



Molecular structure effects on the post irradiation diffusion in polymer gel dosimeters



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HIGHLIGHTS

- A chemical system based on itaconic acid and N-N' methylenebisacrylamide was presented.
- A chemical point of view of the results of the irradiated dosimeters was done.
- A modified monomer was synthesized modifying an itaconic acid molecule.
- Effects on the dosimetric behavior in these new materials were tested.
- Post-irradiation diffusion on the itaconic acid based dosimeters was analyzed.

ARTICLE INFO

Article history:

Received 31 July 2014

Received in revised form

2 February 2015

Accepted 4 March 2015

Available online 6 March 2015

Keywords:

Polymer gel dosimeter

Diffusion

Itaconic acid

Dosimetry

ABSTRACT

Polymer gel dosimeters have specific advantages for recording 3D radiation dose distribution in diagnostic and therapeutic medical applications. But, even in systems where the 3D structure is usually maintained for long periods of time after irradiation, it is still not possible to eliminate the diffusion of the different species in the regions of dose gradients within the gel. As a consequence, information of the dose loses quality over time. In the pursuit of a solution and to improve the understanding of this phenomenon a novel system based on itaconic acid and N-N'-methylene-bisacrylamide (BIS) is hereby proposed. Effects of changes in the chemical structure of the monomers over the dosimetric sensitivity and over the post-irradiation diffusion of species was studied. In this study, one of the carboxylic groups of the itaconic acid molecule was modified with aniline to obtain molecules with similar reactivity but different molecular sizes. Then, dosimeters based on these modified species and on the original ITA molecules were irradiated in an X-ray tomography apparatus at different doses up to 173 Gy. Afterwards, the resulting dosimeters were characterized by Raman spectroscopy and optical absorbance in order to study their feasibility and capabilities as dosimetric systems, and by optical-CT to analyze the post irradiation diffusion.

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1. Introduction

Polymer gel dosimeters have specific advantages for recording 3D radiation dose distribution representing a key factor for most of the therapeutic and diagnostic radiation techniques (Baldock et al., 2010; Doran, 2009). Radiation-induced polymerization and

crosslinking reactions that take place in dosimeters have been studied for different monomers like acrylamide and N-N'-methylene-bisacrylamide (BIS) and most recently for less toxic monomers like N-isopropyl acrylamide (NIPAM) and BIS (Chiu et al., 2014; Huang et al., 2013). The resulting dosimeters presented a linear response with radiation and proved to be excellent candidates for measuring three-dimensional dose distributions, which is a fundamental characteristic of dosimetry systems, as stated by Gore and Kang (Gore and Kang, 1984) on their studies on Fricke

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Gel dosimeters. An important aspect of this development was to stabilize the geometric dose information by incorporating the aqueous Fricke solution into a gel matrix and setting the bases for almost all modern dosimetry systems. Later on, Maryanski et al. (1993) proposed a new type of dosimeters where polymerization of a monomer and cross linker species was induced by radiation. Upon irradiation, water molecules dissociate into OH and H radicals that break the double C=C bonds of co-monomers, the resulting co-monomer radicals interact with other co-monomers and produce a chain reaction to form 3D polymer networks that are spatially retained in a gelatin matrix. The amount of formed polymer is related to the absorbed dose received by the polymer gel. The degradation of the spatial dose information because of ion diffusion represents the main limitation for Fricke gel dosimetry (Baldock et al., 2001). However, the use of polymers instead of ionic species considerably lowers the diffusion effects and if a proper formulation of the dosimetric system is selected, then the irradiation assays and dose distribution measurements can be carried out on different times without losing sensitivity or spatial distribution quality.

In this work a new polymeric system consisting of: (1) a monomer (itaconic acid), (2) a cross linking agent (BIS) acting as radiation induced reactants, (3) agarose or gelatin to maintain spatial distribution upon radiation, and (4) an oxygen scavenger molecule (Tetrakis hydroxymethyl phosphonium chloride THPC) to prevent oxygen free radical polymerization inhibition, is studied. These are the typical constituents of a polymeric dosimeter, however, because of itaconic acid nature that could prevent the gelatin gelification, a phosphate based buffer solution was used instead of water for the preparation of the dosimeters. The monomers ITA and BIS have been already studied for hydrogel formation and the polymerization induced by other radical initiation methods has been demonstrated (Caykara and Akcakaya, 2007).

The diffusion of species in a solution or gelatin matrix depends on several phenomena, chemical interactions, polymer entanglement, molecular size, mesh size, among them (Cherdhirankorn et al., 2009; Masaro and Zhu, 1999). Most of these properties are inherent to each chemical system and can't be varied for a specific dosimeter. Nevertheless, if similar monomer molecules are selected for the dosimeters preparation relevant information can be obtained from their differences upon irradiation.

The main objective of this work is to establish a methodology to study the relationship between the molecular structure of the monomers and the post irradiation changes in polymer gel dosimetric systems. For that purpose different particular goals were defined, first to study the performance of a new polymeric dosimetric system based on itaconic acid and BIS (ITA-BIS). Also, the chemical modification of the itaconic acid molecule by a coupling reaction with aniline is studied (modified ITA). Finally, a methodology to correlate the post irradiation diffusion effects in polymeric dosimeters is applied to the ITA-BIS dosimeters and compared with the preliminary results obtained for dosimeters prepared with the modified ITA and BIS.

2. Materials and methods

2.1. Itaconic acid chemical modification

The synthesis of the new monomer was performed through the formation of an amide bond mediated by a carbodiimide reaction. For that purpose, itaconic acid ($\geq 99\%$ purity) and aniline ($\geq 99.5\%$ purity) purchased from Sigma-Aldrich® were used as reactants, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (commercial grade) was used as carboxyl and amine-reactive zero-

length cross linker together with N-hydroxysuccinimide (98%) (NHS) to enhance the coupling efficiency. Both reactants were also purchased from Sigma-Aldrich®. The solvent used as reaction medium and also for the dosimeters preparation was a buffer solution with equimolar quantities of sodium phosphate monobasic and sodium phosphate dibasic with analytical grade. The molar ratio ITA:Aniline was 1:5 to assure the reaction of most of the itaconic acid. However EDC (1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride) was used as the limiting factor in the reaction in order to avoid the reaction of both acid groups in the ITA molecules, by keeping the molar ratio ITA:EDC above 2:1. The reaction extent was measured by UV-vis spectroscopy recorded with a Shimadzu spectrophotometer UV-260 from 290 to 550 nm every two minutes for a total time of 80 min. Fourier transform infrared spectroscopy (FTIR) was used to analyze the reaction products and reagents and to confirm the ITA-Aniline coupling reaction, A Nicolet 5-SXC FT-IR spectrophotometer was used to obtain the spectra. FTIR spectra were recorded in a spectral range of $4000\text{--}400\text{ cm}^{-1}$ with a resolution of 4 cm^{-1} ; 64 scans were run for each sample.

In order to purify the final product a temperature induced crystallization process was carried out obtaining a solid product by cooling the liquid product from ambient temperature to 4°C for 48 h. The solid product was then filtered and washed twice with the supernatant and then twice with milli-Q grade water at 4°C , this procedure was repeated 3 times. Considering that the melting point of aniline is -6.3°C and that the rest of the reagents are soluble in water, is reasonable to expect an efficient separation of the desired product with the described procedure. Afterwards, the solid material was vacuum filtered using a Büchner flask set-up and finally, the resulting crystals were dried at 37°C until constant weight. FTIR spectroscopy was used to evaluate the chemical composition of the crystals.

The overall coupling yield calculated from a molar balance for the limiting reactant as: (modified ITA moles / original ITA moles $\times 100$) was 32.5%, which was expected because of the specific conditions that were selected to ensure the modification of only one acid group of the ITA molecule at the expense of reducing the reaction yield. The obtained product requires a subsequent purification in order to obtain a product of comparable quality to the other reagents used in this work. Nevertheless, it is still suitable for a qualitative comparison and dosimetric feasibility tests.

2.2. Gel dosimeter preparation

For the ITA-BIS based dosimeters preparation the quantities presented in Table 1 were used, first Gelatin 300 Bloom purchased from FLUKA was mixed at ambient temperature and heated up to 50°C for 30 min, then the temperature was lowered to 37°C to avoid polymerization of the monomers during the dosimeter preparation. BIS was mixed for 15 min and then the ITA was incorporated and stirred for another 15 min. Finally, 10% v/v of the buffer solution with THPC also at 37°C was incorporated and the

Table 1
Dosimeter compositions.

Itaconic Acid Based Dosimeter		Modified Itaconic Acid Based Dosimeter	
Component	Mass % (gr/gr x 100)	Component	Mass % (gr/gr x 100)
Buffer solution	90.13 ± 0.01	Buffer solution	90.62 ± 0.01
Gelatin	5.13 ± 0.01	Gelatin	5.14 ± 0.01
ITA	3.04 ± 0.01	Modified ITA	3.06 ± 0.01
BIS	1.59 ± 0.01	BIS	1.02 ± 0.01
THPC	0.10 ± 0.01	THPC	0.10 ± 0.01

mixture was stirred for 30 min. The final solution was used to fill the cuvette and the layer type vessels leaving no air in the vessels to minimize oxygen inhibition during the irradiation induced polymerization and finally the dosimetry were stored for 24 hr at 4 °C until the irradiation experiments for stabilization purposes. For the dosimeters prepared with the modified ITA, the same procedure was followed but the quantities were determined by the solubility limits of the new molecules.

2.3. Dosimeter irradiation

Samples irradiations were carried out in a conventional X-ray tube with a W anode available at LIIFAMIR® facilities. The tube is connected to a generator with a maximum power of 3 kW that provides electrical current values from 5 to 60 mA, and voltage values from 20 to 60 kV. Different dose levels can be achieved with this setup. In most of the irradiation experiments for the layer type dosimeters an electrical current of 48 mA, voltage of 40 kV, and a 4.5 mm diameter collimator were used obtaining a dose rate of 2.88 Gy/min. To measure the absolute dose rate a Farmer type ionization chamber (PTW-Freiburg TN 30013) was used in water phantoms. For the cuvette type dosimeters, two different irradiation setups were used, first the samples were continuously rotated at 6 rpm during the irradiation experiments in order to obtain a homogeneous absorbed dose within the dosimeter. Then, other samples were irradiated from one side without rotation in order to assess the dosimeter's ability to maintain the three-dimensional absorbed dose distribution. On the other hand, layer type dosimeters were irradiated using a circular collimator. In these experiments a known absorbed dose distribution geometry was obtained in order to study diffusion effects in the sensitive dosimetric material.

2.4. Dosimeter characterization

The degree of polymerization or gel formation within the dosimeters after the irradiation experiments was analyzed by two different methods. First, a chemical description and quantification was performed by Raman Spectroscopy with a Labram HR (Horiba Jobin-Yvon) Raman spectrometer using a 632.8 He–Ne Laser with a 6.3 mW power. In this case, spectra of the irradiated dosimeters were analyzed by comparing the area of some of the characteristic peaks for the stretching of C=C bonds in the ITA and BIS molecule. Also, taking into account the initial concentration in the dosimeters and the number of C=C groups in each monomer the disappearance of each specie as a function of the dose was determined.

Secondly, an in-home apparatus described elsewhere (Valente and Vedelago, 2013) was used to measure the transmitted light in the irradiated layer type dosimeters. The images acquired by this method provided information about density changes after the

irradiation that were used to determine the degree of response to the radiation source. These images were acquired after the dosimeters were irradiated and at different time intervals during 6 days in order to study any changes in the dosimetric system and to determine any post irradiation diffusion effect inherent to the dosimetric material.

2.5. Image analysis and diffusion calculations

From the images obtained at different time intervals after the irradiation of the dosimetric systems, the following image processing methodology was applied. Every image of a time series was normalized by calculating the difference in optical density (ΔOD) for each pixel, then for each irradiated zone in the layer type dosimeters the integration of the ΔOD in all the irradiated zone was performed, and the relative difference between the image obtained at each time and the image acquired immediately after irradiation was used as a comparison parameter. Any change in the area or intensity of the irradiated zone within time are considered by this parameter and the stabilization or diffusion effects on the dosimeters can be inferred in this way. Also dose profiles, at the center of the irradiated zone for different dose values were calculated at different times.

3. Results and discussion

3.1. Itaconic acid modification

The modified itaconic acid was obtained by means of the reaction depicted in Fig. 1, where an amide functional group is formed from one of the itaconic acid's carboxylic group and the amine group of a chosen modifier. In this work aniline was selected as the modifier, mainly because it is a simple molecule which increases the molecular size of the itaconic acid, and that should not decrease the polymerization reactivity compared to the original itaconic acid in a significant amount. Nevertheless, a larger molecular size together with a different electronic distribution in the modified itaconic acid molecule could affect the post irradiation diffusion.

The reaction evolution was followed by UV Visible spectroscopy, aniline was also suitable as the first modifier to study because it has an absorption peak at 448 nm that changes during the reaction. Fig. 2 shows the UV-vis spectroscopy of this reaction, there is a clear change during the reaction that involves the aniline molecule.

To evaluate the effect of visible light over the reaction, the same reaction was simultaneously performed in a dark room maintaining the remaining reaction conditions unchanged. The final product of this reaction was analyzed by UV-vis spectroscopy and compared to the product from the reaction measured continuously

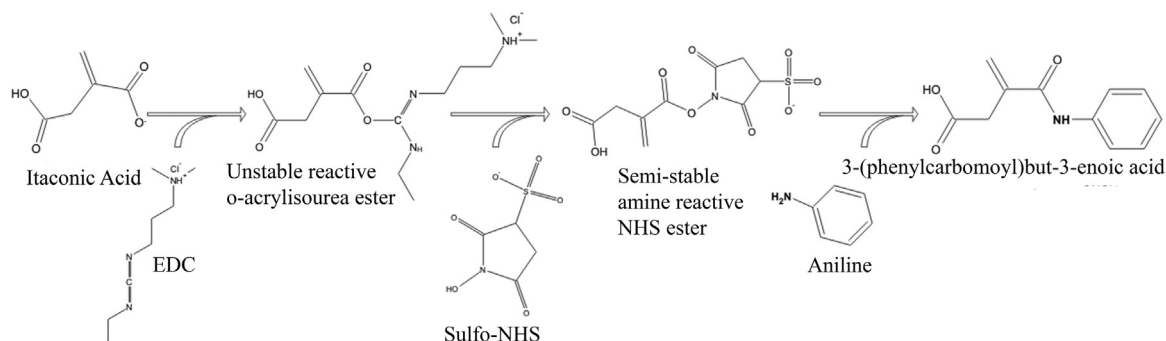


Fig. 1. Aniline and itaconic acid's reaction catalyzed by EDC and NHS to obtain a modified itaconic acid monomer: 3-(phenylcarbomoyl)but-3-enoic acid.

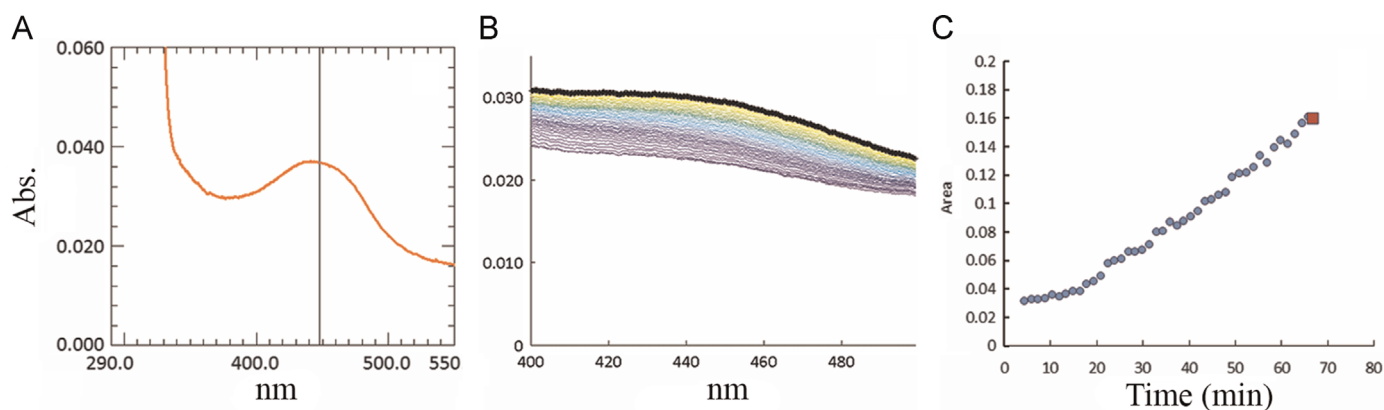


Fig. 2. (A) Characteristic UV visible absorbance peak of aniline. (B) Reaction of aniline and itaconic acid analyzed by UV-vis. for 80 min. (C) Area of the characteristic peak during the reaction.

by UV–vis spectroscopy. The result is also presented in Fig. 2B as the bold black spectrum and in Fig. 2C as the red square.

It is clear from these results that visible light has no effect over the reaction and that UV Visible spectroscopy is suitable for tracking the reaction progression. The final liquid product was also characterized by IR spectroscopy and compared to the reactants dissolved in a buffer solution with the initial concentration in the reaction. Fig. 3 presents the IR spectrograms, by comparing the itaconic acid and the final product spectra.

Finally to check if the reaction led to a molecule with one amide group and one carboxylic group as desired, the pH value of the final product was compared with the one of pure itaconic acid. The results showed that the pH value of the itaconic acid in water was 2 while the modified itaconic acid in the same concentration had a pH value of 4. These results and the presence of the carboxylic acid peaks in the IR spectra indicates that some acid groups reacted to form an amide bond with the aniline molecule, and some other were kept as carboxylic acid groups.

After the purification process a crystalline product of the modified itaconic acid was obtained, the overall yield was 32.5%. A picture of the final product is presented in Fig. 4.

3.2. Itaconic acid dosimeters

Two different types of dosimetry systems were prepared to study the dosimetric capabilities of the system ITA-BIS, first the dosimetric gel was used to fill PMMA cuvettes of $10 \times 10 \times 44 \text{ mm}^3$ (inner size), and then PMMA layer type vessels of $90 \times 90 \times 3 \text{ mm}^3$ (inner size) were prepared to study the post irradiation diffusion effects. For the cuvette geometry the irradiation results were analyzed by Raman spectroscopy to provide a chemical characterization of the polymeric material formed upon the irradiation,

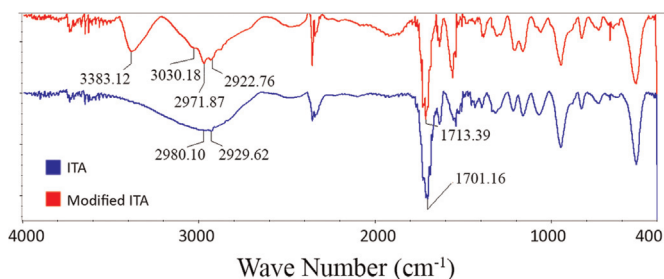


Fig. 3. Absorption spectra of itaconic acid (bottom) and modified itaconic acid (top). The following absorption bands were assigned to itaconic acid: band at 2980 cm^{-1} (O–H) and 1701 cm^{-1} (C=O carboxylic acid). The signals assigned to modified itaconic were: band at 3383 cm^{-1} (N–H secondary amide); 1713 cm^{-1} (C=O carboxylic acid) and the shoulder at 3030 cm^{-1} (C–H aromatic).

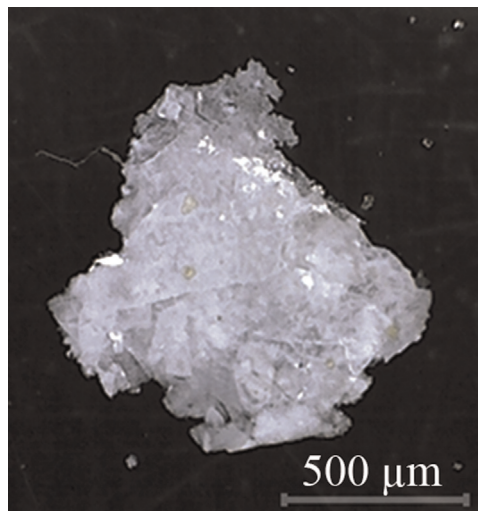


Fig. 4. Crystallized product.

similar procedures were used by (Huang et al., 2013) for dosimetric systems based on NIPAM and BIS monomers. Fig. 5 shows the resulting dosimeters after irradiation at different doses, results below 30 Gy were not represented because the sensitivity of the dosimetric system and were contained within the noise values of the characterization methods. Also, in order to evaluate the spatial capabilities of these type of dosimeters, a collimated X-ray field with a circular shape was used to irradiate two cuvettes and the results of this experiments are shown in Fig. 5B.

Raman spectra of these dosimeters are presented in Fig. 6 and the area analysis of those spectra are represented in Fig. 7. The stretching of the C=C bond in the itaconic acid and BIS molecules were used as characteristic peaks to evaluate the degree of polymerization in the dosimeters. Additionally, taking into account the initial concentration of the monomers and the fact that a molecule of N-N'methylene bisacrylamide has two vinyl groups, the monomers molecular consumption relative to the initial BIS molecules was calculated and represented in Fig. 7B. These results show that itaconic acid molecules are reacting faster than BIS ones at higher doses. Different results were observed for the system NIPAM-BIS in a previous work (Mattea et al., 2013), probably due to the fact that the reaction between BIS and itaconic acid is hindered by steric impediment and the negative charges of the carboxylic groups in the itaconic acid molecules.

From the layer type dosimeters two key results were obtained. First, the sensitivity of the ITA-BIS based dosimeter was calculated by means of optical methods, comparing light transmission values

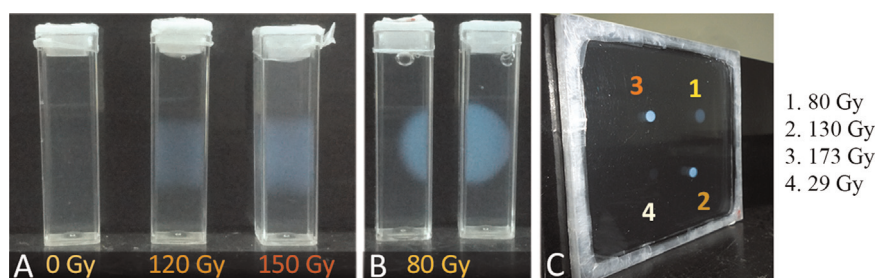


Fig. 5. (A) Cuvette type ITA-BIS dosimeters uniformly irradiated at two different doses (120 and 150 Gy). (B) Spatial capabilities of the ITA-BIS Dosimeters. (C) Layer type ITA-BIS dosimeters irradiated at different doses for diffusion studies.

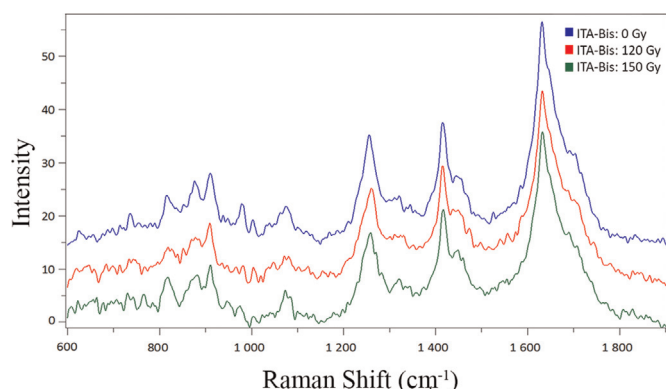


Fig. 6. Raman spectra for 3 cuvette ITA-BIS dosimeters irradiated at different doses.

for each of the irradiated zones. Results for doses up to 175 Gy for the ITA-BIS system, together with some preliminary results for the dosimeters prepared with the modified itaconic acid are presented in Fig. 8.

The error bars on each measurement were obtained from the dispersion of several ΔOD determinations on each irradiated zone of the layer type dosimeter, therefore including the inherent error of the measurement device and of the irradiation setup. The results indicated that the dosimetric system presents a threshold dose of 30 Gy and a linear response between 80 and 175 Gy. In order to measure the saturation point and the linear limit of this system a different irradiation setup is necessary and is planned for future works. Also comparing the range of optical density changes (ΔOD) from the itaconic acid based dosimeter and the modified itaconic acid one, a clear decrease in the sensitivity was observed.

Although this result is not desirable for most of the dosimetric applications, this work is focused on the effect of changes at a

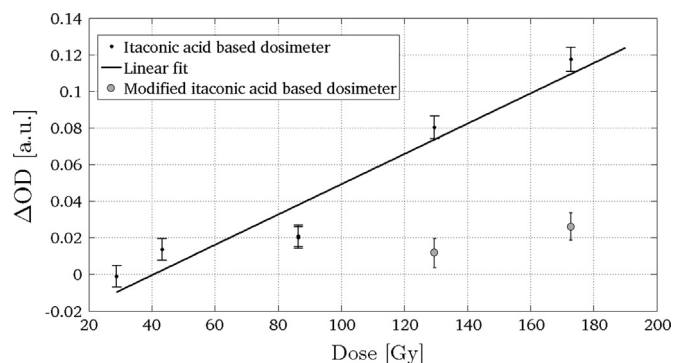


Fig. 8. Response curve for ITA based dosimeters and comparison with modified ITA based dosimeters.

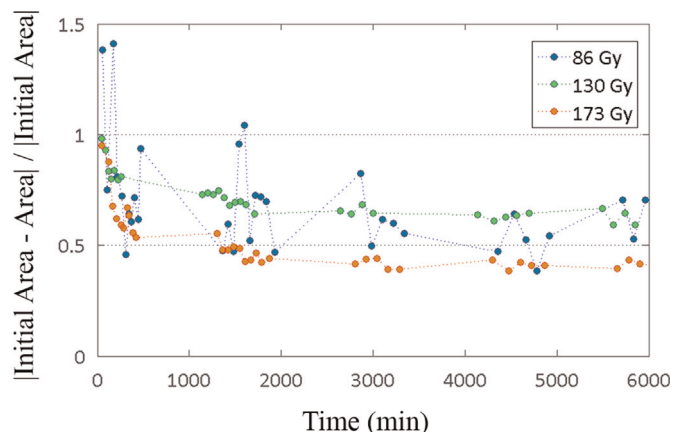


Fig. 9. Temporal evolution of the area of an irradiated zone of a layer type dosimeter irradiated with a dose of 86, 130 and 173 Gy.

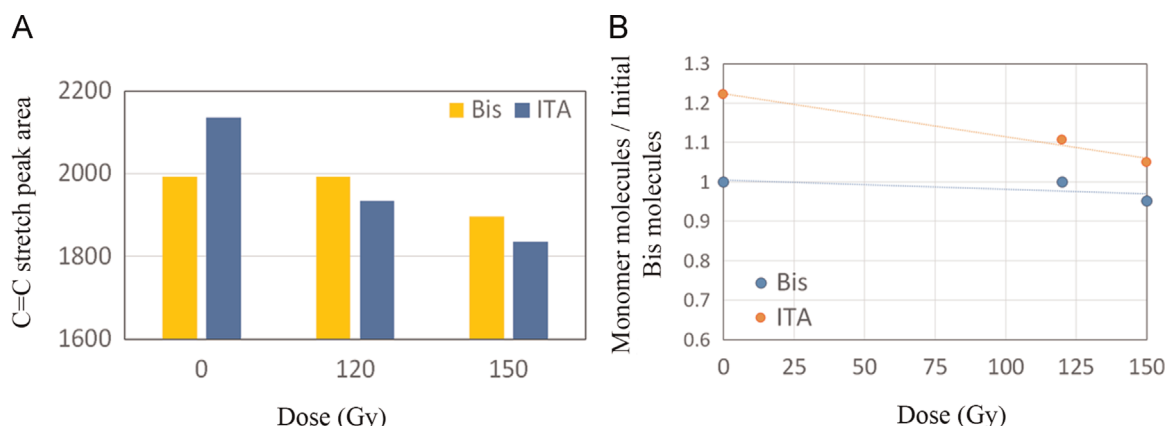


Fig. 7. A) Area of the characteristic peak of the vinyl groups in the ITA-BIS dosimeters at two different doses (120 Gy and 150 Gy). (B) Consumption of BIS and ITA monomers at different doses relative to the number of BIS molecules in the untreated dosimeters.

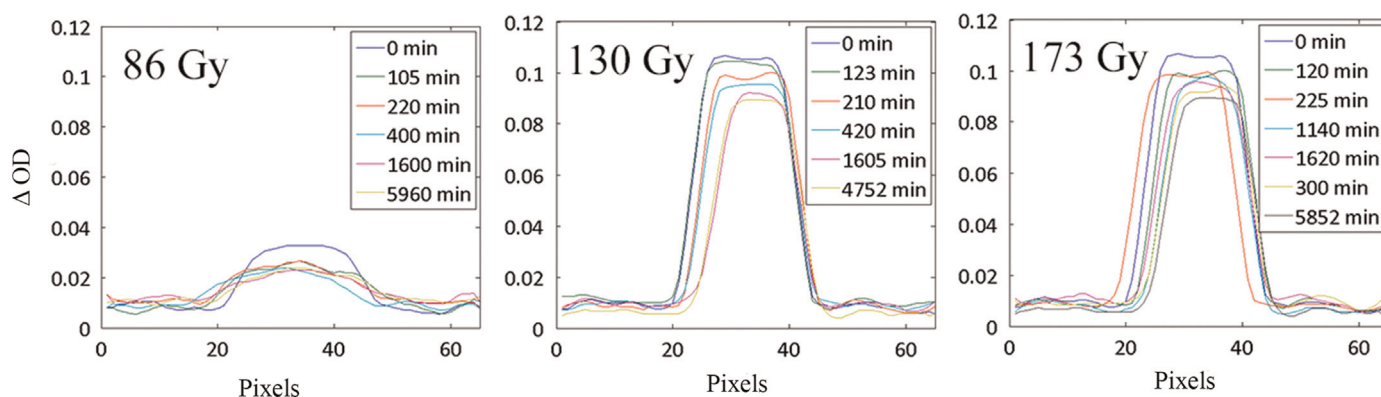


Fig. 10. Temporal evolution of the ΔOD of an irradiated zone of a layer type dosimeter irradiated with a dose of 86, 130 and 173 Gy.

molecular level of the monomers in a dosimeter over the post irradiation diffusion and not only over the dosimetric overall behavior and potential applications. In that regard, the evolution of the different irradiated areas on the layer type dosimeters was studied for a 6 day period. Two parameters were taken into account: the projected area of the intensity distribution in each irradiated zone over time, and the ΔOD profile obtained by cutting the volumetric representation of ΔOD with a plane perpendicular to the layer type dosimeter surface at the center of the irradiated zone. Fig. 9 shows the evolution of the area in layer type dosimeters irradiated at three different doses and Fig. 10 presents the dose profile at different post irradiation times.

Similar criteria to follow diffusion effects were taken by Tseng et al., (2002) but for systems with fast diffusion effects like Fricke gel dosimeters. Similarly to their results, the dose profiles at the center of the irradiated zone becomes narrower while diffusion takes place. A large variation in the area of the irradiated zone is observed in the first 1800 min for the ITA-BIS based dosimeters, after that time no clear effect was observed within the assayed timeframe. The former trend has been described by several authors (De Deene et al., 2000; Huang et al., 2013; Vergote et al., 2009) as common for polymer based dosimeters, where an initial stabilization period is required after irradiation and stable polymers with very low diffusion effects are observed.

3.3. Modified itaconic acid dosimeters

In order to check the feasibility of the modified itaconic acid based system for dosimetry applications, layer type dosimeters were prepared and irradiated with the same methodology as the itaconic based ones. However, the initial concentration of the monomers was not the same since the solubility limit for the modified ITA molecule is slightly lower at the dosimeter storage temperatures. Therefore, less concentrated dosimeters were used in the irradiation experiments presenting lower sensitivity than the ITA-BIS based dosimetric system as can be seen in Fig. 9 by the two gray circles. The lower reactivity could be due to several reasons, first the new molecule presents a different electronic distribution, the presence of an aromatic ring at one extreme of the molecule induces a severe change in the polarity of the molecule and consequently it could affect its reactivity. Also, the purification process in the production of the modified ITA needs further improvement in order to minimize the presence of unreacted aniline and to enhance the final dosimetric characteristics. Nonetheless, the polymerization induced by water ionization from X-ray sources was possible and is currently being improved to provide useful data for the theoretical understating of the effect of changes in the molecular structure over the post irradiation diffusivity in polymer based dosimetric systems.

4. Conclusions

A complete methodology to study the post irradiation diffusion in a new polymeric dosimetry system was successfully developed. The methodology included selecting commercial chemicals that could behave as radiosensitive materials, the chemical synthesis of new monomers suitable for X-ray irradiation response, selecting the concentrations and procedure to prepare the dosimeters, irradiating the dosimeters, and quantifying the diffusion effects present in the dosimeters after their irradiation. In particular, a new dosimetric material based on itaconic acid, N-N'-methylene bisacrylamide, gelatin and tetrakis (hydroxymethyl) phosphonium chloride was presented and its radiation response was studied from a chemical and optical point of view. A linear response was observed when the dosimeters were irradiated in the dose range 80 Gy – 175 Gy, however further optimization is required to establish the dose threshold and the linear limit or saturation point of the dosimetric system. Also a new molecule was synthesized from itaconic acid in order to correlate molecular differences to radiation response in this dosimetric system. The new molecule was very similar to itaconic acid but with an aromatic ring and a carboxylic acid group instead of the two original carboxylic acid groups of itaconic acid. This new molecule presents a different electronic distribution, changes in the reactivity and diffusion behavior compared to itaconic acid. Finally, layer type dosimeters were used to study the post irradiation diffusion effects, optical methods were used to analyze how the intensity and area of an irradiated zone of the dosimeter changes with time, the results for itaconic acid are in agreement with typically reported phenomena for other polymeric systems, which comprises an initial stabilization period followed by a very stable behavior for long periods of time when compared to non-polymeric systems. Longer periods of time are necessary for polymeric diffusion studies and are in progress, to provide diffusion coefficients and comparable data between different chemical compositions or species.

Acknowledgments

This study was partially financed by the Argentinean Government by means of the PIP 112-20110101029 and PIP 11420090100398 projects, and the PICT 2011-0654 FONCyT Res 140/12 and PICT 2008/0398 ANPCyT projects. The authors would also like to thank PME (2006) 1544 grants for Raman measurements in LANN of SNM.

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