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Analytical and rheological studies of modified gel dosimeters exposed to X-ray beams

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ABSTRACT

The need to know the dose of X-rays to be applied to patients suffering diseases such as cancer requires accurate and stable dosimetric devices. Currently, the use of gelatin-based dosimeters has yielded excellent results but lack adequate thermal stability. In this paper a chemical modification of the gelatin (at concentrations typically used for the preparation of dosimeters) using glutaraldehyde as a cross-linking agent is proposed. Through rheological studies it was found that modified gelatin with glutaraldehyde concentrations between 0.15 and 0.50% w/v shows better thermal stability with an increase in elastic modulus of up to 100 times at 37 °C and convenient reaction times for the preparation of the dosimeters. Subsequently, a mathematical model to easily predict the elastic modulus of materials prepared with different concentrations of gelatin and glutaraldehyde was proposed. The analytical response of modified and unmodified materials was evaluated and no significant alteration of the dosimetric sensitivity was found in the dosimeters (based on itaconic acid and N, N′-methylenebisacrylamide) when an X-ray irradiation dose from 0 to 300 Gy was applied. It was found that the best thermal stability of dosimeters prepared with modified gelatin would decrease the loss of information between the irradiation process and the absorbance reading, thereby improving the stability and linear correlation of data.
Overall, the results indicated that the dosimeters could be modified as proposed and achieve significant improvements regarding to their thermal stability, without changing significantly the usual preparation process.

1. Introduction

Diagnostic radiology and radiotherapy help to detect and propose specific ways of treatment for patients and to effectively treat tumor areas. In these techniques, to know the absolute dose and its spatial distribution in a patient is vital and for that, there are different dosimetric tools. Dosimeters based on polymeric gels indirectly quantify the total absorbed dose after being exposed to ionizing radiation [1]. This is possible due to chemical changes that occur after irradiation, where free radicals formed from water molecules initiate a gelation process [2]. The coexistence of monovinyl- and divinyl-monomers capable of polymerizing produces three-dimensional networks (gels) which retain their initial spatial distribution for long periods thanks to the presence of a gelatin matrix [3]. This matrix preserves the dose distribution, minimizing the diffusion of the monomers and gels. One requirement is that these materials have to be similar to human tissues [4], regarding the response to ionizing radiation. Gelatin is normally used because it is an inexpensive material available from natural sources; also the preparation of these materials is simple and requires only equipment which is commonly available in a chemical laboratory. Gelatin is the denatured form of collagen, which is a structural protein widely distributed in the animal world. Collagen is composed of three polypeptide chains arranged in a triple helix structure by the presence of multiple hydrogen bonds [5]. When gelatin is dissolved in hot water, the denatured polypeptide chains can form a gel after the temperature decreases. This process can be attributed to the formation of intermolecular hydrogen bonds through the formation of infinite polypeptide networks. The balance between the formation of intermolecular hydrogen bridges that are responsible for network formation and intramolecular bonds that can return to the helical polypeptide structure is dependent on pH, temperature and concentration of the protein solution [6]. However, the stability of the gels may not be sufficient when the dosimeters are subjected to conditions of high room temperature, since the degradation of dose information may occur due to the rupture of the physically cross-linked structure of the gelatin matrix. To avoid this problem, one of the used strategies is a chemical cross-linking on the gelatin. Proteins that are chemically cross-linked present a significant improvement on

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their mechanical properties and are much more stable in aqueous media [7]. Among the various cross-linking agents that could form networks with gelatin, it is worthwhile mentioning glutaraldehyde, genipin and carbodiimide [8]. Glutaraldehyde is a widely available cross-linking agent and has been used in areas such as microscopy, biosensors, medicine, pharmacy and industry [9–10]. Glutaraldehyde is an almost colorless dialdehyde, that has high reactivity and low cost. It primarily reacts with the amino groups of the side chains of proteins around neutral pH. Although reactivity with lysine, phenylalanine, tyrosine, tryptophan, cysteine, histidine, proline, serine and glycine has been also reported, being the more reactive group the *e*-amino of lysine residues [11]. These polar amino acids are located on the surface of proteins and thus are readily accessible to glutaraldehyde. Furthermore, it has been shown that the products of the reaction of glutaraldehyde with the amino groups have good stability to extreme temperatures. However, the concentrations of protein and glutaraldehyde must be carefully controlled for an optimum cross-linking [12]. Therefore, a strict control of the reaction conditions must be kept to obtain a reproducible response, due to the structural variability of proteins. One way to follow the crosslinking reaction of macromolecules is by studying the changes of their rheological properties [13]. The rheological behavior of protein solutions depends on the molecular weight, the conformation of the molecule and solvent conditions. Rheology is a method widely used to study the process of gel formation. For example, it has been used in reactions where the main goal was to improve the mechanical properties of hyaluronic acid [14]. In these assays, the sample is subjected to an oscillatory deformation with constant amplitude and constant frequency and the response of the material is measured. The response of viscoelastic materials can be decomposed into two components, one in phase (G') and the other out of phase (G'') with the oscillatory deformation, which correspond to elastic and viscous contributions, respectively. Viscoelastic samples show a phase shift between 0 and π/2. The elastic modulus of a hydrogel depends on the cross-linking degree and the charge density in the polymer network, and thus on the concentration or fraction of cross-linked polymer material after the preparation of the hydrogel [15]. Although there are several theories to predict the elastic modulus and the swelling index of cross-linked materials, the correlation between predictions and experimental data is only qualitative. Furthermore, experimental results show that the elastic modulus of some hydrogels corresponds to a potential functionality of the form presented in equation 1 [16] and not to the linear dependence predicted by elasticity theory of rubber materials [17–18]:

$$G' \propto (\varphi_0)^x \tag{1}$$

with $x = 2.1 \pm 0.1$.

In this study, a chemical modification of a gelatin matrix is proposed in order to improve its thermal stability using concentrations and conditions commonly used for dosimetric applications. Furthermore, the analytical response to X-ray irradiation of the modified dosimeters is evaluated. For this purpose, it is proposed to modify the gelatin using glutaraldehyde as the cross-linking agent. Then, the dosimetric response and the rheological properties of modified and unmodified dosimeters are analyzed. For a more complete interpretation of the experimental results, a mathematical model is presented. Experimental and mathematical modeling results obtained in this study will allow preparing dosimeters with modified gelatin resulting in a higher thermal stability without significant changes on the dosimetric response to X-ray radiation.

2. Experimental

2.1. Materials

The following chemicals were purchased: N, N′-methylenebisacrylamide (BIS), itaconic acid (ITA) (≥99% purity), glutaraldehyde (GTA) (50 wt.%, in water; density: 1.106 g/mL), from Sigma-Aldrich. Pigskin gelatin (300 Bloom) was obtained from FLUKA and tetrakis hydroxymethyl phosphonium chloride (THPC) from Sigma-Aldrich. Sodium phosphate monobasic and sodium phosphate dibasic with analytical grade were obtained from Anhedra. The buffer solution was prepared with equimolar amounts of both sodium phosphates monobasic and dibasic in water (0.1 M of each).

2.2. Modification of gelatin

The gelatin powder (5.13 g) was added to the buffer solution (100 mL) in a beaker with magnetic stirring at 400 rpm at room temperature and heated up to 50 °C with a hot plate for 30 min. Then, the temperature was decreased to 37 °C maintaining the stirring. Under these conditions, gelatin remained as a low viscosity liquid.

Glutaraldehyde solution was prepared adding different quantities of concentrated GTA (50 wt.%) to buffer solution. Subsequently, an aliquot of gelatin solution was mixed with an aliquot of glutaraldehyde solution (GTA), as shown in Table 1. The final concentrations of GTA used for the modification of gelatin are also presented in this table. Gelatin–GTA mixture was prepared in this manner for all subsequent tests.

2.3. Effect of GTA on gelatin elasticity at different temperatures

To study the effect of GTA on the gelatin elasticity at different temperatures a sample of gelatin solution at 37 °C was rapidly mixed with different amounts of GTA, as depicted in Table 1. An aliquot of the mixture (500 μL) was immediately placed in the inner plate of a circular geometry of 25 mm diameter of an Anton Paar MCR 301 rheometer. During this process, the gap between the plates was set to 20 mm and immediately after loading the sample, the gap was reduced to 1 mm, lowering the upper geometry. Subsequently, a closed chamber was placed to prevent evaporation of the sample to the environment during the assay. For each sample, the elastic modulus (G'), viscous (G'') and tan delta ($tan\ \delta = G''/G'$) of the material was measured from 4 to 65 °C using a temperature ramp of 3 °C min^{-1}, at constant strain of 1% and frequency of 1 Hz. Each sample was studied by triplicate.

2.4. Kinetics of elasticity of modified gelatin with glutaraldehyde

To perform this study a sample of gelatin solution at 37 °C was rapidly mixed with different amounts of GTA (0, 5.0×10^{-2}, 1.0×10^{-1}, 1.5×10^{-1}, 5×10^{-1} and 1.5×10^{0}% w/v) as depicted in Table 1. An aliquot of the mixture (500 μL) was immediately placed in the inner plate of a circular geometry of 25 mm diameter of an Anton Paar MCR 301 rheometer. During this process, the gap between the plates was set to 20 mm and immediately after loading the sample the gap was reduced to 1 mm, lowering the upper geometry. Subsequently, a closed chamber was placed to prevent evaporation of the sample to the environment during the assay. For each sample, the elastic modulus (G'), viscous (G'') and tan delta ($tan\ \delta = G''/G'$) of the material were studied using a constant strain of 1% and frequency of 1 Hz for 120 min at 37 °C.

Table 1
Modification of gelatin with glutaraldehyde.

Test	Gelatin solution mL	GTA solution μL (% w/v)[a]
0	1.00 ± 0.01	20.0 ± 0.2[b] (0)
1	1.00 ± 0.01	20.0 ± 0.2 (5.0×10^{-4})
2	1.00 ± 0.01	20.0 ± 0.2 (5.0×10^{-3})
3	1.00 ± 0.01	20.0 ± 0.2 (5.0×10^{-2})
4	1.00 ± 0.01	20.0 ± 0.2 (1.0×10^{-1})
5	1.00 ± 0.01	20.0 ± 0.2 (1.5×10^{-1})
6	1.00 ± 0.01	20.0 ± 0.2 (5.0×10^{-1})
7	1.00 ± 0.01	20.0 ± 0.2 (1.5×10^{0})

[a] Final concentration of GTA in the sample.
[b] **V**olume of buffer added.

Table 2
Reagents used for the preparation of dosimeters.

Test	Gelatin solution (mL)	ITA (mg)	BIS (mg)	THPC (mg)	GTA solution μL (% w/v)[a]
ITA-BIS	5.00 ± 0.05	150.0 ± 0.2	79.5 ± 0. 2	20.0 ± 0.2	100[b] (0)
ITA-BIS-GTA	5.00 ± 0.05	150.0 ± 0.2	79.5 ± 0.2	20.0 ± 0.2	100 (1.5×10^{-1})

[a] Final concentration of GTA in the sample.
[b] Volume of buffer added.

2.5. Preparation of dosimeters

The quantities required for the preparation of the ITA-BIS based dosimeters are shown in Table 2. The gelatin solution was prepared as described in Section 2.2. The BIS was added to an aliquot (5 mL) of gelatin solution and stirred for 15 min at 37 °C to prevent polymerization of the monomers during the preparation. Subsequently, ITA was incorporated and the solution was stirred for another 15 min. Finally, the THPC was incorporated and while stirring for 30 min. The solution obtained was rapidly mixed with buffer or GTA solution (Table 2). The final solution was used to fill spectrophotometric vials with a 10 mm path length and 5 mL of final volume. The vials were filled to the brim and closed with a cap to minimize the inhibition by oxygen during the irradiation induced polymerization. Finally, the dosimeters were stored for 24 h at 4 °C, to promote stabilization prior to the irradiation experiments.

2.6. Irradiation of dosimeters

The irradiation of the samples was carried out in a conventional X-ray tube with a W anode in the LIIFAMIRX®-UNC Laboratory (Argentina). The tube is connected to a generator with a maximum output of 3 kW which provides an electric current in the range of 5 to 60 mA and voltage values of 20 to 60 kV, whereby the dose levels are adjusted. The dosimeters were irradiated while the cell was rotated at 6 rpm to obtain a homogeneously absorbed dose. In the irradiation experiments, the electric current and voltage were set to 44 mA and 44 kV, giving a dose rate of (3.02 ± 0.01) Gy/min. Each sample was irradiated with doses of 0 to 300 Gy. To measure the absolute dose rate a Farmer type ionization chamber (PTW-FreiburgTN30013) in water-equivalent phantom was used. The gel formation in the dosimeters after irradiation was analyzed by means of optical transmission. Samples irradiated with different dose values were characterized spectrophotometrically at 430 nm. Every assay was performed by triplicate.

3. Results and discussion

3.1. Effect of GTA on gelatin elasticity at different temperatures

To study the effect of glutaraldehyde in gelatin elasticity at different temperatures, rheological tests were performed. The purpose of these tests was to determine changes in the elasticity of the modified gelatin using concentrations commonly used for the preparation of dosimeters. The temperature ramp was established taken into account the processing temperature (37 °C), the storage temperature (4 °C) and a temperature ramp considering a maximum hypothetical room temperature of 65 °C (4 to 65 °C). While the samples were subjected to the temperature ramp already described, only the rheological results for the final temperature ramp section (4 to 65 °C) is presented in Fig. 1. As shown in Fig. 1(f), the unmodified gelatin has an elastic modulus (G') of 10^3 Pa at temperatures below 20 °C. However, when the temperature increases, the gelatin undergoes a phase transition between 22 and 28 °C, decreasing its elasticity from 10^3 to 10^{-1} Pa. It can be seen in Fig. 1(e) that for a GTA concentration of 5×10^{-4}% w/v the phase transition occurs at a lower temperature, which may indicate that glutaraldehyde would interfere with physical interactions of the chains

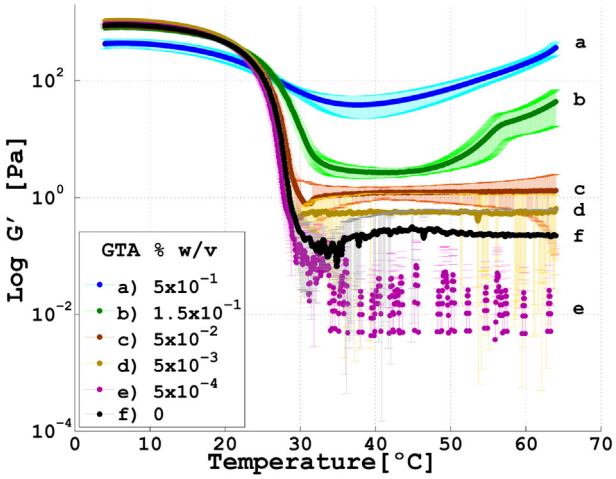

Fig. 1. Elastic modulus (G') vs. temperature (°C) for gelatin with different [GTA] at pH 7.0.

responsible for gel formation, possibly acting as a spacer agent. When GTA concentration was increased from 5×10^{-2} to 5×10^{-3}% w/v the phase transition temperature increases and G' reaches values of 1×10^0 Pa (Fig. 1(c) and (d), respectively). The most important changes are observed at concentrations of 1.5×10^{-1} and 5×10^{-1}% w/v (Fig. 1(a) and (b) respectively). In this case, it is observed that the modified gelatin shows only a minimum in the curve of elasticity around 37 °C (Fig. 1(a)). In general, the transition temperature was modified significantly when [GTA] ≥ 0.15% w/v. The positive slope of elasticity curves indicates the evolution of the curing process where the system has not reached the equilibrium yet. The cross-linking kinetics was studied in subsequent assays.

Fig. 2 shows the *tan* δ average for the different GTA concentrations at different temperatures. The curves are obtained from the ratio between the viscous and elastic modulus (G''/G') at each temperature. This relationship between the modules is a widely used criterion for determining whether a material behaves like fluid or gel. Fig. 2 shows that up to 25 °C the *tan* δ have the common value for elastic gels. However, when the temperature reaches 27.5 °C, *tan* $\delta > 10^{-1}$ when [GTA] = 10^{-3}% w/v, which indicates that they are very lax gels at this temperature. The same behavior is observed when [GTA] ≤ 5×10^{-2}% w/v, which can be clearly noted by the *tan* δ values higher than 10^0,

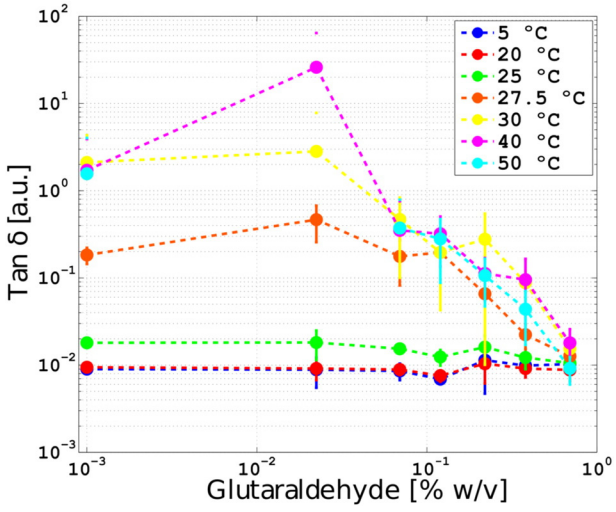

Fig. 2. Tan delta (*tan* δ) vs. concentration of glutaraldehyde added to gelatin at different temperatures.

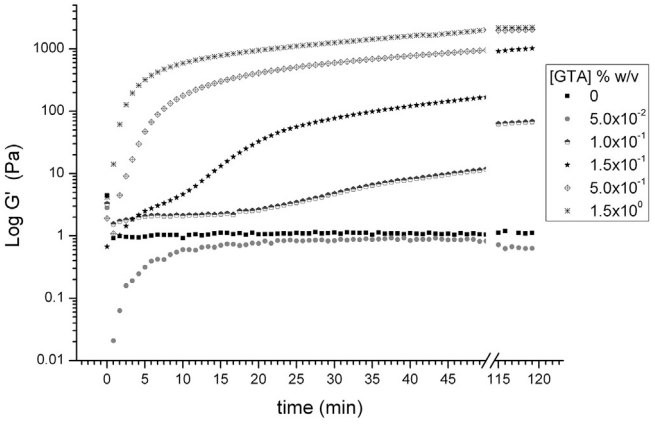

Fig. 3. Elastic modulus (G') vs. time for gelatin with different concentrations of GTA at 37 °C.

indicating that $G'' > G'$ above 30 °C. This effect is more pronounced for GTA concentrations of 5×10^{-2}% w/v, showing a complete liquid gelatin at 40 °C. However, when the [GTA] ≥ 10^{-1}% w/v the curves have a negative slope ($tan\ \delta\ [GTA]^{-1}$) indicating an increased thermal stability of the cross-inked products. Therefore, the modified gelatin under these conditions becomes increasingly independent of temperature and remains as an elastic gel at the different tested temperatures.

The experimental results indicate that the gelatin cross-linking reaction should be performed with [GTA] ≥ 10^{-1}% w/v above the phase transition temperature (27.5 °C), to eliminate the effect of the physical interactions. Thus, the gelatin-GTA reaction could be followed by measuring the elastic modulus during the isothermal curing process. In that case, the measured properties would provide information of changes in the elasticity produced by the GTA, without interference from the physical gel formation during the reaction. It would also be convenient to perform the modification of gelatin with GTA at 37 °C, because at this temperature the $tan\ \delta$ shows major changes with the concentration of GTA. Furthermore, these conditions are advantageous from an operational point of view because it resembles the temperature typically used for the preparation of the dosimeters. Furthermore, all the reagents tolerate these operational conditions.

3.2. Kinetics of elasticity of modified gelatin with glutaraldehyde

To study the cross-linking reaction of gelatin and GTA vs. time at constant temperature, rheological tests were performed. As already discussed in the previous section, the assay was performed at 37 °C and [GTA] ≥ 5×10^{-2}% w/v, because lower concentrations do not significantly improve the thermal stability of the gelatin. As shown in Fig. 3(a), the unmodified gelatin at 37 °C behaves as a viscous liquid, showing no significant changes of its G'. However, at [GTA] ≥ 1×10^{-1}% w/v the gelatin elasticity increases by 70 to 2000 times in the studied range. It was noted that not only the elasticity increases with the major concentration of GTA, but also changes the kinetics of the elastic modulus increase, being progressively slower al low concentrations of GTA. Furthermore, the products obtained with [GTA] = 1.5×10^{-1}, 5.0×10^{-1} to 1.5×10^{0}% w/v reach similar elasticity values, but with the highest concentration gel was formed in a shorter time. However, from a practical point of view, if the gel is formed in a very short time, it may be gelled before the homogenization of the material affecting the final optical properties and the preparation process of the dosimeters. In addition, a rapid cross-linking reaction is usually not necessary because the dosimeters are prepared and then stored until being irradiated for several hours or even a day after their preparation.

3.3. Mathematical modeling of modified gelatin with glutaraldehyde

In order to further analyze the relationship between the glutaraldehyde concentration and elasticity of the gelatin, a mathematical modeling is proposed. In this model, the structure of the gelatin after reacting with glutaraldehyde consists of two types of materials. One is a physical gel, maintained by non-covalent interactions and the other one is a chemically cross-linked gel, maintained by covalent bonds formed between the chains of gelatin and glutaraldehyde.

In that regard, the following expressions are proposed (2–4):

$$G'_q = C_q \left(f_q \varphi_0\right)^{xq} \tag{2}$$

$$G'_f = C_f \left(f_f \varphi_0\right)^{xf} \tag{3}$$

$$G' = G'_q + G'_f \tag{4}$$

where G'_q is the contribution to the elastic modulus of the material by the glutaraldehyde cross-linked fraction, G'_f is the elastic modulus provided by the matrix of non-cross-linked gelatin, C_q and C_f are proportionality constants that somehow consider the difference of energies of each interaction, φ_0 represents the concentration of pigskin gelatin in the hydrogel, f_q and f_f are the fractions of gelatin cross-linked with glutaraldehyde and gelatin with only physical interactions respectively, which were calculated using the following expressions (5–6):

$$f_q = A - Be^{-[\mathrm{GTA}]} \tag{5}$$

$$f_f = 1 - f_q \tag{6}$$

where A and B are constants calculated from the lower GTA concentration necessary to form a hydrogel and the highest possible concentration of GTA estimated from the ratio of lysine and glutaraldehyde groups. The assumptions are that one molecule of glutaraldehyde can only interact with two lysine groups (Lys) in the protein structure of the gelatin.

Resulting in the following equations:

$$A : \frac{[\mathrm{GTA}]_{min} e^{[\mathrm{GTA}]_{min}} - \frac{[Lys]}{2} e^{\frac{[Lys]}{2}}}{\frac{[Lys]}{2}\left(e^{[\mathrm{GTA}]_{min}} - e^{\frac{[Lys]}{2}}\right)} \tag{7}$$

$$B : (A-1)e^{\frac{[Lys]}{2}} \tag{8}$$

However, given the nature of the material, glutaraldehyde concentrations below the minimum on necessary to form a cross-linked gel results in $G' = 0$ in this model. Further improvements to this model will consider an expression equal to the viscous stress of a concentrated liquid monomer or proteins for this range of concentrations, and also the dependence of physically cross-linked hydrogel with temperature. Moreover, the elastic modulus of materials with GTA concentrations above the maximum determined by the number of lysine groups in the protein structure would not alter the value of G'. Therefore, mathematically:

$$G' = \begin{Bmatrix} G'_f, [\mathrm{GTA}] < [\mathrm{GTA}]_{min} \\ G'_f + G'_q, [\mathrm{GTA}]_{min} \leq [\mathrm{GTA}] \leq \frac{[lys]}{2} \\ G'_q, [\mathrm{GTA}] > \frac{[lys]}{2} \end{Bmatrix} \tag{9}$$

While it is not a rigorous model, it represents the base for the calculation of the elastic modulus of materials with chemical and physical cross-linking by knowing some empirical data as the minimum concentration and the number of sites of interaction between the matrix and

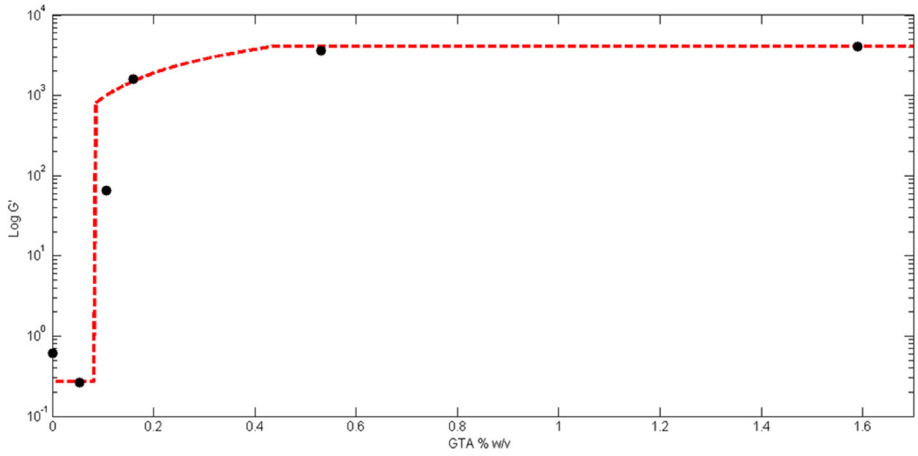

Fig. 4. Elastic modulus (G') vs. concentration of glutaraldehyde (GTA) for modified gelatin at 37 °C and pH 7.0.

the cross-linking agent. Experimental results with this model setting can be observed in Fig. 4.

C_q, C_f, xq and xf values were adjusted using a minimization algorithm included in the Matlab (The MathWorks Inc., Natick MA, USA) software (Table 3).

It is worthwhile to mention that when both effects are considered separately, the exponential values are closer to a linear behavior.

3.4. Comparative study of the response of dosimeters prepared with modified and unmodified gelatin

For this study, ITA-BIS dosimeters were prepared using gelatin in the presence and absence of glutaraldehyde. Each sample was irradiated with X-ray doses from 0 to 300 Gy by triplicate, following the procedure already described in the experimental section. Samples irradiated with different dose values were characterized by UV–visible spectrophotometry at 430 nm. Fig. 5 shows the absorbance as a function of the irradiation dose, in presence and absence of GTA. As shown in this figure, the slope (dosimetric sensitivity) decreases when gelatin was modified with glutaraldehyde. This effect might be due to some absorption by the GTA at the wavelength on which the UV–Vis determination was performed. However, it is noted that the linearity in the response of the dosimeters prepared with modified gelatin is better than the one of unmodified materials by comparing the coefficients of linear correlation ($r^2 = 0.996$ vs. 0.989, respectively). This difference could be caused by the enhanced thermal stability of dosimeters prepared with modified gelatin, in which less data loss would occur between the irradiation process and the absorbance reading.

In Fig. 5, the following expressions to compare the sensitivity of each dosimetric system were obtained (10–11):

$$\text{SlopeITA}-BIS = (5.1 \pm 0.8) \times 10^{-3} a.u./Gy \quad (10)$$

$$\text{SlopeITA}-BIS-\text{GTA} = (4.7 \pm 0.5) \times 10--3 a.u./Gy \quad (11)$$

Therefore, the modification of the gelatin matrix with glutaraldehyde causes a decrease of 8.5% in the mean value of the sensitivity of the ITA-BIS-GTA dosimeter. However, this decrease is within the uncertainty of the calculation method of the dosimetric sensitivity. Moreover, it is observed that the error in the slope is lower for ITA-BIS-GTA dosimeters prepared with modified gelatin, which may be associated with better thermal stability of these systems.

Table 3
Results obtained from the experimental data.

C_q	4.317×10^3
C_f	5.477×10^6
xq	1.355
xf	1.008

4. Conclusions

The need to know the dose of X-rays to be applied in patients suffering from diseases such as cancer require accurate and stable dosimetric devices. Currently, the use of gelatin-based dosimeters has yielded excellent results but lack adequate thermal stability.

In this paper a very simple and inexpensive method that requires no specialized equipment for the chemical modification of the gelatin used for dosimetric applications was proposed. In this method, gelatin was modified (at concentrations typically used for the preparation of dosimeters) using glutaraldehyde as a cross-linking agent. It was found that modified gelatin with GTA concentrations between 0.15 and 0.50% w/v present better thermal stability with an increase in their elastic modulus of up to 100 times at 37 °C and convenient times of reaction in the preparation of the dosimeters. Also, a simple mathematical model to calculate the elastic modulus of materials prepared with different concentrations of gelatin and glutaraldehyde was proposed. The analytical response of modified and unmodified material was evaluated and found a non-significant effect on the dosimetric sensitivity of the dosimeters (prepared with itaconic acid and N, N′-methylenebisacrylamide) when irradiated with doses from 0 to 300 Gy. It was found that the best thermal stability of the modified gelatin based dosimeters would decrease the loss of information between the irradiation process and the absorbance reading, thereby improving the linearity in the data correlation.

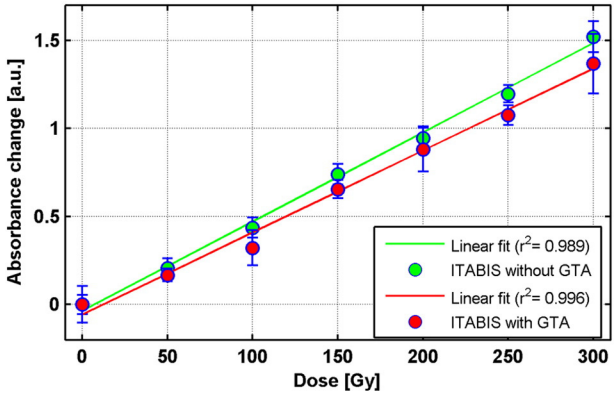

Fig. 5. Dose response curve for ITA-BIS with modified and unmodified gelatin.

In general, the results indicated that the dosimeters could be modified as proposed achieving significant improvements on their thermal stability without significant changes on the usual preparation process.

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