ANALYSIS OF THE EFFECT OF MONOMER CONCENTRATION AND GOLD NANOPARTICLES TOWARDS 2-HYDROXYETHYL METHACRYLATE POLYMER GEL USING MAGNETIC RESONANCE IMAGING (MRI)

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ABSTRACT: *This study makes use the advantage of normoxic polymer gel which composed of 2-Hydroxyethyl Methacrylate (HEMA) as the monomer and N,N'-Methylene-bisacrylamide (BIS) as the crosslinker. To enable the fabrication of polymer gel to be done under the normal atmospheric condition, Ascorbic Acid is added as the anti-oxidant. As past studies had mainly been done using high energy source, this study also focuses on using high energy x-ray source as in linear accelerator (LINAC) as well as diagnostic x-ray unit as the main energy source. Dose response and dose sensitivity are properties investigated in studying the behavior of dose distribution in the polymer gel. Magnetic Resonance Imaging (MRI) is the readout instrument for this study before further analysis using corresponding methods. The result shows that at low x-ray energy, only sample with 5% of monomer exhibit a near standard dose sensitivity value. Higher concentration of monomer does not affect the polymerization significantly at the low energy level. At high x-ray energy, GNPs of 80 nm in size has the highest dose response.*

Keywords: HEMA, MRI, dose sensitivity, polymerization, polymer gel

1. INTRODUCTION

Polymer gel has been widely used as a dosimeter. This is led by the increasing demand due to the conformal radiotherapy and intensity modulated radiotherapy (IMRT) being the primary treatment for cancer. Polymerization and crosslinking of the monomer have been known to occur upon irradiation which is one of the advantages using it as a 3-dimensional (3D) dose dosimeter. Furthermore, polymerization is dose dependent which suits the dose distributions mapping by polymer gel [1-4]. Compared to polymer gel, thermoluminescence (TLD) and ionization chamber, two of the most common 2-dimensional (2D) dosimeters are restricted in giving a 3D spatial dose distribution. The verification of 3D dose distributions becomes highly monitored and continuously researched because in enhancing the result of radiotherapy treatment, the amount of absorbed dose by the healthy tissue has to be reduced.

An earlier generation of polymer gel was developed by Fricke and Morse fabricated which is known as Fricke gel [5]. Day and Stein were the first to develop a radiation-induced polymer gel when they incorporated dyes in polymer gels [6]. Color changes were observed upon the irradiation of polymer gel. MRI has been used as a 3D analysis instrument for polymer gel dosimeter as early as 1990 [7]. Several studies had been done since then to develop polymer gels capable of mapping 3D dose distributions [8,9].

MRI has been proven as a capable instrument in evaluating the dose distributions in polymer gel dosimeters [10-14]. There are studies of dose distributions by brachytherapy that agrees with treatment planning calculations prove the capability of polymer gel in this area [15-16]. Oldham and others used MRI to verify the dose distribution of a nine field tomotherapy in polymer gel and the result is in agreement with the proposed treatment planning [17].

The use of anti-oxidant in developing polymer gel is to minimize the interaction of oxygen molecules with the samples. Oxygen is known for its polymerizing ability when interacts with the monomer in used. The earlier anoxic polymer gel needs to be fabricated by bubbling nitrogen through the sample thus the name, anoxic. Fong and others suggested the use of anti-oxidant in fabricating the polymer gel [18]. With this new method, polymer gel can be developed under the normal atmospheric condition, thus the name normoxic polymer gel.

Dose enhancement is known to be well conducted using materials with high atomic number. For this reason, gold nanoparticles (GNPs) had shown a promising potential as a dose enhancer when irradiated by x-rays [23]. Interactions of x-ray and GNPs cause the photoelectric effect to occur, besides the formation of Auger electrons [24].

2. METHODOLOGY

For this study, 2-Hydroxyethyl Methacrylate (HEMA) was chosen as the monomer. N,N'-Methylene-bisacrylamide (BIS) is the crosslinker which acts as a secondary monomer that helps the crosslinking upon polymerization. One of the most important aspects to be taken into measure was the polymerization due to oxidation was used as an anti-oxidant which scavenges the oxygen molecules thus preventing polymerization. To hold the samples in a stable and measurable form, gelatin from bovine was consumed. The composition of each element involved in the fabrication of polymer gel is shown in Table 1. To minimize the effect of oxygen on polymerization, deionized water was used. It is heated to ~55ºC before gelatin is added. Gelatin was the first component put into the water because it took the longest time to dissolve. Then BIS was mixed into the mixture before adding Ascorbic Acid and monomer.

Table 1 List of elements and their compositions

Element composition	Portion concentration (%w/w)
Gelatin	5
2-Hydroxyethyl methacrylate (HEMA)	5 - 9
N,N'-Methylene-bisacrylamide (BIS)	3
Deionized water	80 – 84
Ascorbic acid	5 mM

The prepared samples were then poured into 4 milliliters cuvettes and let cool before sealing the cuvettes. It is important to store all the samples in a low-temperature environment for about 24 hours prior to irradiation. This was to set the samples into gel form.

GNPs were prepared by the Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia. The sizes of GNPs are 15 nm, 20 nm, 40 nm, 50 nm, and 80 nm. Each sample was mixed with 1 milliliter of GNPs each. The same procedure of gel fabrication was repeated for gel doped with GNPs.

For this study, two types of irradiation source were used. The first one was the diagnostic x-ray machine which emits energy in kilovoltage provided by Biophysics Lab, School of Physics, Universiti Sains Malaysia. The energy set for this study ranging from 0-130 kVp. The second source of energy was the linear accelerator (LINAC), in cooperation with Pantai Mutiara Hospital, Penang. In this study, LINAC was used to study the effect of the size of GNPs on polymerization.

Magnetic Imaging Resonance (MRI) was the readout instrument for analysis of data. Cooperation gave by the Advance Medical and Dental Institute, Universiti Sains Malaysia smoothen the process with MRI. From the T2-weighted images obtained from MRI were analyzed to map R2 as a function of dose. The two-point method was applied where for each sequence, pixels signal intensities were calculated [19]. The transverse relaxation rate (R2) was determined using this equation [20]:

$$R2 = \frac{\ln S1/S2}{TE2-TE1} \qquad 2.1$$

where TE1 and TE2 are the echo time and S1 and S2 are the MR signal intensities correspond to the respective TE.

The details of MRI imaging protocol are as shown in Table 2.

Table 2 Imaging protocol of MRI

Parameter	
Time Echo (TE) 1	20 ms
Time Echo (TE) 2	300 ms
Time Relaxation (TR)	3500 ms
Slice Thickness	3 mm
Matrix Size	256 x 256
NEX	3

3. RESULTS AND DISCUSSION

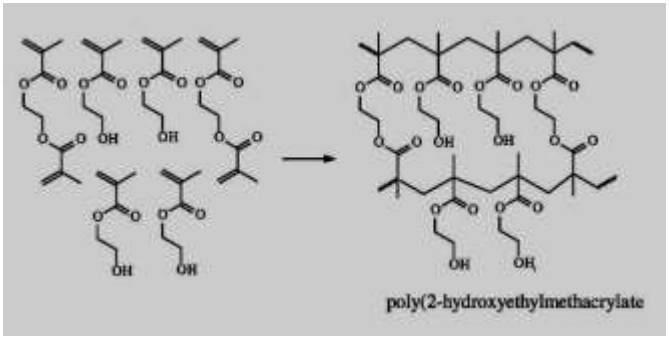

Fig (1) Polymerization of 2-Hydroxyethyl Methacrylate (HEMA)

Since HEMA is a radiation-induced polymer gel, the polymerization occurs upon irradiation of samples by the energy source and chemically enhanced by the crosslinker used, BIS. **Fig (2)** shows the linear relation of R2 as the function of dose. Generally, R2 value increases with increasing dose. A study using PAGAT polymer gel has shown that value of R2 at high dose resembles more of an exponential distribution rather than linear [21]. This is due to the saturated composition of polymer formed post irradiation [22]. The diagnostic x-ray machine emits significantly low energy compared to, for example, linear accelerator (LINAC) thus resulting in a small increment of R2. This small increment exhibits that the intensity of polymerization is directly proportional to the irradiation dose at low energy.

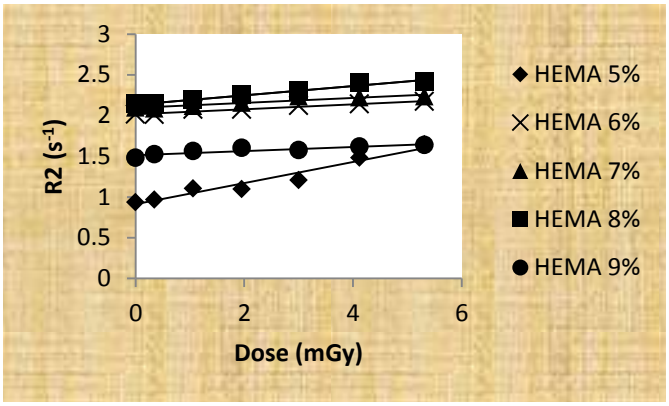

Fig (2) Transverse relaxation rate R2 as a function of dose for various concentration of HEMA

The goodness of fit between the fitted linear lines and the data points was measured using the coefficient of determination, R^2. R^2 is ranging from 0 to 1, where the higher value of R^2 means the data fit closer to the linear lines. From the plot of R2 against Dose as shown in **Fig (2)**, the value of R^2 and dose sensitivity was obtained. Table 3 exhibits the value of R^2 and dose sensitivity for each sample with different HEMA concentration. All linear lines produce high R^2 value (>0.8) indicates there is a strong linear relationship between R2 and dose given.

Table 3 Value of R^2 and dose sensitivity for each concentration of HEMA

Concentration(%)	R^2	Dose Sensitivity (s-1Gy-1)
5	0.9523	0.1300
6	0.9566	0.0303
7	0.9566	0.0306
8	0.9776	0.0570
9	0.8101	0.0250

The gradient of the linear relation between R2 and dose can be interpreted as the dose sensitivity using the following equation [20]:

$$R2 = \alpha D + R_o \qquad 3.1$$

where α is the gradient of the R2 and dose linear plot which represents the dose response and R_o is the R2 background.

As shown in **Fig (3)**, the sample with 5% of monomer has the optimum dose sensitivity. Dose sensitivity decreases with increasing monomer concentration but rises a little at 8% of monomer.

The emission of very low x-ray energy excites only a small amount of HEMA monomer to be crosslinked with each other. The amount of HEMA monomers that are ready to polymerize in the 9% sample is much higher than the 5% sample. However, in the 9% sample, due to low irradiation energy, the number of monomers crosslinked with each other is relatively low. In the 5% sample, the amount of polymerization ready monomer is relatively low compared to the 9% sample. So, the crosslinking of monomer rate is much higher in percentage in relative to the total amount of monomer.

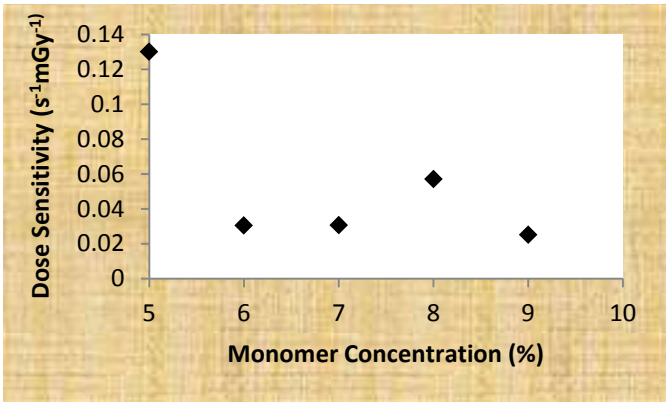

Fig (3) the plot of dose sensitivity against monomer concentration

One thing to be concerned, the dose sensitivity obtained is quite low compared to past studies. For the highest dose sensitivity which by the 5% samples, 0.130 $s^{-1}Gy^{-1}$ is quite low compared to dose sensitivity of PAGAT [21] which ranging around 0.180 – 0.190 $s^{-1}Gy^{-1}$. For other concentration of monomer, the dose sensitivity is considered too low.

To study the effect of the size of GNPs, the concentration of polymer gel was set at a constant value of 9% and irradiated at different doses. The dose source was from LINAC ranging from 10- 50 Gy. The result is presented in **Fig (4).**

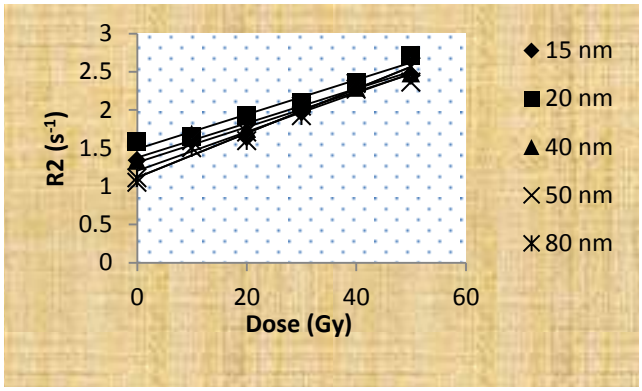

Fig (4) Transverse relaxation rate R2 as a function of dose at high x-ray energy

By introducing GNPs, the R^2 value increases to more than 0.90. This shows the linear relationship between R2 and dose is stronger in the presence of GNPs.

Table 4 is the value of R^2 and dose sensitivity for every different size of GNPs

GNPs size (nm)	R^2	Dose Sensitivity (s-1Gy-1)
15	0.9647	0.0231
20	0.9670	0.0227
40	0.9829	0.0225
50	0.9463	0.0255
80	0.9809	0.0289

Compared to the monomer concentration, the GNPs size seems to affect more polymerization. The increase in R2 is more significant with increasing dose. The large size of GNPs provides a large area of surface for reaction. This increases the chance of the reaction of GNPs towards dose enhancement.

A plot of dose sensitivity as a function of the size GNPs is mapped to observe the effect of GNPs on the dose sensitivity as shown in **Fig (5)**. As shown in **Fig (5)**, increasing size of GNPs from 15 nm to 40 nm, the dose sensitivity had a slight decrease. When the size of GNPs are further increased to 50 nm and 80 nm, the dose sensitivity increases as well. The largest size of GNPs which is 80 nm has the highest dose sensitivity.

However, in general, the effect of GNPs size towards dose sensitivity is not as great as the monomer concentration did.

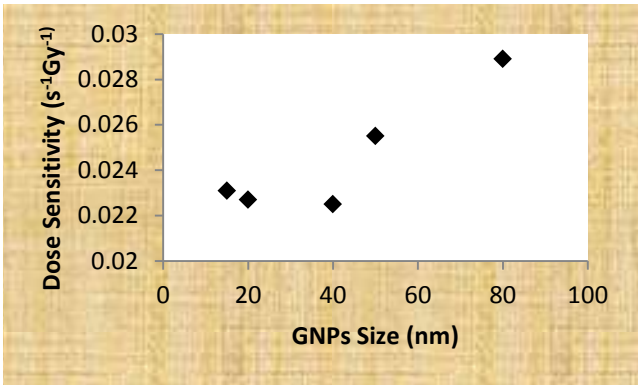

Fig (5) the plot of dose sensitivity against GNPs size

4. CONCLUSIONS

Two aspects of concern in this study are the concentration of monomer and the irradiation dose.

The dose irradiated was at the very low energy level. Although the R2 value is directly proportional to the dose, we can conclude that using the proposed concentration of monomers, HEMA is not dose sensitive at low energy.

As far as the concentration of monomer is concerned, at low energy, only sample with 5 % of monomer exhibits a near standard dose sensitivity property.

At high energy, GNPs size effect is directly proportional to the dose sensitivity with GNPs of 80 nm in size has the highest dose sensitivity.

For future study, there are a few considerations can be taken into measure. Firstly, the same parameter of monomer concentration and GNPs size could be used to compare the effect of both towards polymerization at low and high x-ray energy. Other factors that might play a role in affecting the dose sensitivity are the crosslinker and anti-oxidant. There are a few other anti-oxidant agents known to work fine with polymer gel such as THPC. In future studies, these factors will be taken into consideration.

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5. REFERENCE

[1] Dole, M., The Radiation Chemistry of Macromolecules, Volume 1 and 2. Academic Press, New York, (1973).

[2] Platzer, N., Irradiation of Polymers. American Chemical Society, Washington DC, (1967).

[3] Wilson, J. E., Radiation Chemistry of Monomers, Polymers and Plastics. Marcel Dekker Inc., New York, (1974).

[4] Charlesby A., Radiation Effects in Materials. Pergamon Press, Oxford, (1960).

[5] Fricke, H. and Morse, S., "The chemical action of roentgen rays on dilute ferrous sulfate solutions as a measure of radiation dose" *Am. J. Roent. Radium Ther. Nucl. Med.* **18:** 430-432 (1927).

[6] Day, M. J. and Stein, G., "Chemical effects of ionizing radiation in some gels" *Nature*, **166**: 146–147 (1950).

[7] Schulz, R. J., deGuzman, A. F., Nguyen, D. B. and Gore, J. C., "Dose-response curves for Fricke in fused agarose gels as obtained by nuclear magnetic resonance" *Phys. Med. Biol.* **35:** 1611-22 (1990).

[8] Maryanski, M. J., Gore, J. C., and Schulz, R. J., "3D radiation dosimetry by MRI: solvent proton relaxation enhancements by radiation-controlled polymerisation and crosslinking in gels" *Proc. Soc. Magn. Reson. Med.*, p. 1325, (1992).

[9] Maryanski, M. J., Gore, J. C., Kennan, R. P., Schulz, R. J., "NMR relaxation enhancement in gels polymerised and cross-linked by ionsing radiation: a new approach to 3D dosimetry by MRI" *Magn. Reson. Imag.*, **11**: 253–258, (1993).

[10] Maryanski, M. J., Schulz, R. J., Ibbott, G. S., Gatenby, J. C., Xie, J., Horton, D., and Gore, J. C., "Magnetic resonance imaging of radiation dose distributions using a polymer gel dosimeter" *Phys. Med. Biol.*, **39**: 1437–1455, (1994).

[11] DeDeene, Y., DeWagter, C., VanDuyse, B., Derycke, S., DeNeve, W., and Achten, E., "Three dimensional dosimetry using polymer gel and magnetic resonance imaging applied to the verification of conformal radiation therapy in head and neck cancer" *Radiother. Oncol.*, **48**: 283–91, (1998).

[12] Maryanski, M. J., Ibbott, G. S., Schulz, R. J., Gore, J. C., "Radiation therapy dosimetry using magnetic resonance imaging of polymer gels" *Med. Phys.*, **23**: 699–705, (1996).

[13] DeDeene, Y., DeWagter, C., VanDuyse, B., Derycke, S., Mersseman, B., DeGersem, W., Voet, T., Achten, E., and DeNeve, W., "Validation of MR based polymer gel dosimetry as a preclinical three dimensional tool in contromal radiotherapy" *Magn. Reson. Med.*, **43**: 116–125, (2000).

[14] Ibbott, G. S., Maryanski, M. J., Eastman, P., Holcomb, S. D., Zhang, Y., Avison, R., Sanders, M., and Gore J. C., "Three-dimensional visualization and measurement of conformal dose distributions using magnetic resonance imaging of BANG polymer gel dosimeter" *Int. J. Radiat. Oncol. Biol. Phys.*, **38**: 1097–1103, (1997).

[15] McJury, M., Oldham, M., Cosgrove, V. P., Murphy, P. S., Doran, S., Leach M. O., and Webb S., "Radiation dosimetry using polymer gels: methods and applications" *Brit. J. Radiol.*, **73**: 919–929, (2000).

[16] Hasson, B. F., "Chemical dosimetry in the near-zone of brachytherapy sources" *Med. Phys.*, **23**: 803, (1996).

[17] Oldham, M., Baustert, I., Lord, C., Smith, T. A. D., McJury, M., and Leach. M. O., "An investigation into the dosimetry of a nine field tomotherapy irradiation

using BANG-gel dosimetry" *Phys. Med. Biol.*, **43**: 1113–1120, (1998).

[18] Fong, P., Keil, D. C., Does, M. D., and Gore, J. C., "Polymer gels for magnetic resonance imaging of radiation dose distributions at normal room atmosphere" *Phys. Med. Biol.*, **46**: 3105–3113, (2001).

[19] Bankamp, A., Schad, L. R., "Comparison of TSE, TGSE, and CPMG measurement techniques for MR polymer gel dosimetry" *Magn. Reson. Ima.*, **21**: 929 – 939, (2003).

[20] Maryanski, M. J., Gore, J. C., and Schulz, R. J., "Three-dimensional detection, dosimetry and imaging of an energy field by formation of a polymer in a gel" US Patent, 5321357,

[21] Venning, A. J., Hill, B., Brindha, S., Healy B. J., and Baldock, C., "Investigation of the PAGAT polymer gel dosimeter using magnetic resonance imaging" *Phy. in Med. and BioL.*, **50:**3875 (2005).

[22] De Deene, Y., Hanselaer, P., De Wagter, C., Achten, E., and De Neve, W., "An investigation of the chemical stability of a monomer/polymer gel dosimeter" *Phy. in Med. and Biol.*, **45**: 859 (2000).

[23] Spiers F.W., "The influence of energy absorption and electron range on dosage in irradiated bone" *Br J Radiol.***22**:521-533(1949).

[24] Asghar Mesbahi, "A review on gold nanoparticles radiosensitization effect in radiation therapy of cancer" *Reports of Practical Oncology & Radiotherapy,* **15:**176-180 (2010).