Medical Applications

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Dosimetry in Nanoparticles-aided Radiotherapy

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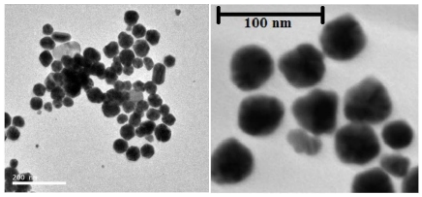

TEM images of gold and silver NPs

ABSTRACT

In nanoparticles-(NPs) aided radiotherapy, cancer cells selectively receive higher radiation dose due to high-Z NPs (gold and silver). Analytical and MC computation shows similar dose enhancement for gold and silver for photon energy ranging from 50-70 keV. Hence, silver can be a cost-effective alternative to gold for NPs-aided brachytherapy using 170Tm source. For dosimetric verification, a method using in-house synthesised NPs-loaded alginate film and unlaminated radiochromic film is explored. Further, radiation sensitivity of in-house synthesized Tryptophan-coated gold NPs and Gallic-acid coated silver NPs are investigated using in-vitro measurement.

KEYWORDS: *Dose enhancement, NPs-aided radiotherapy, unlaminated film dosimetry*

Introduction

Radiotherapy (RT) is one of the important modality for cancer treatment. However, the lack of selectivity between the tumor and the normal cells is one of the main limitation of RT [1]. In the treatment of radioresistant tumour, relatively higher radiation dose is required. The delivery of higher tumor dose is limited due to the lower tolerance dose of the normal cells present in the vicinity of the tumor [2]. This problem can be solved by making tomour more radiosensitive compare to the healthy tissues. The radiosenstisation of the tumour can be achived by infusing nanoparticles (NPs) in the tumour. Due to the hypoxic nature of tumour, the tumor vascularization structure has high porosity (pore size ~ 400 nm). The size of NPs (10-100 nm) being smaller than this pore size can passage from blood to the tumor cells and accumulate there. The preferential accumulation of NPs inside the tumor cells can be achieved via active and passive targeting methods [3]. The NPs of high atomic number with superior biocompatibility are preferred radio-sensitizing agents [4].

The therapeutic technique of increasing radio-sensitivity of cancer cells due to the infusion of NPs is known as NPs-aided RT [5]. The dose enhancement factor (DEF), ratio of dose to the tumor infused with and without NPs, is used to measure the radio-sensitivity. The dose enhancement in the tumour can be attributed to higher photoelectric cross section of high-Z NPs present in the tumour. As the photoelectric cross section is higher at lower energies, the low energy photon emitting brachytherapy sources or similar modalities producing photon/X-rays of lower energy are useful for NPs-aided RT.

Dose enhancement studies for clinical brachytherapy sources: Monte Carlo study

Gold NPs (AuNPs) are being used as radio-sensitizer due to their high-Z and bio-compatibility. However, they are relatively expensive and there is a need of cost effective alternatives to AuNPs. In recent years, the bio-compatible silver NPs (AgNPs) have been developed. To study the equivalence between AuNPs and AgNPs in terms of dose enhancement, the DEFs were estimated for photons ranging from 20 to 1250 keV using EGSnrc based Monte Carlo code. Almost same dose enhancements were observed for AuNPs and AgNPs at photon energies ranging from 50-70 keV (Fig.1) [6]. ^{170}Tm source (E_{avg}: 66.7 keV) lies in this optimal energy range. Hence, the dose enhancements in the prostate tumour for ^{170}Tm and other low energy brachytherapy sources were estimated (Table 1).

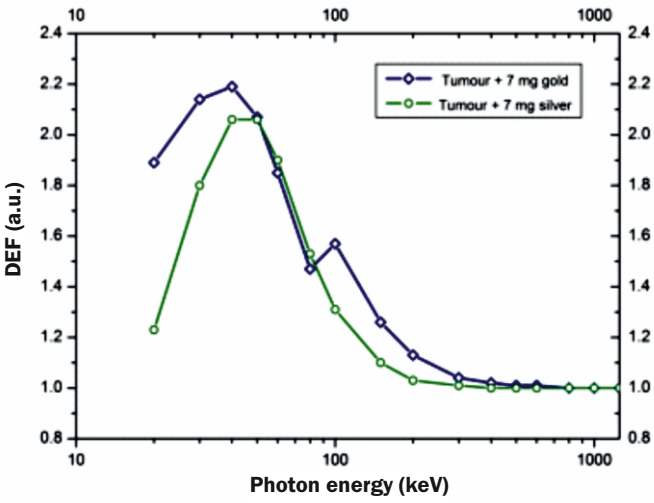

Fig.1: Comparison of DEFs for tumour infused with gold and silver.

Table 1: Monte Carlo estimated dose enhancement factor for brachytherapy sources.

Brachytherapy Source	Average DEF (Gold)	Average DEF (Silver)
^{170}Tm (E_{avg}: 66.7 keV)	1.94±0.01	1.92±0.01
^{125}I (E_{avg}: 28 keV)	1.98±0.01	1.56±0.01
50 kVp (E_{avg}: 66.7 keV)	2.06±0.01	1.61±0.01
^{103}Pd (E_{avg}: 21 keV)	1.60±0.01	1.17 ±0.01
^{169}Yb (E_{avg}: 93 keV)	1.65±0.01	1.57 ±0.01

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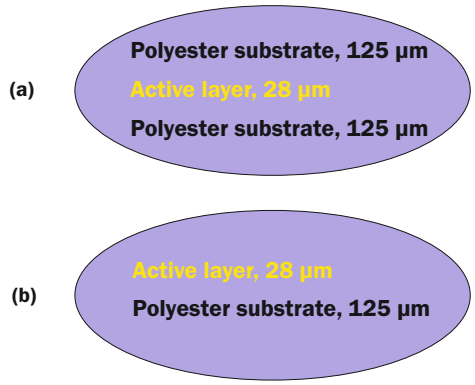

Fig.2: Schematic diagram of (a) laminated and (b) unlaminated Gafchromic EBT3 film.

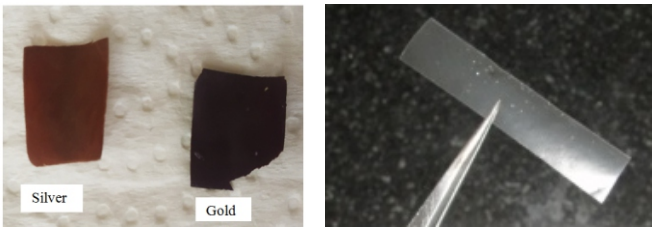

Fig.3: (a) Photograph showing pieces of silver nanoparticles embedded alginate film (left) and gold nanoparticles embedded alginate film (right) and (b) Alginate film.

In the case of ^{170}Tm source, DEFs of 1.94±0.01 and 1.92±0.01 were recorded for AuNPs and AgNPs, respectively [7]. Hence, the AgNPs can be cost effective alternatives to AuNPs when the treatment is delivered using ^{170}Tm brachytherapy source.

Experimental Measurement of DEFs

The routinely used radiochromic film dosimeters (e.g. Gafchromic EBT3 film) find limited applications as the dose enhancement is mainly driven by low range photoelectrons and Auger electrons produced in the immediate micro-environment of NPs. The polyester layer (125 µm) present in Gafchromic EBT3 film makes dose enhancement difficult to measure. Hence, Gafchromic EBT3 film was customized (i.e. unlaminated film) by ISP technologies, USA, on our request (Fig.2). This customized film, *unlaminated EBT3 film,* was explored for the quantification of dose enhancement.

For the dosimetric measurement, AuNPs-embedded alginate film (AuNPs-Alg film) and AgNPs-embedded alginate film (AgNPs-Alg film) were synthesised (Fig.3). These films were characterised using standard technique. The surface plasmon resonance (SPR) at 400 nm and 550 nm was recorded for AgNPs and AuNPs, respectively during UV-Vis absorption spectroscopy. The Atomic Force Microscopy measured average particle size of AgNPs and AuNPs were found to be 13±2 nm and 15±2 nm, respectively.

The combination of NPs-embedded films and unlaminated EBT3 film was explored for the measurement of DEFs for ISO wide spectrum X-rays (E_{avg} ranging from 57 to 137 keV), high energy X-rays (6 and 10 MV) and 50 kVp X-rays generated by electronic brachytherapy device. The unlaminated EBT3 film can able to measure the dose enhancement (Max DEF of 29%) [8, 9]. However, the laminated film could not measure any kind of dose enhancement.

Dose Enhancement Using In-vitro Measurement

Tryptophan-coated AuNPs (Trp-AuNPs) and Gallic-acid coated AgNPs (Gal-AgNPs) were synthesized in-house (Fig.4). The SPR of AuNPs and AgNPs was recorded at 550 nm and 420 nm, respectively. TEM measured average particle size of AuNPs and AgNPs was 49.5±5.1 nm and 40.5±3.1 nm, respectively. The cytotoxicity and time dependent absorption of NPs in breast carcinoma cells (MCF-7 cells) was studied to optimise the parameter required for higher radiosensitization at lower cytotoxicity. Depending on the % cell viability (Trp-AuNPs: 93.85 to 89% and Gal-AgNPs: 85.98 to 82.10 %) at different concentrations, NPs concentration of 0.5 mM was optimised to attain % cell viability ≥ 85%. The time dependant absorption of NPs shows that the internalisation of NPs increased rapidly up to 24 hr (Fig.5). Hence, 24 hr time interval between NPs infusion and radiation delivery was optimised.

Fig.6 shows the % cell survival of breast carcinoma cells due to radiation dose from low energy X-rays (30, 57 and 104 keV) and high energy gamma rays from telecobalt unit.

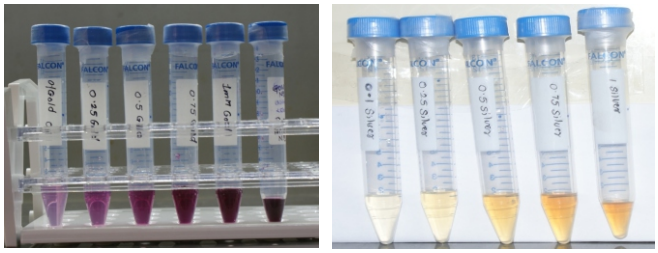

Fig.4: Photographs showing different concentrations of (a) gold NPs and (b) silver NPs.

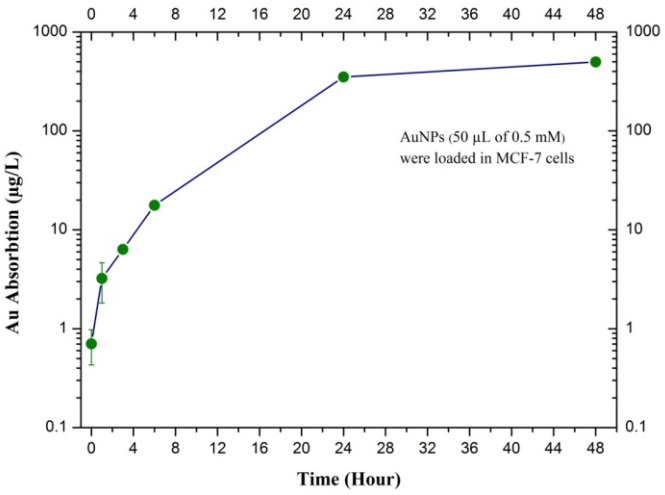

Fig.5: Time dependant absorption of Trp-AuNPs.

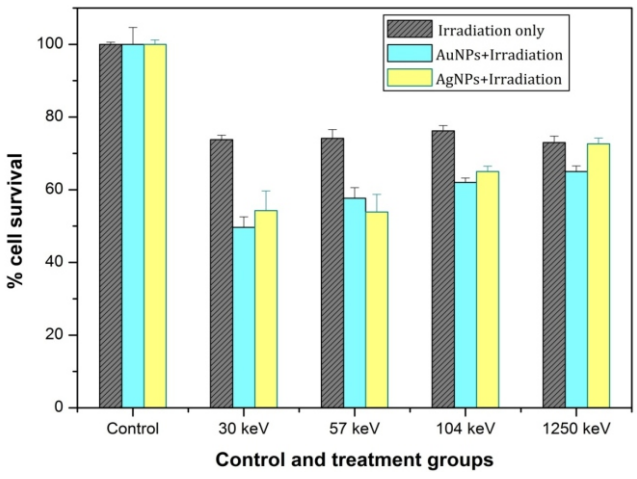

Fig.6: Cell survival of control group and treatment groups.

The radiation sensitivity of 1.50 to 1.23 (Trp-AuNPs) and 1.35 to 1.17 (Gal-AgNPs) was observed for X-rays ranging from 30-104 keV. However, high energy gamma rays could not show radio-sensitisation effect.

Conclusion

The significant dose enhancement is observed for low energy photons. Hence, ^{170}Tm based brachytherapy, 50 kVp X-rays from electronic brachytherapy and/or similar modalities producing X-ray or gamma radiations of optimal energy can be used for NPs-aided RT. A proposed dosimetry method of using unlaminated radiochromic film can be used to measure DEFs. Further, Trp-AuNPs and Gal-AgNPs can be used as a radio sensitizer for NPs-aided RT. However, our results are based on an *in-vitro* measurement. The detailed investigations using *in-vivo* techniques and detailed clinical trials are necessary before its clinical use.

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