

Dose enhancement effect of gold nanoparticles on MAGICA polymer gel in mega voltage radiation therapy

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ABSTRACT

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Background: Radiation-sensitive polymer gels are among the most promising three-dimensional dose verification tools and tissue-like developed to date. Among the special features of this type of dosimeters, is be doped with other elements or chemicals which made them appropriate for investigating of dose enhancement with contrast agents, by high atomic number. **Material and Methods:** In this study, To evaluate dose characteristic of the normoxic polymer gel (MAGICA) such as dose response, dose sensitivity and dose resolution And To find the gold nanoparticles (50 nm) effects of the normoxic polymer gel such as a DEF in mega voltage radiation therapy (18 MV-X ray). Also it is compared by method of Monte Carlo simulation with MCNPX Code. **Results:** The results shown that the MAGICA polymer gel dose response in dose range of 0 to 600 cGy is linear and dose resolution in this range, is less than 0.7 Gy. MAGICA Polymer gel dosimeter response R_2 was increased by added gold nanoparticles. Absorbed dose enhancement factor by adding of gold nanoparticles with the 0.1, 0.2, 0.4 mM concentrations was 10%, 2% and 4% respectively. **Conclusion:** In this study, Shielding effect or self absorption happened on 0.2 mM & 0.4 mM. And optimum gold nanoparticles concentration to achieved maximum absorbed dose is 0.1mM, so that is useable for clinical studies.

Keywords: Dose enhancement, gold nanoparticles, MAGICA, gel dosimetry.

INTRODUCTION

Polymer gel dosimeter is a promising type of radiation dosimetry method used in medical radiation therapy ⁽¹⁾. The advantage of gel dosimetry include tissue-like elemental composition, high spatial resolution, capability for three-dimensional (3D) dose measurements, and possibility of preparing dosimeters of varying sizes and geometries ⁽²⁾. The tissue equivalent property of polymer gels also serves

as a good phantom to simulate the application of medical radiation to the human body. Polymer gel dosimeters are able to directly measure the effects of contrast agents or metallic radiation dose enhancers such as iodine and gold nanoparticles (AuNps) inside the dosimeter. In gel dosimeters, contrast agents may have uniform dispersion within the dosimeter and therefore the effects of this material can be directly quantified. Physical measurement of the dose enhancement produced by high Z materials with other types of radiation dosimeters, such as

film and ionization chambers, are quite complicated, although there have been some attempts to use these dosimeters^(3,4). Physical measurement was done for dose enhancement produced by high Z materials such as iodine in normoxic polymer gels⁽⁵⁻⁷⁾. The use of dosimeters does have its limits; researchers must rely on Monte Carlo simulation. In this study, for the first time, MAGICA polymer gel was used with AuNps and dose enhancement was evaluated by gel dosimetry in close relation to the Monte Carlo simulation of irradiation condition within megavoltage X-ray field.

Polymer gel dosimeter is known by the acronym MAGICA (Methacrylic Ascorbic in Gelatin Initiated by Copper with Agarose added) it was selected because it can be prepared in normal room atmosphere easier and faster than the other gel types such as BANG[®], PAG and etc.

MATERIALS AND METHODS

Monte Carlo simulation of MV X-ray unit and phantom

Radiation transport in matter using Monte Carlo method was used as described in MCNPX version 2.4 Code to determine photoelectric, Compton, pair-creation and Rayleigh cross sections and calculate dose deposition in MAGICA polymer gel. Mass attenuation coefficients of MAGICA gel were calculated and compare to water. The Varian 2100 C/D accelerator head was simulated by using the open literature information for 18 MV photons. The phantom size was 25×25×11 cm³ and SSD was 100 cm for all simulations. F8 tally was used for deposited energy calculation. Simulations were done by using three 2.4 GHz Pentium 4 processor and time of the single simulation was about 20 days for obtaining the less than 1.6% relative error in gel vial area. Photon and electron energy cut-offs were set to 10 keV and 100 keV in the entire geometry, respectively. The number of histories for each simulation was estimated to be 9.5×10³ in

number.

AuNPs preparation

In contemporary research, various synthesis techniques are being developed for AuNps fabrication. In this study, AuNps of 50 nm size obtained from PNF Co. (Tehran, Iran) as gold nanoparticles in aqueous solution with 7 mg/ml (7000 ppm) concentration. In PNF Company, nanoparticles are produced by applying extra high electric voltage and current, and the primary bulk wire with 0.1 mm diameter is converted into the nanoparticles via pulse explosive process.

Gel fabrication

For preparing of MAGICA gel dosimeter, gelatin (type A, 250 bloom, sigma-Aldrich co, USA) was added to 64% of de-ionized water (BDH laboratory supplies, UK) and allowed to swell for 30 minutes in room temperature. An electrical heating plate provided with magnetic stirring was used to heat the solution up to 49 °C. To produce the agarose (sigma-Aldrich co, USA) solution, first de-ionized water heated about 70 °C, and then agarose added and stirred until to be solved. When gelatin and agarose solution reached to the same temperature about 47 °C, the two solutions were mixed and allowed to cool down to gelling agent of 37 °C, then the mixture of hydroquinone (BDH laboratory supplies, UK), Methacrylic acid (sigma-Aldrich co, USA), CuSo₄ (sigma-Aldrich co, USA) was added to the mixture of agarose and gelatin. Some free radicals are always found in water that can initiate the polymerization reaction (self polymerization). Hydroquinone was used to band these free radicals and to inhibit self polymerization. Under irradiation H and OH radicals were produced and initiated the polymerization reaction. Methacrylic acid was a monomer that converts to polymer by irradiation. Ascorbic acid acted as antioxidant that scavenged the oxygen of the gel and acted as polymerization inhibitor. CuSo₄ was a catalyst for binding the oxygen to ascorbic acid^(8, 9). When the preparation of final polymer solution was completed, MAGICA gel separated in four

portions. One part is 400 ml for MAGICA gel and three parts in same capacities separated into 200 ml for incorporation different concentration gold nanoparticle in MAGICA gel by routine mechanical mix without heating.

Three different AuNp concentrations were considered: 0.1mM, 0.2mM, and 0.4 mM. After preparation of MAGICA and Gold Nano-MAGICA (GN-MAGICA) they were poured into calibration tubes and test vials for putting in a refrigerator at about 4 °C.

Irradiation procedures

Gel samples were irradiated with 18 MV photon beams from Varian 2100 C/D(Varian Medical Systems, Palo Alto, CA) linear accelerator. The control MAGICA gel vial and GN-MAGICA vials were arranged randomly in the water-filled phantom size 25×25×10 cm³ (figure 1). The irradiation set up for GN-AGICA is listed in table 1. Also, for calibrating MAGICA gel, calibration tubes were fixed in the water-filled phantom that is shown in figure. 2. These tubes were irradiated with doses in the range of 0-600 cGy (0, 100, 250, 500,600 cGy) for 18 MV photon beam with an SSD equal to 100 cm and afield size of 25×25 cm². Dosimetry by ionization chamber (Farmer, PTW co) was done to ensure that a proper and uniform dose was received by the polymer gel medium within the radiation field.

MRI reading and preparing an R₂ map

Several methods exist for dose response read out in gel dosimetry such as optical CT, Raman spectroscopy, nuclear MR, MRI and etc. In this study the proton magnetic properties variation was exhibited by magnetic resonance imaging (MRI). Gels were imaged using a 0.5 T MRI (Philips) 24 hours after irradiation to ensure that the polymerization mechanism has completely MRI was done. An MRI protocol that minimized the noise in 0.5 T MR Image was found (table 2).

In this study, we used the appropriate shimming for magnetic field in homogeneity correction in imaging area. The gel phantom was put in head coil as show in figure 3. To ensure that the obtained R₂ values were not influenced by possible temperature gradients in the gel, phantoms were left in MRI room 4 hours before scanning. Since the gel temperature during imaging increased up to 3°C, a little motion artifact is expected in MR image. R₂(=1/T₂) maps were computed using modified radiotherapy gel

Table 1. Irradiation Set up information.

Field size	25× 25cm ²
SSD(source to surface distance)	100 cm
Dose rate	424 MU
Dose	500 cGy



Figure 1. Arrangement of gel vial.



Figure2. MAGICA calibration tubes arrangement.

dosimetry image processing software coded in MATLAB (version 7.3.0.2.6 Math works). There are three methods for R_2 map extraction from MR Images; a) two points method, b) many point method, and c) Maximum-likelihood estimation (10). In many points method the R_2 map is obtained by fitting the MRI signals indifferent echoes in equation 1.

$$S = S_0 \exp(-R_2 TE) \quad (1)$$

Where S_0 is the signal corresponding with the un-relaxed magnetization or, from a theoretical point of view, which corresponds with an echo time $TE=0$. To obtain dose from R_2 map, calibration curve was needed. Gel dose response vs. absorbed dose was linear in the different ranges and follows the equation 2.

$$R_{(2,i)} = R_{(2,0)} + D_i \quad (2)$$

The $R_{(2,i)}$ value in each test tube i , is defined as the mean R_2 in a region of interest (ROI) of uniform dose.

Table 2. Optimum imaging protocol used in a Philips 0.5 T MRI system.

TR	1500 ms
TE	20-160 ms
Echo No	8
FOV	230 mm
MS (matrix size)	256 mm ² × 256
NEX	3
Slice thickness	3 mm (calibration tubes) 5 mm(GN_MAGICA vials)
No Slice	5

Table 3. Coverage factor adapted from ISO 1995.

Level of confidence	Kp
95%	1.96
68%	1
52%	$\frac{1}{\sqrt{2}}$



Figure3. Gel vials put in center in the head coil.

RESULTS AND DISCUSSION

MAGICA response to the 18 MV X-ray beam was characterized by MCNPX code simulated mass attenuation coefficients as shown in figure. 4. Response of MAGICA gel, R_2 irradiated with 18 MV photons, show in figure 5. As it can be seen the calibration curve is almost linear within the range of 0-600 cGy which has been experienced in this study with gel sensitivity of about 0.0109 s⁻¹ cGy. $D^{p\Delta}$ is defined as the minimal separation between two absorbed dose such that they may

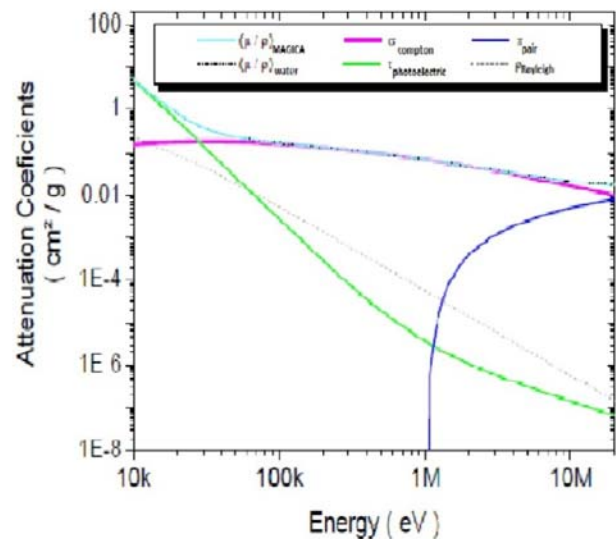


Figure4. Mass attenuation coefficients of MAGICA gel and water determined by MCNPX code. Cross-sections to Compton, photoelectric, pair-production and Rayleigh scattering are referred by σ_{Compton} , $\tau_{\text{photoelectric}}$, π_{pair} and ρ_{Rayleigh} symbols respectively.

be distinguished with a given level of confidence (p). The minimal detectable dose (MDD) is D_{Δ}^p as the dose approach to zero. D_{Δ}^p Can be written as equation 3.

$$D_{\Delta}^p = K_p \sqrt{2} \sigma_D \quad (3)$$

Where K_p is the coverage factor that is given in ISO (International Organization for Standardization) 1995⁽¹¹⁾ (table 3). Dose resolution Curve shown in figure 6, for dose levels less than 500 cGy, it has resolution less than 0.7 Gy. Of course, for higher doses, this quantity increases to 1 cGy. Also, for verification of dosimeter behavior of MAGICA polymer gel, Farmer chamber dosimeter has been used. The percentage depth dose curve of two dosimeters was compared with each other that are shown in figure 7. According to the figure 7, it is concluded that they have appropriate accordance so that, it's P-value is $0.001 < 0.05$. R_2 graphs have been investigated based on gold nanoparticles concentrations and they are shown for irradiated and non-irradiated states in figure 8.

The signal of non-irradiated tubes of MAGICA and GN-MAGICA were also evaluated and shown in figure 8a. In figure 8b show that the dose enhancement measurements performed in GN-MAGICA with different concentrations of AuNps with same dose 500 cGy. The shown error bars in this graph is standard deviation of R_2 for mean of four samples. Dose Enhancement

factor (DEF) can be derived from figure 8b and equation 4.

$$DEF = \frac{R_{2(GN-MAGICA)} - R_{2(MAGICA)}}{R_{2(MAGICA)}} \quad (4)$$

Achieved DEFs for 0.1mM, 0.2mM, 0.4mM AuNps concentrations in GN-MAGICA are 10%, 2% and 4%, respectively. Results of DEF calculation shows that the maximum DEF of about 10% is belonged to the AuNps concentrations of 0.1mM and it is the optimum concentration of gold nanoparticles that has been obtained in this study.

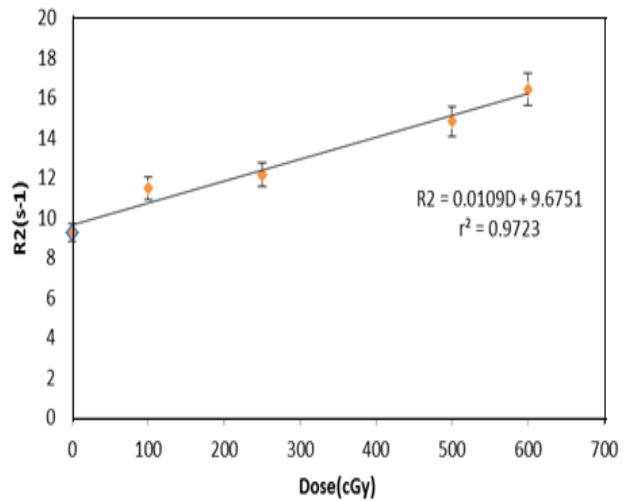


Figure 5. The MAGICA polymer gel calibration curve.

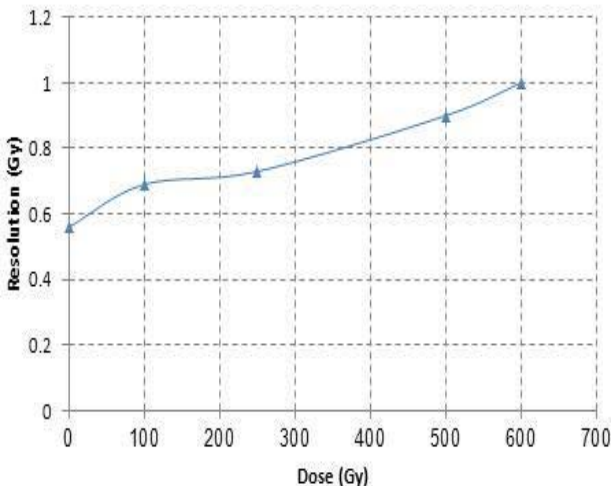


Figure 6. Dose resolution curve.

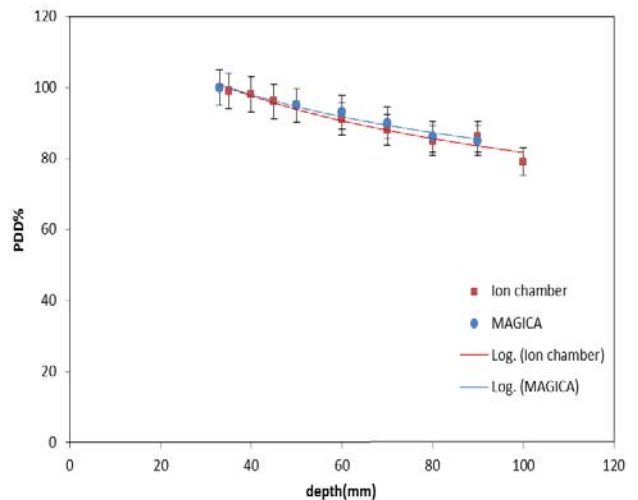


Figure 7. Depth dose curve MAGICA gel and ion chamber.

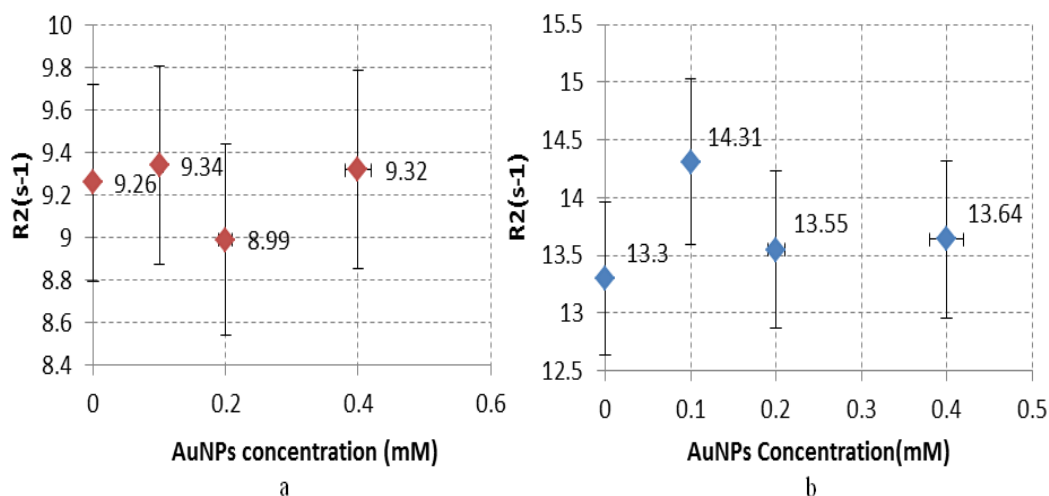


Figure 8. Signals from MAGICA and gold nanoparticle MAGICA was shown: a) the signal of non-irradiated tubes; b) the signal of irradiated vials.

CONCLUSION

The mass attenuation coefficients of MAGICA polymer gel, has an appropriate accordance with water mass attenuation coefficient in higher energy ranges than 10 keV. By adding of gold nanoparticles, the amount of R₂ signals while irradiation increased. So that it was the indicative of relative complete polymerization process of gel. Also the procedure of R₂ graph based on the concentration of gold nanoparticles in a state that gel vials weren't irradiated and R₂ graph based on the concentration of gold nanoparticles in a state that gel vials were irradiated, has been equal.

Maximum achieved amount of DEF in the concentration of 0.1mM, is 10% that the decrease procedure is seen respectively in concentrations of 0.4mM, 0.2mM and it is indicative of self absorption effect or shielding effect. Self absorption effect for gold nanoparticles with 0.2mM concentration has been more to the 0.4 mM. Because 18 MV energy has been used, the phenomenon of pair production was predominant in this energy. Totally, it can be said the optimum of gold nanoparticle concentration with 50 nm size in this investigation has been 0.1mM. Also despite the gold nanoparticles with 50 nm diameters aren't beam sensitive

spontaneously, but they can be used as medical increasing agent. And polymer gel is an appropriate for investigation of nanoparticles effects.

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