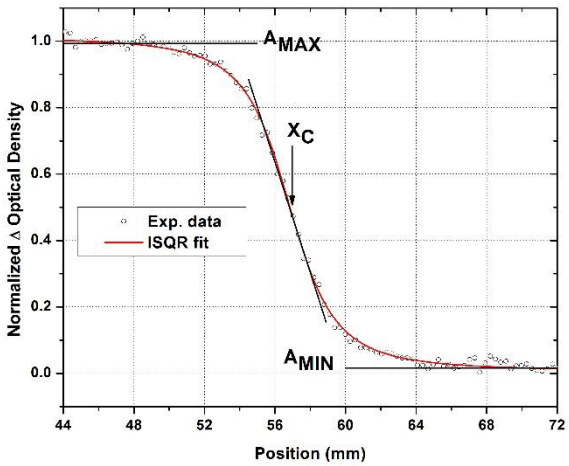

Fig. 7. Typical fit of a Δ(OD) profile. The shown profile is from a FGLD layer with 1.0% of laponite, measured 3 hours after irradiation.

Fig. 8 shows the typical time trend of the curvature parameter *n* for the three types of gel dosimeters.

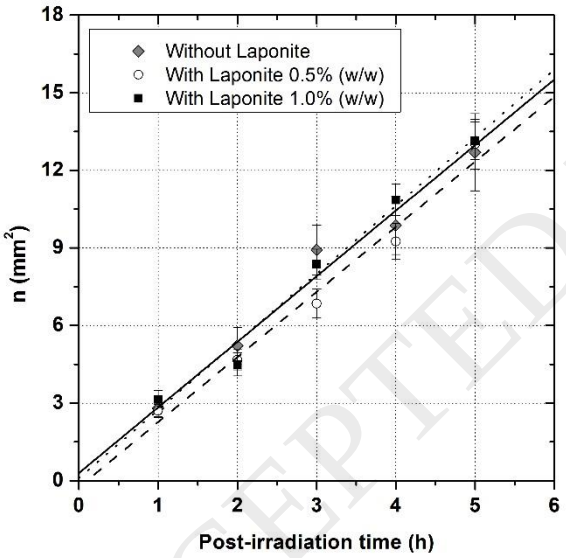

Fig. 8. Plot of the curvature parameter *n* as a function of post-irradiation time for FGLD without laponite, FGLD with laponite 0.5% w/w and FGLD with laponite 1.0% w/w. The error bars, corresponding to one standard deviation, were obtained by the ISQR fits.

For each gel, a straight line was fitted to the experimental data, obtaining the diffusion coefficients reported in Table 2.

Table 2 - Diffusion coefficients for the various gel dosimeters

Gel	Diffusion coefficient D (mm^2/h)
FG without NCP	0.54±0.04
NCP-FG 0.5%	0.53±0.04
NCP-FG 1%	0.55±0.05

No significant differences (*i.e.* within one standard deviation) among the diffusion coefficients of the investigated gel dosimeters were observed. The obtained results are very similar to those found in literature for FG dosimeters prepared with gelatine [33]. Therefore, in the Fricke-XO gel dosimeters here studied, the addition of NCP, in the amount of 0.5% or 1.0%, do not seem to affect the motion of radio-inducted ferric ions into the gel matrix.

Since this behavior is reasonably related to the structural integrity of laponite gel under the experimental conditions used, DLS measurements were performed. DLS spectra of laponite acid aqueous dispersions showed that, at the tested concentration, laponite formed stable aggregates with a peak at about 70 nm (solid black line in Figure 9a). The DLS spectra did not change after one week (Fig.9a – dashed black line) and their DCR values were comparable (249.2 and 280.9 kcps, respectively), attesting the stability of the formed aggregates. DLS measurements of the resuspended gelatin-laponite gel showed a peak at about 70 nm that can be ascribed to laponite aggregates, as already observed in control acid laponite dispersion. In addition, the DLS profile shows aggregates with a peak having the maximum at 270 nm (Fig.9b – red dashed line). Considering that the scattered light scales with the sixth power of particle size, [34], the relative height of the peak at 70 nm may be underestimated with respect to the peak at 270 nm.

Differently, control gelatin sample showed a trimodal DLS distribution (peaks at 10, 73 and 510 nm) and low DCR value (22.9 kcps), which suggested a low concentration of size-defined aggregates (Fig. 9b – dot blue line). Noteworthy, the features of 270 nm were not visible in control gelatine sample and this can be attributed to the electrostatic interaction between gelatin and clay particles. Indeed, the isoelectric point of the gelatine used for this study lays in the pH range 7.0-9.0 [35]. Therefore, gelatine has a net positive charge at a pH below 7.0 and a net negative charge at a pH above 9.0. Differently, zeta- potential of 1% w/w laponite dispersion at pH 1.8 was assessed equal to -1.1 mV, in accordance to previous works [22,36]. When pH is lower than 7, as in our gel samples, positive gelatine interacts with oppositely charged laponite. Although this interaction has

been observed, it does not imply reticulation of laponite and gelatine, which may explain that the diffusion coefficient is not affected by the inclusion of laponite.

Finally, it is worth reminding that the use of an acid environment for Fricke-XO gel dosimeters preparation, leading to a pH value lower than 3, is required for optimizing the Fe^{3+}-XO complexation and consequently the dosimeters properties [6,29,30,32,37]. Different laponite aggregates and complexation structures in gelatine may occur at higher pH, as observed in other media [22,23].

Fricke-XO gel dosimeters featuring these structures could, in principle, present a reduced diffusion of ferric ions. However, their optical absorbance and dosimetry properties are expected to be impaired by the non-optimized pH value.

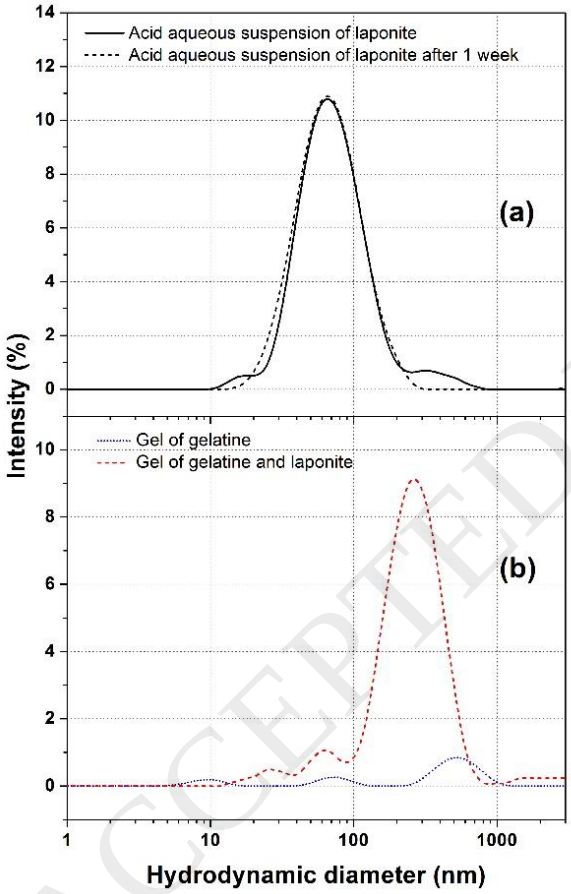

Fig. 9. DLS profiles of acid laponite dispersion after addition of 97 mM sulphuric acid before (black solid line) and after (black dashed line) one week (a). DLS profiles of acid laponite dispersion after addition of 97 mM sulphuric acid (black solid line), resuspendend gelatine/laponite gel (red dashed line) and resuspended gelatine control gel (blue dot line) (b). All the intensity data were set according to their DCR.

4. Conclusions

Optical absorbance studies of nanocomposite Fricke xylenol orange gel dosimeters were carried out. A procedure for incorporating nano-sized clay particles into Fricke xylenol orange gel dosimeters, using porcine gelatine as gelling agent, was successfully developed.

The satisfactory level of transparency showed by the gel samples enabled their optical absorbance analyses in the visible region for the dosimetric purposes.

The absorbance spectra shape proved to slightly depend on the NCP concentration and varied with the absorbed dose. The addition of laponite in the investigated amounts did not alter significantly the main dosimetric properties of the FG dosimeters in terms of sensitivity and linear dose response.

However, in spite of the fact that laponite-gelatine interactions were observed by DLS measurements, the lack of reticulation proved to not improve the ferric ions diffusion rate. Therefore, the addition of nanoparticles, in the tested concentrations, did not add any significant value to the investigated Fricke gel dosimeters.

Finally, the results confirm the recent outcomes that contributed to the interpretation of various characteristics that cause troubles in the utilization of FG dosimeters, mainly for measurements at low doses. In particular, a no negligible dependence of the dose-response curve parameters on the wavelength was observed, confirming the importance of the optimization of the optical analyses in Fricke gel dosimetry.

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