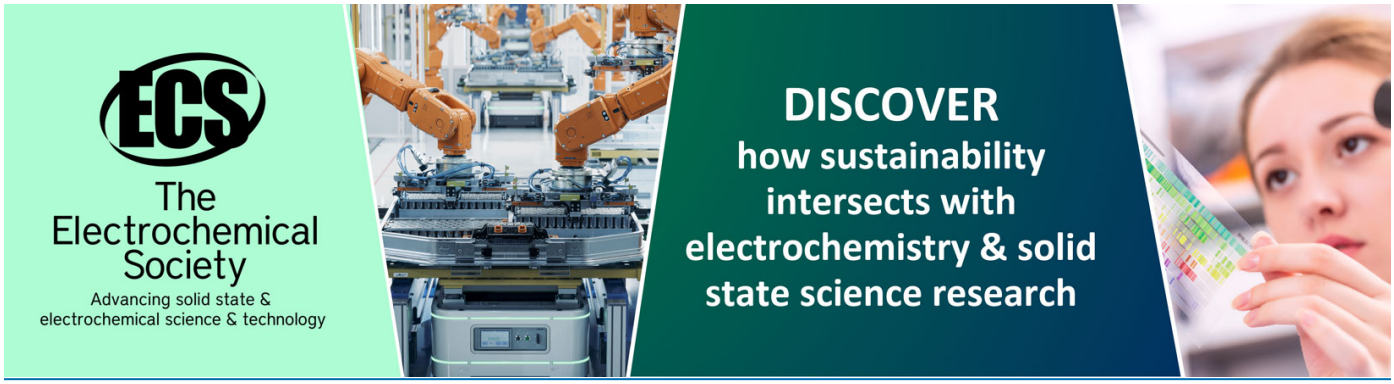
# Gel dosimetry measurement of dose enhancement bismuth-based nanoparticles in radiation therapy





IOP Conf. Series: Journal of Physics: Conf. Series **1305** (2019) 012046 doi:10.1088/1742-6596/1305/1/012046

# Gel dosimetry measurement of dose enhancement bismuth-based nanoparticles in radiation therapy

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**Abstract:** Recently bismuth-based nanoparticles as a promising radiosensitizer have drawn great attention in radiation therapy. To prove physical dose enhancement effect of the nanoparticles, gel dosimeters can be considered as an ideal method. This study aims to prove the applicability of bismuth ferrite nanoparticles as a magnetic localized dose enhancement agent by gel dosimetry method. Bismuth ferrite nanoparticle was synthesized by the conventional sol-gel method. Then we investigated dose enhancement property of the nanoparticles with gel dosimetry. MAGIC Polymer Gel dosimeters with nanoparticles were prepared and irradiated. According to gel dosimetry assay, for 0.5 mg/ml concentration of bismuth ferrite nanoparticles dose enhancement factor were obtained as 2 and 1.6 at 160 keV and average energy of 380 keV, respectively. Moreover, radiosensitiser effect of bismuth ferrite nanoparticles in presence of a low dose rate brachytherapy source (125-I) was investigated by Monte Carlo method. Whereas bismuth ferrite nanoparticles have magnetic property, we made a biodegradable spacer (fiducial) brachytherapy loaded with the nanoparticles for delivering nanoparticles and drug by applying an external magnetic field.

## 1. Introduction

Over the two last decades, extensive studies have been drawn on nanoparticles as radiosensitizer in radiation therapy. High atomic number nanoparticles can increase deposited dose in tumore locally due to production of photoelectric effect and agure electron. A large number of high-Z metal nanoparticles have been widely investigated as radiosensitizer such as gold, bismuth, platinum, tungsten, and gadalinium [1, 2]. In recent years, many studies have been focused on bismuth-based nanoparticles as radiosensitizer and contrast agent in radiation therapy and imaging due to high atomic number (Z=82), high photoelectric absorption, low cost, and low toxicity [3, 4]. Auger electron and photoelectrons which are produced for nanoparticles have short range, then it would be difficult to measure dose enhancement from nanoparticles by routine dosimeters. To deal with this challenge, 3D dosimeters [5, 6] can be a good choice [7].

In this study, we employed MAGIC Polymer Gel dosimeter to confirm radiosensitizer effect of bismuth ferrite nanoparticles ($BiFeO_3$). Moreover, dose amplification effect of $BiFeO_3$ nanoparticles for high concentration and bigger size at low dose rate (LDR) brachytherapy source was investigated by Monte Carlo modeling.

In spite of the large body of studies on delivering nanoparticles, delivering sufficient amount of nanoparticles concentration into the tumor is challenging. As a solution to delivering nanoparticles for

internal radiation therapy (Brachytherapy), Kumar *et al* [8], and Sinha *et al* [9], suggested that the fiducial markers and spacers could be used as a carrier of nanoparticles and radiation-sensitizing drugs at brachytherapy. In radiation therapy, fiducial markers and spacers are used to determine the position of the tumor for improving special accuracy. In this study, taking the advantage of the magnetic property of bismuth ferrite nanoparticles, we tried to design a spacer (fiducial) for delivering nanoparticles and drugs. Inductive heating property of the $BiFeO_3$ nanoparticles can raise the temperature in presence of the alternative magnetic field, which increases the biodegradation rate and as a result the releasing of nanoparticles and drug from a biodegradation polymer spacer. Drug release from the biodegradable spacers was measured in presence of the magnetic field and without it.

## 2. Methods

### 2.1. *Synthesis of $BiFeO_3$ nanoparticles*

Bismuth ferrite nanoparticles ($BiFeO_3$) were prepared based on Wang *et al* work [10]. In brief, bismuth nitrate $Bi(NO_3)_3 \cdot 5H_2O$ and iron nitrate $Fe(NO_3)_3 \cdot 9H_2O$ were dissolved in ethylene glycol (EG). The mixture was stirred at 140 ˚C to get the gel. The gel was heated to 450 ˚C for 30 min. Finally, to obtain the nanoparticles, the powder was washed and dried in vacuum at 60 ˚C. Size of the nanoparticles was measured by Image J 1.6.0_24 G software for more than 100 particles, which were chosen randomly from SEM image. It is found that nanoparticles' size is of 28nm±5.5. Biocompatibility of the nanoparticles was confirmed at previous works [3, 11].

### *2.2. Gel dosimetry*

To approve dose enhancement effect of $BiFeO_3$ nanoparticles as a radiosensitizer, MAGIC gel dosimeter was prepared based on the Fong *et al* [12] method with some modifications. In order to improve the sensitivity of the gel and oxygen scavenging, tetrakis (hydroxymethyl) phosphonium chloride (THPC) was added to the gel. Prepared gel was divided into two groups. One group without nanoparticles and the other with 0.5 mg/ml nanoparticles. The gels were irradiated at 160 keV energy ( RS-2000 x-ray biological irradiator 25 mA with 0.3 mm Cu filter) and the average energy of 380 keV (Iridium (Ir -192), after loading Varian GammaMed plusIX, brachytherapy source). After one week, the gels were read out by MRI scanner (Philips -3TNX, Netherlands) with a head coil (Figure 1and 2).

### *2.3. Monte Carlo simulation*

Iodine 125 (125-I, SelectSeed 130.002) as low dose rate (LDR) brachytherapy source was chosen for evaluation dose enhancement effect of $BiFeO_3$ nanoparticles [13]. The I-125 source was modeled by general-purpose Monte Carlo N-Particle Transport (MCNP6) code. In order to validate the code, we calculated TG-43 parameters such as radial dose function g(r) and anisotropy function $F(r,\theta)$. After validation of the radiation source, 100 nm $BiFeO_3$ nanoparticles with concentrations of 7 and 15 mg were simulated in a cubic tumor with dimension of $1\times1\times1$ $cm^3$ that was placed in 1 cm from the source. The cube was divided into cells with dimension of $2\times2\times2$ $mm^3$ and each cell was filled with smaller cells according to the concentration of nanoparticles. Dose distribution was calculated by F6 tally (MeV/g) and simulation was performed for $10^8$ histories.

### *2.4. $BiFeO_3$ nanoparticles-loaded brachytherapy spacer*

Biodegradable spacer (fiducial) brachytherapy loaded with nanoparticles and drug was prepared based on Kumar *et al* [7] work with some modification. To prepare spacers, 500 mg poly (lactic-co-glycolic acid) PLGA (50/50), 10% Polyethylene glycol (PEG) and 50mg of docetaxel were dissolved in 1 ml acetone. The mixture of nanoparticles and acetone was added to PLGA solution. The mixture of all materials was stirred until obtained a viscous paste. The paste was transferred to a silicone tube in diameter of 1mm by a syringe. The tube was dried at 46 ˚C and after that dried material in shape of the tube was cut in 5mm to get spacers. Spacers were divided in two group for measuring drug release, one with applying external magnetic field and another without it. The spacers were placed in tubes

with phosphate-buffered saline (PBS, pH 7.4) and the tubes were incubated at incubator-shaker (37˚C, 100 rpm). Every day one group of spacers were exposed to the alternative magnetic field (AMF) for 10 min. Then each day 0.5 ml PBS of each group (with and without applying AMF) was removed and replaced with fresh phosphate-buffered saline (PBS). The removed PBS was used for measuring drug release by UV-Visible spectrophotometer.

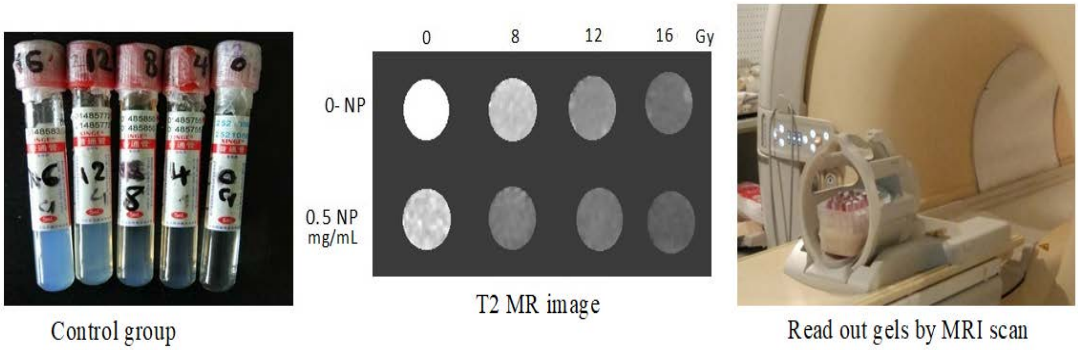


**Figure 1.** Gel dosimeter samples irradiated at 160 keV energy of photo and T2 MRI image**.**

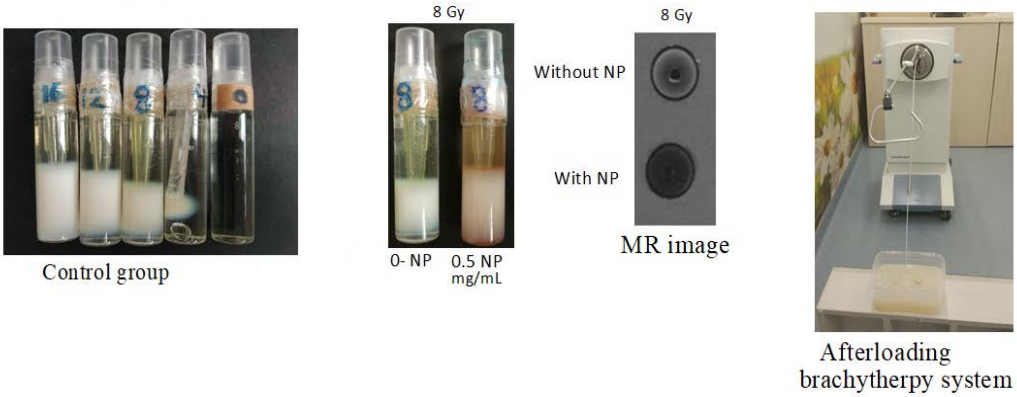


**Figure 2.** Gel samples irradiated at 380 Mean keV energy of photon iridium source by afterloading brachytherapy system.

## 3. Results and Discussion

MR imaging was performed to read polymer gel dosimeters. The spin-spin relaxation rate ($R_2$) as a function of absorbed radiation dose for gel samples with and without $BiFeO_3$ nanoparticles was shown in Figure 3 a and b. Gel data are fitted by a linear function, which indicates good correlations (R=0.99). Dose enhancement factor obtained DEF=2 at lower energy of 160 keV, while the factor is DEF=1.6 at higher average energy of 380 keV due to inverse proportion of photoelectric cross section to energy. The ability of the nanoparticles as a dose enhancement clearly is shown in Figure 1 and 2 from comparing gel tubes and MR image.

Results of Monte Carlo simulation of 125-I source for calculating the radial dose function, g(r) and the anisotropy function, F(r, θ) in this and a previous study with the same source is shown in Figure 4. The simulation results exhibited a good agreement for TG-43 parameters from the simulation and previous study [13]. Figure 5 shows enhancement in energy deposited with depth for bismuth and bismuth ferrite nanoparticles in size of 100 nm with 7 and 15 mg concentrations. Energy deposited in cells increases with concentration of nanoparticles

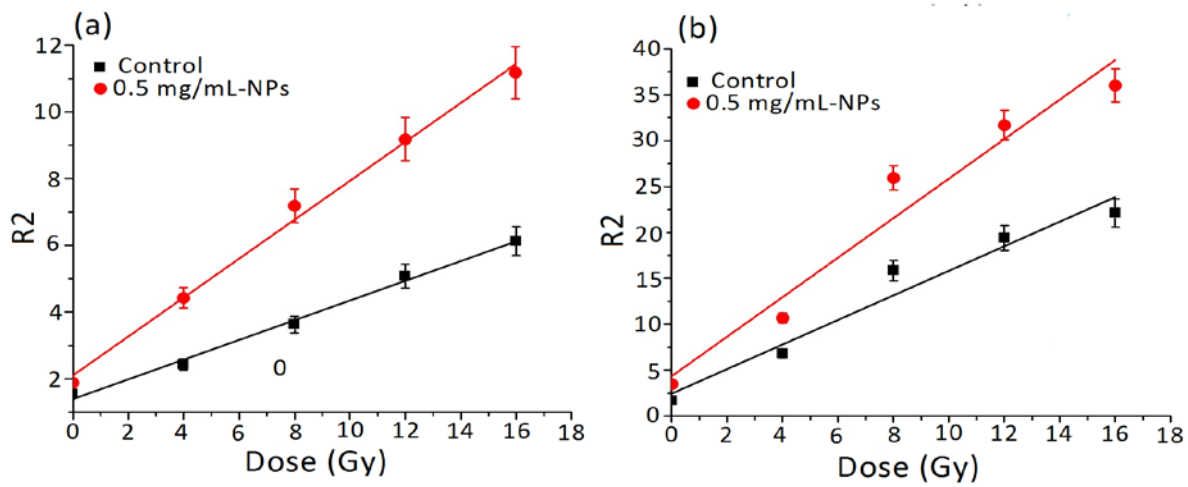


**Figure 3.** Gel dosimetry (a) dose response curves for gel pure and gel+$BiFeO_3$-Np irradiated at energy of 160 keV. (b) At average energy of 380 keV.

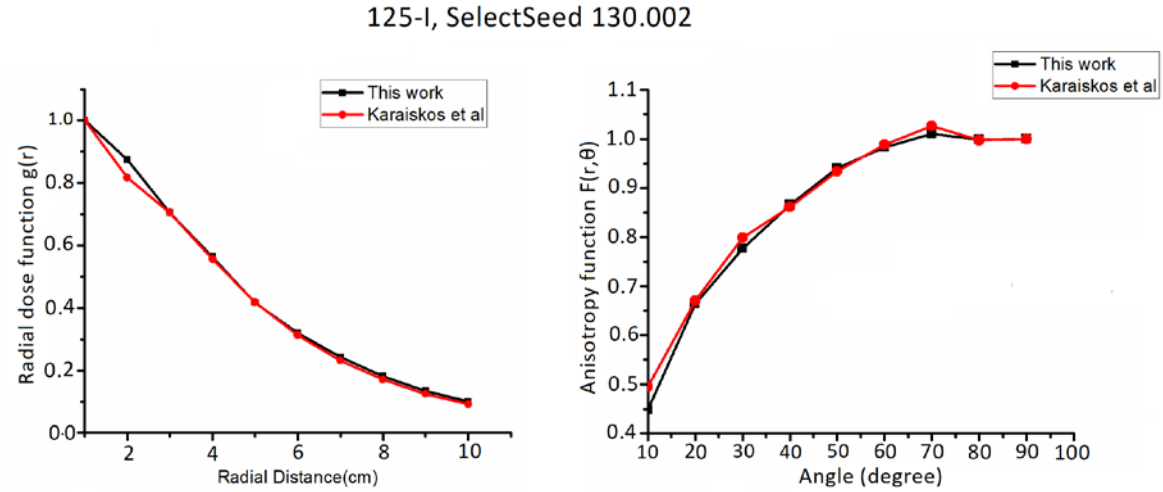


**Figure 4.** Comparison of radial dose function and anisotropy function of I-125, Selectseed 130.002 from the study and Karaiskos *et al* [13].

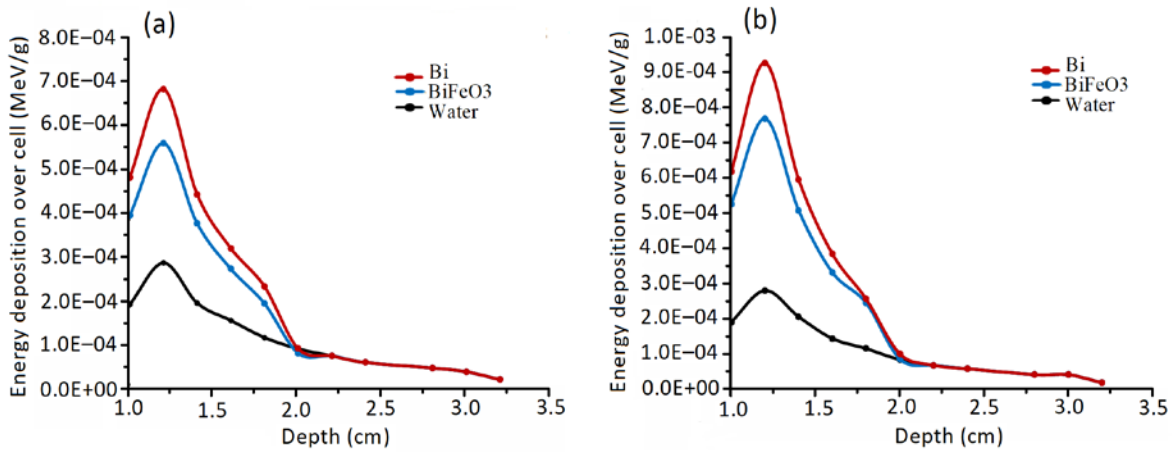


**Figure 5.** Energy deposition for bismuth and bismuth ferrite nanoparticles as dose enhancement agent (a) for 7mg and (b) for 15 mg.

Magnetic bismuth ferrite nanoparticles and docetaxel drug were loaded on PLGA-PEG spacers (Figure 6). The release profile of docetaxel drug from spacers (fiducials) with and without applying magnetic field was shown in Figure 6. After 10 days, 44% of the drug was released from spacers without applying magnetic field while it increased up to 90 % for the spacers with applying a magnetic field.

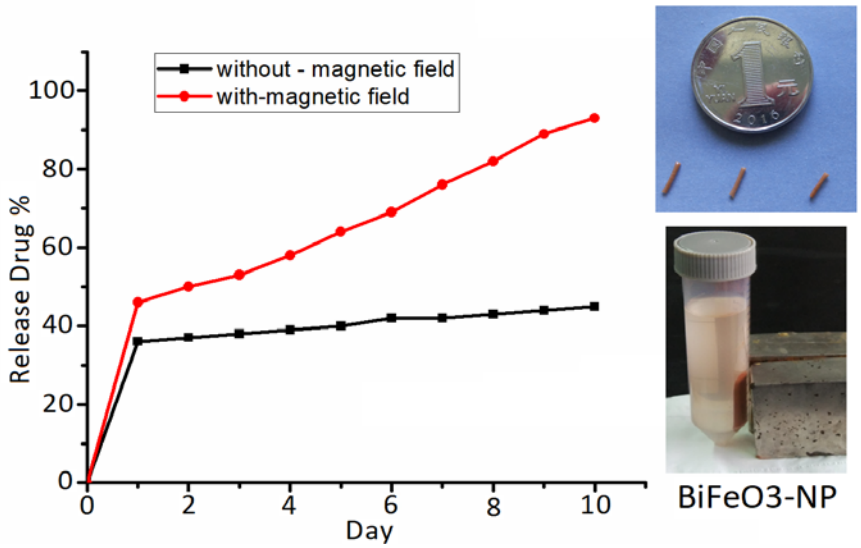


**Figure 6.** Drug release percentage from spacer (fiducial) with applying a magnetic field and without magnetic field.

## 4. Conclusion

In summary, we evaluated dose enhancement effect of bismuth ferrite nanoparticles with gel dosimetry and Monte Carlo modeling. The results proved that significant dose enhancement of the nanoparticles by polymer gel dosimeters which are one of a useful tool for the purpose. Moreover, based on inductive heating property of the $BiFeO_3$ nanoparticles in an alternative external magnetic field we designed a control delivery system for combination chemoradiation therapy.

## 5. References

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