Novel GTA-PVA Fricke gels for three-dimensional dose mapping in radiotherapy

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One of the most recent and promising developments in radiotherapy dosimetry was the introduction of 3D radiation-sensitive gels. These gels present tissue equivalent composition and density, so they also serve as phantoms, and their response is largely independent of radiation quality and dose rate. Some gels are infused with ferrous sulfate and rely on the radiation-induced oxidation of ferrous ions to ferric ions (Fricke-gels). These formulations suffer from spontaneous-oxidation and diffusion of ferric ions after irradiation; chelating agents such as xylenol-orange significantly reduces the latter. Other gel types consist of dispersed monomers, and rely on radiation-induced cross-linking; they form stable polymer structures, but they are typically affected by significant toxicity. In a large multicenter study, we developed and investigated new formulations of Fricke-gels based on poly-vinyl alcohol chemically cross-linked with glutaraldehyde. The formulation is safe and easy to manufacture, with a sensitivity of 0.073 Gy^{-1} and a diffusion coefficient of 0.17 mm^2/h, it arguably offers the best all-around performance of current Fricke-infused gels. The main original outcomes of the study are described in this work, while reference is made to separate reports for specific procedures and results.

HIGHLIGHTS:
New chemically cross-linked radiation sensitive gels were developed and validated in multicenter study.
Gels are made with GTA and PVA, and they are infused with ferrous ammonium sulfate and xylenol orange.
Gels have high sensitivity, low diffusion and they are easy and safe to manufacture.
Imaging can be done with standard optical techniques, but also with low-field-intensity MRI scanners for the extremities.

Keywords: Three-dimensional dosimetry Poly-vinyl alcohol, Glutaraldehyde, Ferrous sulfate, Xylenol-orange, Spectrophotometry, Optical tomography, Magnetic resonance imaging

1. Introduction

Radiation dosimetry in radiotherapy (RT) has the twofold goal of ensuring the clinical quality of the treatment and the radiation protection of the patient (d'Errico, 2006). Benchmark dosimetry for acceptance testing and commissioning of RT systems is still based on ionization chambers (Low et al., 2011). However, even the smallest chambers cannot resolve the steep dose gradients of up to 30–50% per millimeter generated by advanced conformal, intensity modulated techniques.

Techniques based on silicon diodes, thermoluminescent or photostimulable chips and films have been developed, as well as radiochromic films; however, none of them allows three-dimensional measurements (d'Errico, 2006; Devic, 2011; IAEA, 2013; Marrazzo et al., 2013; Aldosari et al., 2014; Ahmed et al.,

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2014; Petasecca et al., 2015; Souza et al., 2017). In this context, one of the most recent and promising developments for RT dosimetry was the introduction of radiation-sensitive gels (Gore et al., 1984; Appleby et al., 1986; Schulz et al., 1990). These gels are widely considered the only true 3D dosimeters available for radiotherapy applications. They present tissue equivalent composition and density, so they also serve as phantoms, and their response is largely independent of radiation quality and dose rate. Some formulations are infused with ferrous sulfate, and rely on the radiation-induced oxidation of ferrous ions to ferric ions (Fricke-gels) (Gore et al., 1984; Gambarini et al., 1994; Luciani et al., 1996). Others consist of monomers and cross-linkers dispersed in a gelatinous medium, and rely on radiation-induced polymerization, which creates a stable polymer structure in response to free radicals generated by water radiolysis (Maryanski et al., 1993; Fong et al., 2001). The monomers and cross-linkers of choice are acrylic-type compounds, because they do not present significant dose-rate and temperature dependence. With both categories of gels, irradiation causes variations of water-proton nuclear magnetic resonance relaxation times. These variations correlate with the dose absorbed locally and can be imaged using Magnetic Resonance Imaging (MRI). Changes in color and/or opacification of the gels also occur upon irradiation, allowing the use of optical tomography or spectrophotometry techniques.

Gels based on radiation-induced cross-linking are the main focus of recent research (Oldham, 2017). However, they often contain highly toxic chemical species: acrylamide, for example, is known to be a severe neurotoxin and a suspected carcinogen. Thus, they require safety precautions, such as preparation in a vented biosafety hood and use of gloves and goggles, making their manufacturing unwieldy and hazardous. Therefore, our research aimed at developing new Fricke-infused hydrogel formulations. Historically, the most widely-used matrices for Fricke-infused gels have been two natural compounds: gelatine—a hydrolyzed form of collagen extracted from animal skin, bones, and connective tissues, and agarose—a polysaccharide polymer extracted from seaweed.

The natural origin of gelatine involves an inherent variability in purity and composition due to age and species of the animal source, and due to the complexity of extraction and purification processes. Different gelatine batches present different properties, and therefore gelatine-based products inevitably present variable characteristics. Spontaneous gelling of gelatine involves the creation of inter-chain links, mainly hydrogen bonds, between the functional groups of the amino-acid residues of the chains. Since gelatine extraction processes yield variable length chains, crosslinking, diffusion and permeability characteristics are all affected. External cross-linking agents may also be used, but cross-linking is problematic because of the chemical and structural complexity of gelatine. A further drawback encountered with gelatine formulations is their degradation over time.

Agarose has also been widely used as a matrix for Fricke-infused gels; indeed, some agarose gels are reportedly more sensitive to radiation than either aqueous solutions or gelatine systems infused with ferrous sulfate (Olsson et al., 1989). However, agarose also has a series of drawbacks: first of all, as with gelatine, its natural origin affects the reproducibility of its structure and of its cross-linking. Moreover, agarose gels are translucent, rather than transparent, which hinders optical absorbance measurements (Bero et al., 2000). A further drawback is that agarose must be raised to high temperatures (90–95 °C) to properly dissolve and then form a gel while cooling down, which may cause a loss of dissolved oxygen (Hazle et al., 1991).

Because of the above-listed limitations of gelatine and agarose, we focused our research on synthetic matrices. Our goal was developing and fully describing new dosimetric gel formulations based on poly-vinyl alcohol (PVA), offering high stability, sensitivity and ease of manufacture. The project was structured as a multi-center study: the University of Pisa developed and shared the PVA-based formulations, performing diffusion and dosimetry studies with spectrophotometry and low-field MRI; the University of Palermo optimized the MRI acquisition sequences and investigated various influence parameters; the Polytechnic of Milan and the University of Pavia focused on the stoichiometry of the complexation of xylenol-orange and ferric ions; the University of Milan further studied gelatine dosimeters, the current golden standard; finally, the Federal University of Sergipe performed independent reproducibility studies.

2. Materials and methods

Based on recent and promising studies (Chu et al., 2000; Smith et al., 2015), we focused our efforts on poly-vinyl alcohol gels. PVA is a polymer with a simple chemical structure, it is water-soluble, non-toxic, inexpensive and suitable for manufacturing hydrogels via physical or chemical routes. PVA is synthesized through well-established processes that allow an accurate selection of the molecular weight distribution, i.e., the length of the chains. Consistency between different batches is very high and so is the reproducibility of derived products.

The easiest physical method to produce PVA gels is subjecting an aqueous solution of PVA to freeze-thaw cycles. At low temperature, segments of PVA chains are coordinated into microcrystalline structures that act as cross-links. The formation of micro-crystals is favored by the structural simplicity of the polymer and by the presence of numerous hydroxyl groups that coordinate through hydrogen bonds. Once formed, the crystals are stable enough not to dissolve at room temperature. Repetition of freeze-thaw cycles facilitates the growth of micro-crystals and the formation of new ones. The final characteristics of these hydrogels depend on various parameters, such as the number of thermal cycles, the temperature reached in the cycles, the cooling and heating rates, as well as the concentration of the polymer and its molecular weight. A drawback for some applications is that these hydrogels are not completely transparent, but may range from translucent to completely opaque. A good balance between transparency and mechanical or diffusion properties can be obtained only for small-size samples, while larger items almost inevitably present structural inhomogeneities.

Alternatively, the production of PVA hydrogels may be achieved by chemical pathways, using suitable cross-linking agents. The chemical structure of PVA offers the possibility to choose from a variety of cross-linking agents. Among them is glutaraldehyde (GTA), a small molecule that easily reacts with the PVA hydroxyl groups, creating bridges between the chains. GTA is a relatively non-toxic substance and its PVA cross-linking reaction occurs at room temperature, yielding hydrogels that are transparent to light. Several characteristics of the GTA-PVA gels depend on the degree of cross-linking and can be easily modulated by adjusting the concentration of PVA, its molecular weight and the GTA/PVA ratio.

Our dosimeters are made with 10% w/v PVA and cross-linked by adding glutaraldehyde, according to procedures detailed elsewhere (Marini et al., 2017). The gels are infused with Fricke-solution: 25 mM sulfuric acid and 0.5 mM iron ammonium sulfate, along with 0.165 mM xylenol-orange (XO). Fricke infused gels suffer from spontaneous oxidation and diffusion of ferric ions after irradiation. The latter can be significantly reduced by adding to the formulation a large-molecule chelating-agent such as xylenol-orange (Appleby and Leghrouz, 1991). Our formulation is liquid when kept refrigerated and undergoes gelification when raised to room temperature. The gelification process was analyzed with a small amplitude rheometer where the sample is exposed to a vibrating needle to

assess its hardening (Fig. 1a). A Fricke-infused formulation based on 3% w/v gelatine was used for a comparative analysis (Gambarini et al., 2017).

Following irradiation with high-energy x-rays at clinical RT facilities, spot absorbance measurements for dose-response studies, as well absorbance-position profiles for diffusion studies, were acquired with a Cary-4000 UV-VIS spectrophotometer (Agilent Technologies, Danbury, CT, USA). The device is equipped with a moving tray (Fig. 1b) and it can acquire absorbance measurements at 1 mm steps along the cuvette longitudinal axis. In a concerted action with the international company Radosys Kft. from Budapest (Hungary), we also developed a prototype scanner for optical tomography of the gels. The scanner uses a pencil beam of laser light and is equipped with an original ray-tracing approach to detect and correct beam refraction and reflection at the interfaces of gel containers (Fig. 1c).

Since the optical scanner is currently undergoing type-testing, 3D scans of the gels were performed using magnetic resonance imaging. Clinical units operating at 1.5 T have been used extensively in studies of Fricke infused gels. Therefore, we acquired reference data on a 1.5 T Signa unit (GE Healthcare, Chicago, IL, USA) in Pisa, and a 1.5 T Achieva unit (Philips, Best, the Netherlands) in Palermo. In both cases, we used head coils and optimized inversion recovery sequences to acquire T_1 weighted maps; we then derived the relaxation rate $R_1 = 1/T_1$, i.e. the inverse of the longitudinal (or spin-lattice) relaxation time T_1, using in-house software. In addition, we explored imaging with both low- and high-intensity field MRI. In particular, we used a 0.3 T O-Scan extremity-scanner (Esaote, Florence, Italy), using a knee coil and inversion recovery sequences, and a 7 T Pharmascan small-animal scanner (Bruker, Billerica, MA, USA), providing a high spatial resolution of 200 μm.

3. Results and discussion

Our attempts to produce homogenous cryogenic PVA gels using freeze-thaw cycles were not satisfactory. Even small-size samples cast in spectrophotometry cuvettes are highly opaque compared to chemically cross-linked GTA-PVA gels (Fig. 2). Furthermore, cryo-gels present light absorbance values whose standard deviation is twice that of GTA-PVA gels (Fig. 3). These inhomogeneities become macroscopic when larger volume cryo-gel samples are produced (Fig. 4).

Conversely, GTA-PVA Fricke-XO gels are transparent, homogeneous and present a reproducible dosimetric performance. Proof of their reproducibility are the independent measurements of the dose response and of the diffusion coefficient that were done in our multicenter study. Gels manufactured at the Universities of Pisa and Sergipe according to our protocol were irradiated up to 200 Gy and presented the absorbance values reported in Fig. 5. Plotted data are averages of several measurement series; they agree within the error bars (included in the symbols) and indicate a sensitivity of 0.073 Gy^{-1} in the linear portion of the curve. Diffusion effects were measured independently at the Universities of Pisa and Palermo by delivering 10 Gy to partially-shielded cuvettes, thus producing

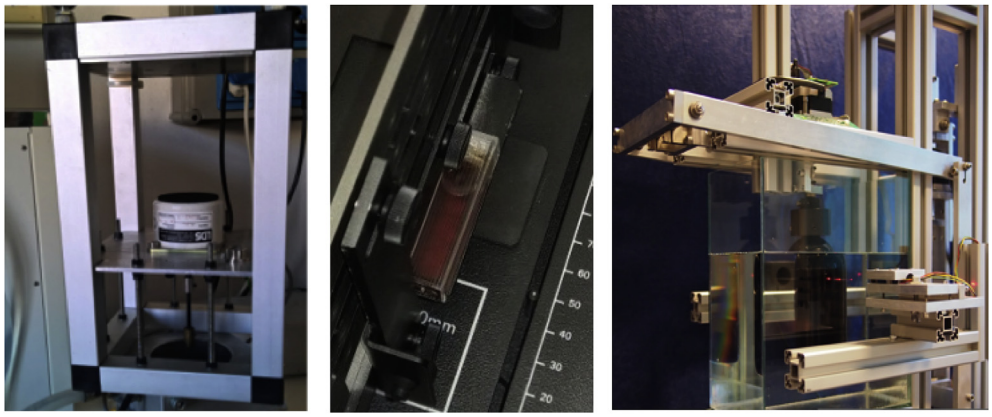

Fig. 1. a) Small amplitude oscillatory rheometer; b) Scanning UV-VIS spectrophotomer; c) 3D optical tomography prototype.

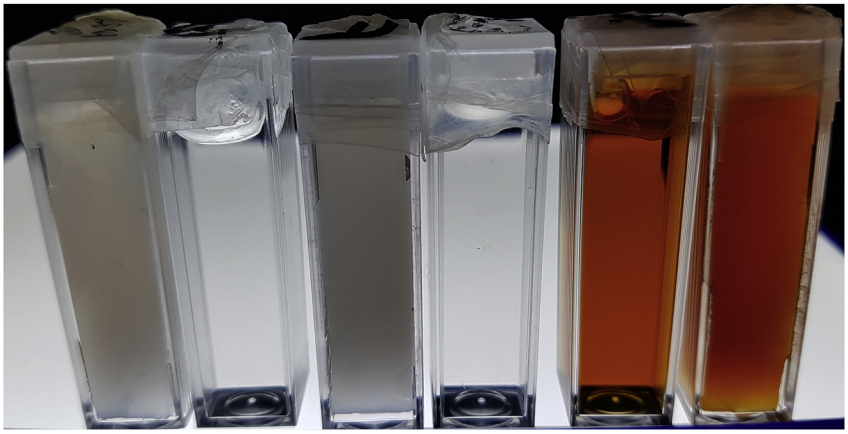

Fig. 2. Photograph showing the transparency of GTA-PVA gels versus the opacity of cryogenic PVA gels. From left to right: plain cryo-gel; plain GTA gel; Fricke cryo-gel; Fricke GTA gel; Fricke GTA gel with XO; Fricke cryo-gel with XO.

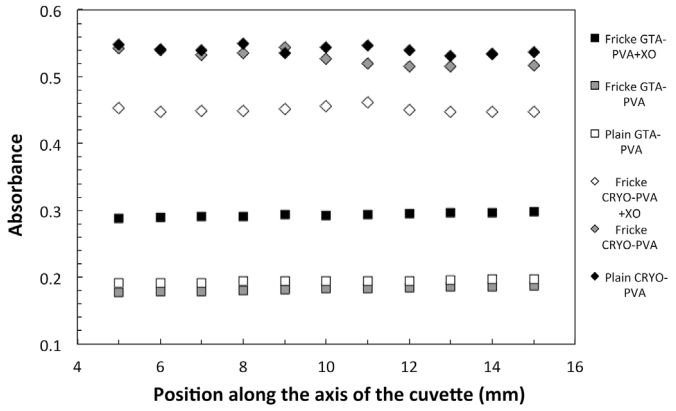

Fig. 3. Spectrophotometric scans of the different PVA gel compositions shown in Fig. 2, the standard deviation of the cryogenic gels is about double that of GTA cross-linked gels.

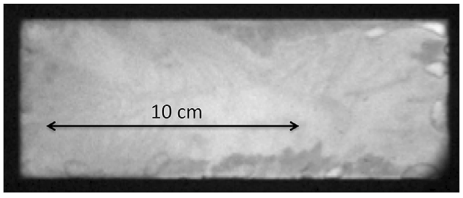

Fig. 4. Macroscopic inhomogeneities in the T_1 weighted MRI image of a ½ L cryogenic PVA gel scanned at 1.5 T using a head coil and an inversion–recovery sequence optimized for brain scans.

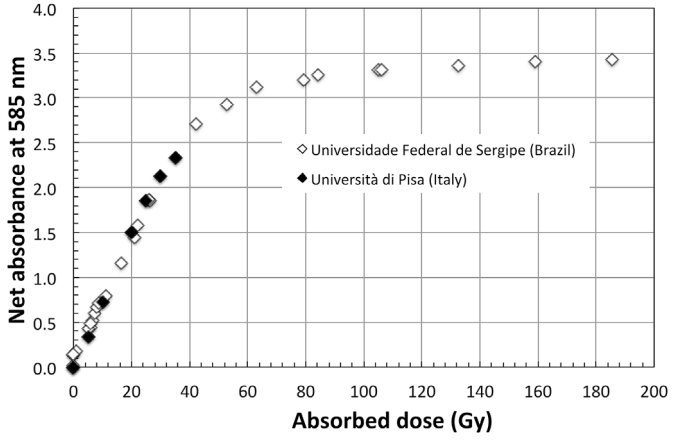

Fig. 5. Dose response of Fricke-XO GTA-PVA gels measured with UV-VIS spectrometry at the University of Pisa, Italy, and at the Federal University of Sergipe, Brazil; onset of saturation is observed at around 30 Gy.

sharp dose gradients. In Pisa, absorbance profiles were acquired as a function of elapsed time with the Cary 4000 scanning spectrophotometer. Results analyzed with the method by Kron et al. (1997), yielded a diffusion coefficient of 0.17 mm^2/h. In Palermo, gels produced with the same amount of GTA, and thus the same cross-linking and diffusion properties, were similarly irradiated and then scanned with the 7 T Pharmascan MRI scanner. The outcome was a diffusion coefficient of 0.18 mm^2/h (Marrale et al., 2017). Achieving the same results through completely independent experiments supports the reliability and reproducibility of this gel matrix. Moreover, a sensitivity of 0.073 Gy^{-1} and a diffusion coefficient of 0.17 mm^2/h are arguably the best all-around performance of current Fricke-infused gels.

High field-intensity MRI units, like the 7 T Pharmascan, are only available at few research centers, while standard 1.5 T units are typically burdened by heavy clinical workloads. Therefore, we started developing optical tomography techniques and we also investigated the use of low-field MRI scanners that are more often available. While results from our optical tomography prototype are not available yet, we did achieve convincing evidence that low-field MRI scanners can provide 3D dose maps adequate both in terms of contrast and of spatial resolution. Fig. 6 shows a photograph and a 0.3 T MRI map of gels irradiated to increasing absorbed doses. The signal-to-noise ratio of the images is adequate for dosimetric purposes, and the spatial resolution (nominally 0.4 mm) is sufficient to show the 1 mm thick wall of the spectrophotometry cuvettes. With fields of view typically ranging from 10 to 20 cm and comparable scan lengths, these units can image dosimetric gels of several liters and possibly accommodate a full head phantom.

The dose response curves based on UV-VIS spectrophotometry show the onset of a saturation shoulder around 30 Gy (Fig. 5). This is due to the progressive depletion of XO that is no longer available for complexation with ferric ions, resulting in a leveling out of the absorbance. Conversely, corresponding to a dose of 30 Gy, the T_1 weighted MRI signal shows an increasing slope (Fig. 7). This suggests that when ferric ions are free, rather than complexed with XO, they affect more the proton relaxation rates. This interpretation is supported directly by MRI scans of GTA-PVA gels manufactured with and without XO (Collura et al., 2017), showing a threefold higher signal when XO is absent (Fig. 8). This effect is currently further investigated, along with the influence of XO in the gel matrix on the ferrous-ferric ion reaction yield.

Our group also performed a systematic analysis of the absorption spectra of Fricke-XO gels, providing new insights into the complexation between XO and Fe^{3+} ions. The latter is known to play a key role in the dosimetric response of the gels, especially at low doses, but it is difficult to investigate, mainly because of the difficulty to have pure XO. Our method was complexation-titration followed by UV-VIS spectroscopy: increasing and well-defined concentrations of Fe^{3+} were added to a XO solution and absorbance spectra were recorded at each concentration (Liosi et al., 2017).

UV-VIS absorbance spectra for Fe^{3+}/XO molar ratios increasing from 0 to 5 are reported in Fig. 9. The peak at 585 nm increases with the concentration of ferric ions, as expected. However, the absorbance spectra cannot be explained assuming that the only complex occurring between xylenol-orange and ferric ions is one-to-one. Thus, we performed an original analysis using the "equilibrium restricted factor" approach (Vander Griend et al., 2008) that calculates simulated absorption spectra assuming the presence of different complexes: not only XO-Fe^{3+}, but also XO-$(Fe^{3+})_2$, $(XO)_2$-Fe^{3+} and $(XO)_3$-Fe^{3+}. The presence of the expected XO-Fe^{3+} and of some XO-$(Fe^{3+})_2$ complexes is consistent with the observed absorbance spectra for high concentrations of ferric ions, like those produced by high-dose irradiations. However, at low ferric ion concentrations, contributions of the other complexes are relevant, and this may explain the deviation observed at low absorbed doses from a linear response without threshold.

4. Conclusions

Our multicenter collaboration developed a novel GTA-PVA gel formulation for three-dimensional dose mapping in radiotherapy that offers what is arguably the best all-around performance of current Fricke-infused gels. Compared to dosimeters based on natural gelling agents, our formulation offers high reproducibility and sensitivity, low diffusion and controlled degree of cross-

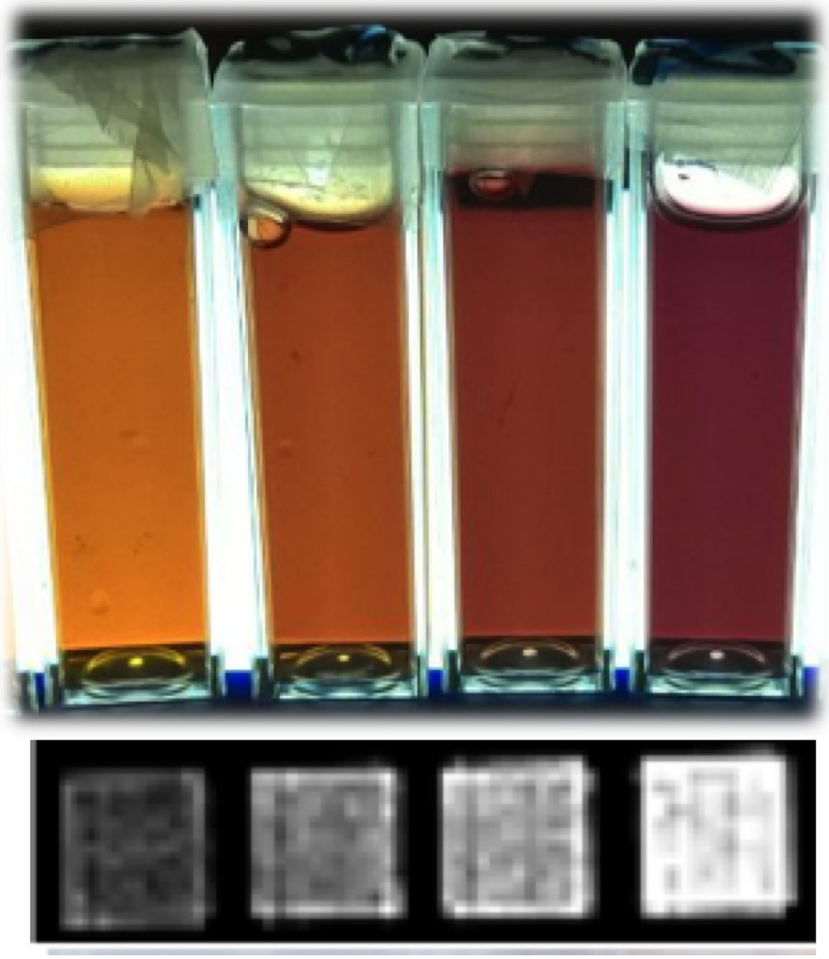

Fig. 6. Photograph and T_1-weighted 0.3 T MRI maps of Fricke-XO GTA-PVA gel cuvettes (1 cm side) irradiated to increasing absorbed doses.

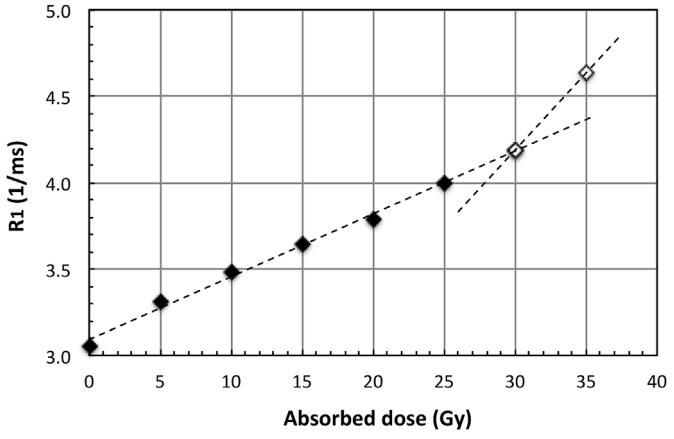

Fig. 7. Graph of the R_1 relaxation rate of Fricke-XO PVA-GTA gels measured as a function of absorbed dose with a 0.3 T MRI extremity scanner; a change in slope is visible around 30 Gy.

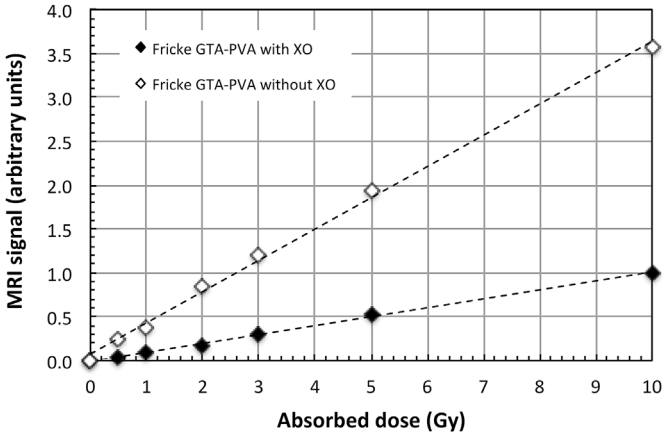

Fig. 8. Graph of T_1 weighted MRI signal intensities of Fricke GTA-PVA gels with and without xylenol-orange, measured as a function of absorbed dose with a 1.5 T scanner.

linking; compared to monomer-based gels, ours is non-toxic. Furthermore, thanks to their high transparency, our dosimeters can be read out with optical techniques as well as with magnetic resonance imaging with high- or low-intensity scanners. The spatial distribution of the signal is quite stable, with a diffusion coefficient of only 0.17 mm^2/h. The dose response is linear up to 30 Gy and the sensitivity of 0.073 Gy^{-1} is comparable to the best gelatine-based formulations. An inherent limitation of 3D gels is that they are single-use dosimeters. Some partly reusable commercial formulations have been recently introduced (Juang et al., 2015); however, the signal is not fully zeroed and the dosimeters can only be used a limited number of times. Our current goal is developing dosimetric gels that can be completely annealed and reversed to the pre-irradiated state, in order to be truly reusable.

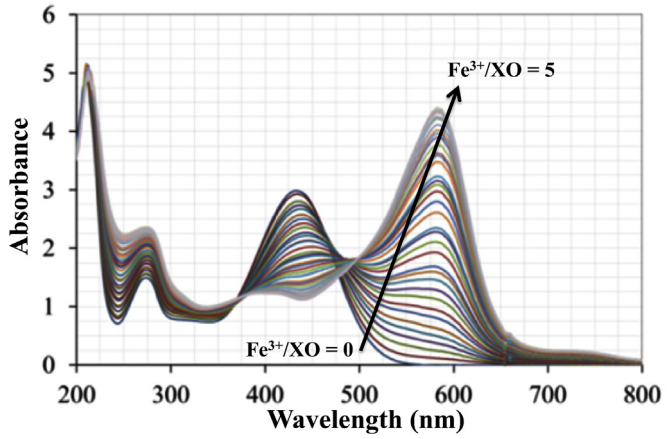

Fig. 9. UV-VIS spectra of solutions of 0.165 mM xylenol-orange in 25 mM sulfuric acid as a function of increasing Fe^{3+}/XO molar ratios.

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