Optimisation of the MAGAT gel dosimeter compositions

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ABSTRACT

Background: An effective polymer gel dosimeter can be fabricated by varying the composition of its chemical components. *Materials and Methods:* The MAGAT gel dosimeter formulations that used different compositions of Methacrylic acid (MAA) and gelatin were extensively investigated in the present study according to the R2–dose response and R2–dose sensitivity. The irradiation of MAGAT gel was performed by 6-MV photon beam at a dose range 1 to 10 Gy and was imaged by 1.5T Magnetic Resonance Imaging (MRI). The dose response of MAGAT gel dosimeter was obtained from spin-spin relaxation rate (R2) of MRI signal. *Results:* The MAGAT gel dosimeter composed of 5% gelatin and 6% MAA gave the highest sensitivity (1.1180 $s^{-1}Gy^{-1}$). *Conclusion:* Understanding the effects of the compositional changes will help to clarify the mechanisms involved in the dose response of the MAGAT gel dosimeter.

Keywords: MAGAT gel dosimeter, spin-spin relaxation rate (R2), dose response, MRI imaging.

INTRODUCTION

Complex radiotherapy techniques such as stereotactic radiosurgery, brachytherapy, conformal therapy and intensity modulated radiotherapy provide three-dimensional spatial dose distributions. One of the final steps in quality assurance of patient specific planning is to ensure close matching between the dose delivered to the patient and the dose calculated by the treatment planning system (TPS). Tissue equivalent polymer gels are capable of recording three dimensional dose distributions. Polymer gel is fabricated from radiation sensitive chemicals such as aqueous gels. Upon irradiation polymerization occurs due to radiation-induced changes in the chemical species. The use of a radiation sensitive gel for radiation dosimetry was first suggested in the 1950s where radiation induced colour changes in dyes were related to the received radiation dose [1,2]. Polymer gel dosimeters were developed as an alternative to Fricke gels. Unlike the Fricke system diffusion complication is minimised in polymer gel hence can be used to verify the spatial dose distribution in complex radiotherapy [3,4].

The change in dose distribution can be recorded in three dimensions (3D) by various methods such as magnetic resonance imaging (MRI), X-ray computed tomography (x-CT), ultrasound, optical CT and vibrational spectroscopy [5]. To date, magnetic resonance imaging (MRI) is the commonly used technique for recording 3D dose information in a polymer gel [3,4,6,7]. MRI can non-invasively and non-destructively measure the magnetization of hydrogen atoms in water molecules with high spatial resolution in three dimensions.

Recently different polymer gel formulations have been developed and their characteristics studied for their viability as potential 3D

dosimeters. The Methacrylic Acid Gelatin (MAG) system is considered the most standard gel dosimeter with superior sensitivity and dose resolution [8, 9]. The potential of 3D dosimetry from Fricke gel dosimeter by MRI evaluations sparked numerous research in gel dosimetry.

The main objective of this paper is to understand the effects of the compositional changes that will help to clarify the mechanisms involved in the dose response of the MAGAT gel dosimeter. Even though many researchers were worked on the MAGAT gel dosimeter, very few researchers were reported the detail of compositional changes of MAGAT gel dosimeter. Each composition was studied in terms of concentration to determine their effect towards the dose response. These data are very useful to obtain the best sensitivity with respect that thepolymer gel dosimeter can be optimized for clinical applications (since the characteristics of the polymer gel can be varied according to its concentrations).

MATERIALS AND METHODS

Fabrication of gel dosimeter

The gel formulation consisted of methacrylic acid (Acros, Organics), gelatin (250 bloom, Bovine) (Sigma Aldrich), de-ionised water, ascorbic acid (Sigma Aldrich) and Tetrakis (hydroxymethyl)phosphonium chloride (THPC) (Sigma Aldrich). The Methacrylic Acid Gelatin and Tetrakis (hydroxymethyl)phosphonium chloride (MAGAT) polymer gels were manufactured under normal atmospheric conditions. The gelatin was mixed with de-ionised water in a mixing vessel and was continuously stirred at approximately 48°C until the gel was completely dissolved and a clear solution was obtained. The solution was cooled to 40°C then the methacrylic acid monomer was added and continuously stirred until the monomer was completely dissolved. For manufacturing the normoxic polymer gel, an anti-oxidant was finally added to minimise the oxygen exposed to the solution [6, 10]. The fabrication procedures of gel solution are shown as figure 1. The MAGAT gels were then poured into 4 ml tissue equivalent polystyrene cuvettes of inner dimensions 1 cm × 1 cm × 4.5 cm (width × length × height) with the top sealed by a parafilm tape. Finally they were wrapped in aluminium foils to avoid any preliminary polymerisation from the ambient light. The sample vials were stored at 4°C before irradiation. In this study, the concentrations of MAGAT gel varied as shown in table 1. The concentrations of methacrylic acid and gelatin were varied in order to obtain the optimum dose response with respect to the MRI signal.

Table 1. MAGAT gel compositions.

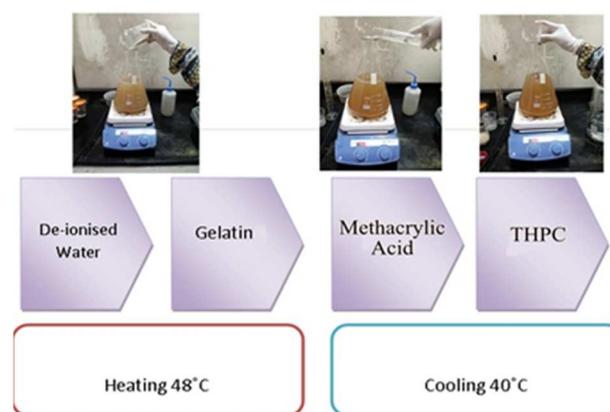| Composition	MAGAT concentration
Gelatin	%9-0 (w/w)
Methacrylic Acid	%9-2 (w/w)
THPC	10mM
De-ionised water	%98-82 (w/w)
Dose range	10-0Gy

Figure 1. The fabrication of normoxic MAG dosimeter.

Irradiation of gel dosimeter

Irradiations were performed using a 6-MV photon beam by a linear accelerator (Primus LINAC, Siemens), with a field size of 10 cm × 10 cm at the isocentre and at 100 cm source axis distance (SAD). The dose rate was 3 Gy min^{-1}. The samples were irradiated from 0 to 10 Gy by parallel opposed beams so that the gels received a uniform dose at 5 cm depth. One sample of each batch is left unirradiated for background measurement. Solid water phantom slabs were placed above and below the Perspex cuvette holder and the samples were placed at the midregion of the phantom as shown in figure 2.
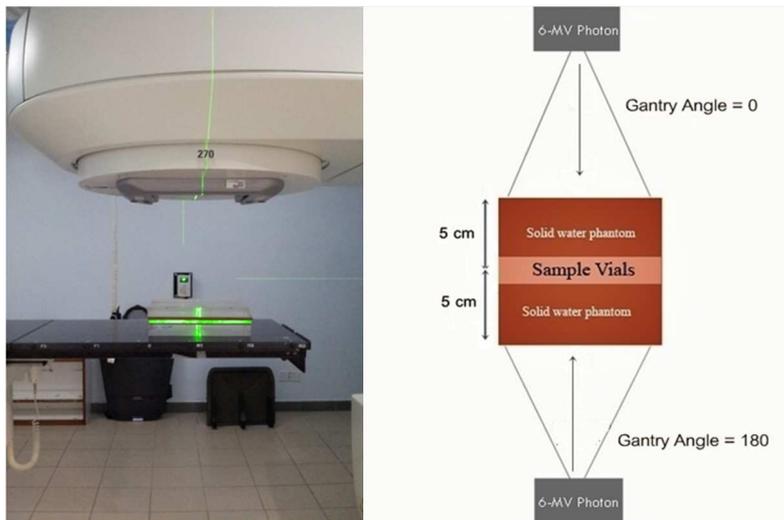
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Figure 2. The irradiation of MAGAT gel dosimeter by 6-MV photon beam using source axis distance 100 cm (a) Real irradiation image, (b) Illustration of irradiation process.

The irradiation were done a day post-manufacturing.

MRI imaging technique

All the sample vials were inserted in a dedicated styrofoam holder and placed in a MRI Signa HDxt 1.5 T whole body scanner using a head coil. All of the samples were imaged a day post-irradiation. The imaging sequence applied was a single spin-echo sequence with time echoes of TE1 = 20 ms and TE2 = 300 ms and a relaxation time (TR) of 3500 ms. The other scanning parameters used such as NEX = 3, slice thickness = 5 mm, slice spacing = 0 mm, FOV = 22 mm and flip angle = 90°. The T2 dicom images were transferred to a personal computer and analyzed using MATLAB 7.1 (Math Works, Inc.) software. From the time series of T2-weighted images (TE = 20 ms, and TE = 300 ms), R2-maps were calculated using equation (1) from these images for each sequence pixel by pixel basis using pixel signal intensities and applying the two-point method [11].

$$R2 = \frac{\ln S1 - \ln S2}{TE2 - TE1} \qquad (1)$$

Where; S_1, S_2 is the measured MR signal intensity at a given echo time (TE) and R2 is the transverse relaxation rate.

R2 maps can be converted to dose maps using a linear dose response equation (2) that has been reported by several independent investigators [12-14].

$$R2 = \alpha D + Ro \qquad (2)$$

where; α is the slope of the dose–R2 curve, R_o is R2 background and R2 is R2 value of the irradiated gel.

The statistical software that were used to measure the pixel intensity and calculate the linear dose response are using MATLAB 7.1 (Math Works, Inc.) software, ImageJ and Microsoft Excel. For the statistical test, the simple linear regression, correlation and standard deviation were calculated.

RESULTS AND DISCUSSION

Optimisation of the R2–dose response at various gelatin and MAA compositions

Figures 3 - 6 illustrate the R2 as a function of the absorbed dose for the MAGAT dosimeter at two different concentrations of MAA and gelatin. The absorbed doses selected were from 0 Gy to 20 Gy. The R2 values were linearly proportional to the dose up to 10 Gy. This linear dose response was maintained even though the MAA and gelatin concentrations were increased. However, in the dose range beyond 10 Gy and up to 20 Gy, the response was non-linear due to the saturation of the gel as nearly all the monomers

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were converted to polymers. The pixel value of the T2-weighted image decreased with the dose as the attenuation of the signal intensity increased. At a high dose, maximum polymerisation occurs which causes a small change in the pixel intensity and results in the signal being saturated. The optimum gelatin concentration that showed a large variation in the dose response of the MAGAT gel dosimeter at various concentrations of MAA was from 4% to 9% as shown in figure 3 and figure 4. In contrast, at various concentrations of gelatin, the optimum concentration of MAA needed to provide a large variation of the dose response was from 6% to 9% as shown in figure 5 and figure 6.

R2–dose sensitivity of the MAGAT gel dosimeter at different concentrations of MAA

An increase in monomer concentration in a polymer gel dosimeter increases the sensitivity [15-17] as can be seen in the results of the present study presented in figure 7. The sensitivity increment of the MAGAT gel dosimeter depends on the MAA concentration. The larger the concentration of MAA (from 2% to 9%), the greater the number of acrylic monomers available to react in the polymerisation process. It was found that the optimal concentration of 6% MAA and 5% gelatin in the MAGAT polymer gel dosimeter resulted in the largest change in the R2–dose response.

As suggested by the International Commission on Radiation Units (ICRU), the
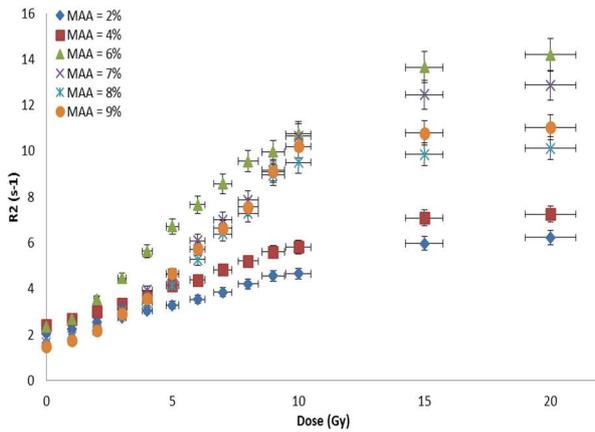

Figure 3. MAGAT gel dosimeter composed of 4% gelatin and at various concentrations of MAA.
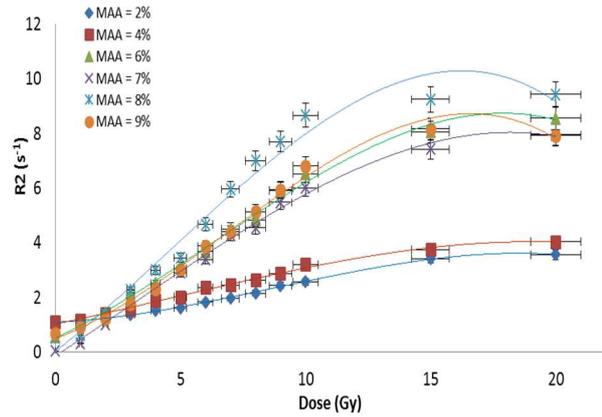

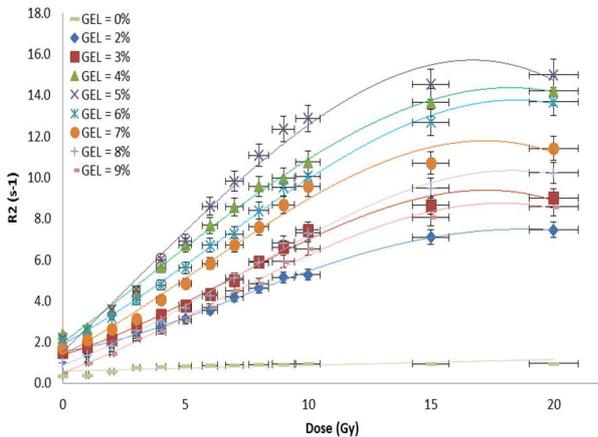**Figure 4.** MAGAT gel dosimeter composed of 9% gelatin and at various concentrations of MAA.

Figure 5. Transverse relaxation rate (R2) as a function of absorbed dose (D) for MAGAT gel dosimeter composed of 6% MAA and at various concentrations of gelatin.

Figure 6. Transverse relaxation rate (R2) as a function of absorbed dose (D) for MAGAT gel dosimeter composed of 9% MAA and at various concentrations of gelatin.
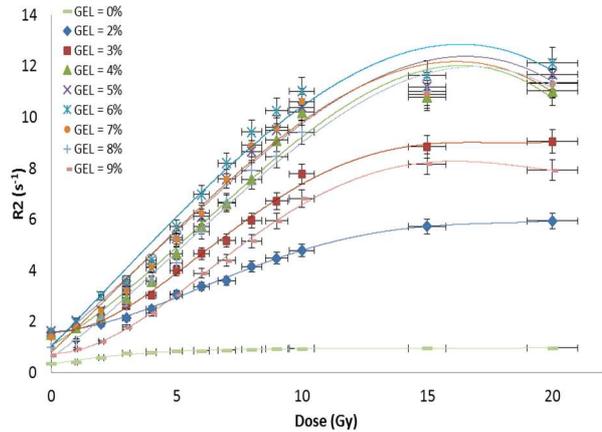
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accuracy of the absorbed dose has to be within 5% of the true dose. As obtained from previous study [21], the accuracy of MAGAT gel dosimeter at concentration of 6% MAA and 5% gelatin was within 5 %. Therefore, the MAGAT gel had the highest sensitivity of 1.118 $s^{-1}Gy^{-1}$ and a linear regression of 0.9957 at concentration of 6% MAA and 5% gelatin. However, the MAGAT gel exhibited lower dose sensitivity with the single spin echo sequence compared to a dose sensitivity of 3.2 $s^{-1}Gy^{-1}$ with the multiple spin echo sequence. However, the level of sensitivity would still be considered high if compared to the sensitivity of other types of gel dosimeters [9]. Table 2 shows the specific concentration of gelatin and MAA that gave the maximum polymerisation of the MAGAT gel dosimeter at the highest sensitivity. From the results presented in the table, it may be concluded that at various concentrations of gelatin from 2% to 9%, the MAA concentration within 6%–9% produced the highest dose response and sensitivity.
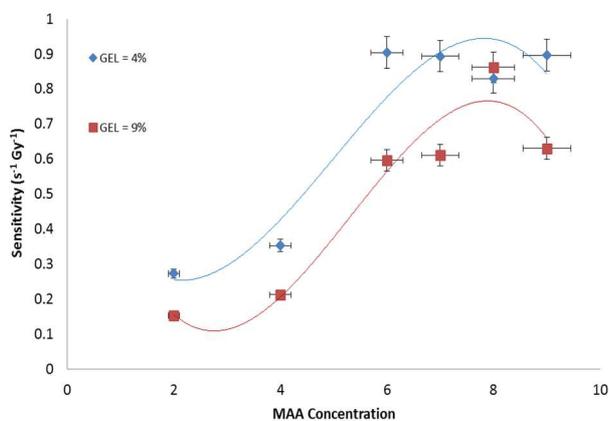
R2–dose sensitivity of the MAGAT gel dosimeter at different concentrations of gelatin

The concentrations of gelatin were varied from 0% to 9% in order to determine the role of gelatin in the dose response of the MAGAT gel dosimeter through the polymerisation reaction. Gelatin is a mixture of polypeptides and proteins derived from different amino acids which are bonded by peptide bonds (-NH-CO-). It functions as a matrix gel solution and also retains the spatial information of the gel by inhibiting polymer diffusion. It is noted in the results illustrated in figure 5 and figure 6 that the MAGAT formulation without the gelatin showed no changes in the R2–dose response even at a high dose, indicating that no polymerisation reaction occurred. An increase in gelatin concentration from 3% to 5% led to an increase in R2–dose response and R2–dose sensitivity as shown in figure 8.
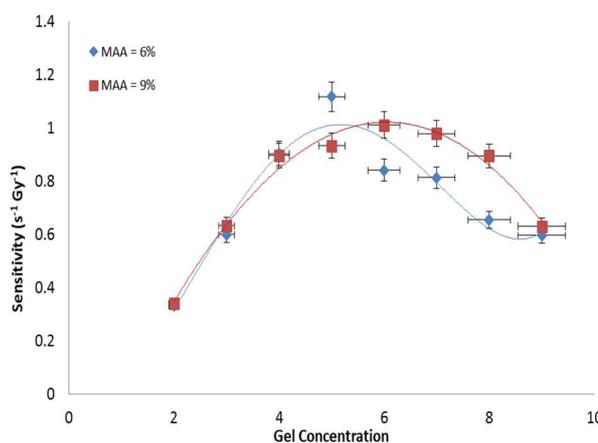

Figure 7. The sensitivity of MAGAT gel dosimeter as a function of MAA concentration at different gelatin.

Figure 8. The sensitivity of MAGAT gel dosimeter as a function of gelatin concentration at different MAA.

Table 2. The concentration of MAA at various concentration of gelatin for maximum polymerization and sensitivity.

Gelatin concentration (%)	MAA concentration (%)
2	6 - 9
3	6 - 9
4	6 - 9
5	6
6	9
7	9
8	9
9	8

For various concentrations of MAA from 2% to 9%, the maximum polymerisation occurred in the 4%–6% range of gelatin concentrations as shown in table 3. Thereafter, the R2–dose response began to decrease with the increase of the gelatin from 7% to 9%. This may be attributed to the fact that MAA has a significant effect on the ageing process of gelatin. At moderate gelatin concentrations in the MAGAT gel dosimeter, the MAA polymer grafts on the

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gelatin which has a stabilising effect. At high gelatin concentrations there is a surplus of gelatin that is susceptible to ageing effects that are probably enhanced by the MAA [18].

An increase in the gelatin concentration in a polymer gel dosimeter causes an increase in its viscosity. It is assumed that the propagation and termination rates of radical chain co-polymerization are decreased in the presence of gelatin [19]. Both propagation and termination reactions are diffusion-controlled reactions, and are likely to be affected by the high viscosity of the gelatin solvent. This is confirmed by the diffusion measurements in the present study which showed a decrease in the monomer diffusion constant for a higher gelatin concentration.

Lepage *et al.*, [20] suggested that the initiation rate of the monomers may decrease with increasing gelatin concentration, caused by scavenging of the initiating radicals by the gelatin. Based on their findings, Lepage *et al.*, [20] suggested that the increase in gelatin concentration leads to increased scavenging of initiator fragments and/or increased chain transfer reactions. This results in a decrease in the polymerisation rate and the overall gel sensitivity. These propositions have been adapted in a model of the kinetic mechanisms in the PAG dosimeter [7]. In the model, the gelatin is assumed to act as an inhibitor consuming the actively growing polymer radicals. When the radical time constant Tp is plotted against gelatin concentration, an exponential decay is observed. This confirms that there must be an interaction between the gelatin and the polymer macro-radicals.

The polymerisation reaction of a polymer gel dosimeter is governed by various factors such as temperature, monomer concentrations, gelatin concentrations and other elements in a gel dosimeter recipe. Thus, different concentrations of gelatin and monomer will yield different polymerisation rates and this may vary the polymer gel dosimeter's dose response and dose sensitivity. As stated above, gelatin may react via different roles and reactions; however, a specific mechanism for the different reactions of gelatin and monomers has not been identified.

Table 3. The concentration of gelatin and at various concentration of MAA for maximum polymerization and sensitivity.

MAA Concentration (%)	Gelatin Concentration (%)
2	4
4	4
6	5
7	5
8	5 - 6
9	6

CONCLUSION

The MAGAT gel dosimeter composed of 5% gelatin and 6% MAA gave the highest sensitivity (1.1180 $s^{-1}Gy^{-1}$). The results of the present study's show that an appropriate combination of gelatin and monomer concentrations is important to obtain a high polymerisation rate in MAGAT gel systems.

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Conflict of interest: *Declared none.*

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