Formaldehyde increases MAGIC gel dosimeter melting point and sensitivity

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Abstract. Polymeric gel dosimeters are being used to verify three-dimensional (3D) dose distributions of different types of radiotherapy treatments, especially the most complexes ones. An important factor that can limit the wider use of this kind of dosimeter is temperature, as gel melting can destroy 3D information. This work shows that the addition of formaldehyde to the gel preparation increases the melting point, allowing its use in warmer environments, including up to body temperature. An addition of 3% in mass of the formaldehyde solution to a MAGIC type gel dosimeter increased its melting point from 25 to 69°C. Also important were a 10.5% increase in gel sensitivity and an expressive decrease in relaxation rate R2 uncertainty that added to the agreement of the depth dose distribution measurement with the expected dosimetric data of the LINAC show the potential applicability of this new dosimeter for 3D dose verification.

1. Introduction
Gel dosimeters are a new type of dosimeters for the evaluation of complex dose distribution in radiation therapy, with the unique characteristic of allowing three dimensional dose visualization [1]. The normoxic polymeric [2] gels are gaining special attention because they are easier to be manufactured compared to the gels initially proposed [3].

With the advances in treatment techniques that use ionizing radiation and the need of verifying these procedures before the treatment of the patients, gel dosimeters are really a promising alternative dosimetric system. However, there are several factors that may disturb their ability to precisely measure dose distributions, one of them is temperature [4], since at relatively low temperatures, around 25°C, the gel, in its current formulation, can melt and 3D dose information is lost.

Madsen [5] used formaldehyde to increase the melting point of certain gels used in ultrasound phantoms simulations with good results. Studies to increase the gelatin melting temperature aiming the use of gelatin as drug capsules for oral intake were also performed by other authors [6,7,8,9]. These studies show that the presence of formaldehyde increases cross-linking, leading to an increase of melting temperature. Thus, motivated by these previous studies, we herein study the influence of formaldehyde in MAGIC gels as an alternative to increase its melting point and the influence of formaldehyde addition in the gel dosimetric response.
2. Materials and Methods

2.1. Gel manufacturing

Gelatin (bovine skin, 250 Bloom, Gelita®) was added to water at room temperature and then heated to 45°C, where the mixture was kept until the gelatin had completely melted, after approximately 30 minutes. The heater was then turned off and the mixture was cooled to 35°C, when ascorbic acid (Vetec®), copper sulfate (Vetec®) and the formaldehyde (Merck®), as a water solution with 37% minimum, stabilized with 10% methanol, were added. All reagents were used without additional purification. After approximately 5 minutes the methacrylic acid (Acros®) was finally added. The solution was stirred continuously during the entire mixing procedure. The ideal concentration of formaldehyde to increase the melting point was studied. Table 1 shows the gel compositions analyzed.

Table 1 – Gel composition for a 50 ml volume with varying amounts of formaldehyde to assess its effect on gel’s melting point. In all samples 4.1g of gelatin bovine skin, 250 Bloom; 17.6 mg of ascorbic acid; 2.95g of methacrylic acid and 1 mg of copper sulfate were used. The formaldehyde solution used contains a minimum of 37% and was stabilized in 10% methanol.

| Sample | Ultra Pure Deionized Water (ml) | Formaldehyde Solution (ml) | Formaldehyde Solution (% mass) | Melting Point (ºC) |
|--------|---------------------------------|-----------------------------|---------------------------------|---------------------|
| 1      | 42.00                           | ---                         | ---                             | 25.0                |
| 2      | 41.50                           | 0.50                        | 1                               | 24.5                |
| 3      | 41.25                           | 0.75                        | 1.5                             | 26.5                |
| 4      | 41.00                           | 1.00                        | 2                               | 27.0                |
| 5      | 40.75                           | 1.25                        | 2.5                             | 29.0                |
| 6      | 40.50                           | 1.50                        | 3                               | 69.0                |

2.1.1. Melting point study. To study the melting point, each sample (table 1) was poured in a 50ml beaker. All gels were stored in a refrigerator, at a temperature of 10°C, for one day before use. The samples were heated and their temperatures were monitored with a digital thermometer until completely melting of the gel, we considered the melting point as the temperature in which the gel lost its gel appearance and became a viscous solution.

2.1.2. Sensitivity study: MAGIC x MAGIC with formaldehyde. To compare the sensitivity of MAGIC gels two sets of gels were prepared at the same time and with the same conditions, except for the addition of formaldehyde to one of the samples (same composition as sample 6, table 1) and the other was left without it (same composition as sample 1, table 1). For this study, the gels were poured into a 5ml cylindrical blood collection tube with low vacuum and sealed for further irradiation and imaging.

2.1.3. Gelatin Bloom study. As an alternative to increase the melting point of gels, Mcjury [10] have shown that using gelatin with higher strength, or Bloom, would increase the melting point of the gel. Hence, such influence was studied over MAGIC gels with formaldehyde. For this study, we prepared two samples of 50ml of gel (same composition as sample 6, table 1) using gelatin of 300 and 250 bloom. We also poured the gel into the 5ml cylindrical vacuum tubes.

2.1.3. Depth Dose Measurement. To measure the depth dose distribution we prepared 100 ml of gel (same proportions of sample 6, table 1) and poured the gel into a test-tube.

2.2. Irradiation

The gel phantoms for the sensitivity and the bloom study were irradiated with cobalt 60, in a Gammatron-Siemens unit. We used single beans with its central axis parallel to the diameter of the cylindrical tubes inserted in a plastic slab that assured the build-up region at the front surface of the gel. Doses of 1, 2, 3, 4, 5 and 10 Gy were delivered and one tube was not irradiated, as a reference. For the depth dose measurements a 6 MV photon beam delivered by a Varian 600CD linear
accelerator was used. Each test-tube was irradiated separately in a water phantom which provided lateral scattering, with radiation incident normal to the bottom of the test-tube, following the work of Oldham et al [11]. Both equipments are routinely checked for its dose rate according to the 398 IAEA protocol, yielding an uncertainty smaller than 3%.

2.3. MRI Acquisition
MR images were acquired after the thermal equilibrium of the gel tubes with the MR scanner room temperature, 1 day after the irradiation, to allow enough time for reaction completion and uniform thermal equilibrium.

MRI images to evaluate R2 were acquired using a 1.5 T scanner (Siemens, Magneton Vision) with a head coil and single spin echo sequences with echo times of 22, 60 and 120 ms, a repetition time of 3000 ms and a matrix size of 128 × 256 pixels. The slice thickness was 5mm and the FOV was 240 mm. The transverse relaxation rate R2 was calculated using a specific program developed by our group [12] in MatLabR_ 6.5 (Mathworks Inc). The transverse relaxation rate R2 was evaluated on a pixel wise basis of a selected region of interest (ROI) and a histogram was used to assess its distribution. The ROI was selected on the entire gel area and a Gaussian distribution was assumed with its peak value representing the mean R2 value; its standard deviation was also calculated.

3. Results and Discussions
The presence of formaldehyde in the gel preparation increased the gel melting point as indicated in table 1. For gel preparation with 3% in volume concentration of the formaldehyde solution (sample 6) the melting point was 69°C, which is high enough to allow convenient gel manipulation in all clinical environments, without the need of a thermal protection during its transportation to prevent the loss of the dose distribution in the volume irradiated.

Comparing the radiation dose–response curves of MAGIC gel with and without formaldehyde (figure 1 – a), we can see that the gel containing formaldehyde presents a higher sensitivity and smaller errors bars for low and high dose points - this seems to indicate that the presence of this compound yield a more uniform gel. Formaldehyde increases gel melting point by increasing the cross-linking reactions in gelatin molecules [13,14] possibly requiring a higher thermal energy to break down the chemical bonds.

![Figure 1](a) Dose response curves for the two MAGIC gels, with (sample 6) and without formaldehyde (sample 1). (b) Influence of the gelatin Bloom in the sensitivity of the MAGIC gel dosimeters. It can be seen that the higher the Bloom the smaller is the sensitivity to radiation. For both figures, the lines connecting the experimental points represent a linear fit of the data and the error bars represent the standard deviation of the mean values in the selected ROI.
The increase in the gelatin bloom for increasing the melting point is not appropriate for our goals, since a decrease in the gels’ sensitivity was also observed (figure 1 - b).

The test-tube image used to access the depth dose distribution and the R2 distribution are shown in figure 2 – (a) and (b). The plot of the depth dose normalized to its maximum value is in great concordance with the expected values according to the dosimetric data of the used LINAC (figure 2 – c), showing the potential of the MAGIC gel with formaldehyde to measure dose distributions.

**Figure 2** – (a) MRI image of the test-tube (b) R2 distribution in the MRI image (c) Depth dose distribution normalized to the maximum value compared to the dosimetry table.

4. Conclusions
The addition of formaldehyde to MAGIC type gel dosimeters increases the melting point, up to 69°C, and the dosimeter sensitivity by about 10.5% when compared to standard MAGIC gels. It also decreased the uncertainty in R2. The depth dose measurement in accordance to the dosimetric data confirms the potential of the new dosimeter to measure dose distributions. We can also say that the new formulation of this gel is more reliable for 3D dose distribution measurements and is easier to handle.

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