Applied Radiation and Isotopes xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

# Integration of Fricke gel dosimetry with Ag nanoparticles for experimental dose enhancement determination in theranostics

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## HIGHLIGHTS

- Novel dosimetry integrating gel and nanoparticles is presented.
- Ag-infused Fricke gel dosimeter preparation and dose-response are reported.
- Experimental and Monte Carlo approaches were applied to study dose-enhancement.
- On-line X-ray fluorescence was correlated with dosimeter properties.
- Promising performance was obtained for future applications.

## ARTICLE INFO

*Keywords:*
Fricke gel dosimetry
Ag nanoparticles
Dose enhancement

## ABSTRACT

The use and implementation of nanoparticles in medicine has grown exponentially in the last twenty years. Their main applications include drug delivery, theranostics, tissue engineering and magneto function. Dosimetry techniques can take advantage of inorganic nanoparticles properties and their combination with gel dosimetry techniques could be used as a first step for their later inclusion in radio-diagnostics or radiotherapy treatments. The present study presents preliminary results of properly synthesized and purified silver nanoparticles integration with Fricke gel dosimeters. Used nanoparticles presented mean sizes ranging from 2 to 20 nm, with a lognormal distribution. Xylenol orange concentration in Fricke gel dosimeter was adjust in order to allow sample's optical readout, accounting nanoparticles plasmon. Dose enhancement was assessed irradiating dosimeters setting X-ray beams energies below and above silver K-edge. Monte Carlo simulations were used to estimate the dose enhancement in the experiments and compare with the trend obtained in the experimental results.

## 1. Introduction

Radiation dosimetry is devoted to measure the amount of energy deposited by ionizing radiation. Measurements are carried out by dedicated devices, typically known as dosimeters, with the aim of estimating the effective dose received by exposed phantoms or patients. Nowadays, different approaches and techniques are available for achieving reliable radiation dosimetry, including gene expression, somatic mutations, gas ionization, thermoluminescence, optically stimulated luminescence, electron paramagnetic resonance, neutron activation, gels, films, among others; all of them providing specific advantages and disadvantages in terms of accuracy, biological interpretation, analytical dose reconstruction and other issues. From a physical point of view, international protocols for radiation dosimetry clearly establish absorbed dose to water as the reference starting point for any validated traceable dosimetry technique.

Nanoparticles are materials with overall dimensions in the nanoscale, they have numerous advantages over their bulk analogues, most of them related to their high surface area to volume ratio, which enhances and favor different types of chemical reactions and provides a

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https://doi.org/10.1016/j.apradiso.2018.02.028
Received 12 December 2017; Received in revised form 22 February 2018; Accepted 22 February 2018

large number of surface modifications sites to engineer multifunctional materials. These properties and advantages have been exploited in almost any field of application like medicine, food industry, energy or environmental projects. In regard to oncology and cancer therapy, nanomaterials have been already successfully applied as non-targeted delivery systems with many Food and Drug Administration (FDA) approved examples and some targeted, stimuli and combined delivery systems which are in Phase II/III (Shi et al., 2016). Also, some nanomaterials have been approved by the FDA and the European Medicines Agency (EMA) as imaging agents (Anselmo and Mitragotri, 2016), which proves the potential and future perspective of nanomaterials. At the same time, a growing number of new promising materials for oncological therapies arise every year that must fulfil certain issues and challenges for their clinical use (Chapman et al., 2013). There are a broad number of studies on materials that combine imaging and therapy in oncological treatments, which gave birth to theranostic nanoparticles, defined as those that combine tumor imaging with therapeutic efficacy (Kiessling et al., 2014). Among the different types of materials suitable for theranostics, those based on inorganic materials can be used together with X-ray therapy to enhance local dose delivery and to monitor the evolution of the therapy by means of their characteristic X-ray fluorescence emission signal (Huang et al., 2011; Titus et al., 2016). Therefore, methods able to account for absorbed dose and possible dose enhancement becomes necessary and extremely useful for any treatment design. Gel dosimetry is a suitable tool thanks to its tissue-equivalence and ability to register 3D dose distributions (Baldock et al., 2010). One of the most used gel dosimeters is Fricke gel, which consists mainly of a gel matrix containing ferrous sulfate ($Fe^{+2}$) that, when exposed to ionizing radiation, is oxidized to ferric sulfate ($Fe^{+3}$) at a rate proportional to the absorbed dose (Schreiner, 2004). When combined with an adequate colorant such as xylenol orange, these systems are suitable for optical transmission readings of the sensitive material (Kelly et al., 1998; Del Lama et al., 2017). To the date, there are very few reports about the use of nanoparticles with this dosimeters, gold nanoparticles where studied by Herold et al. (Herold et al., 2000) showing a dose enhancement. Also, cerium oxide nanoparticles were included in to this dosimeters (Ebenezer Suman Babu et al., 2017) where a response sensitivity enhancement was mentioned but dose enhancement was not proved or studied.

The present work focuses on a preliminary analysis on the feasibility and reliability of integrating high Z nanoparticles, like silver nanoparticles (AgNPs), with Fricke gel dosimeters, aimed at profiting from the potential individual advantages of the dosimetry system and the AgNPs. The main goal of this study is to prove the feasibility of using Fricke gel dosimetry to measure the increase in the absorbed dose mainly due to secondary electrons produced by silver re-emissions; as well as exhibiting potentiality for external monitoring by detecting and recording Ag K-lines emissions. Spatial distribution of AgNPs concentration may be assessed by detecting Ag K-lines during irradiation, thus providing a promising framework for tumor targeting and, simultaneously, a local dose enhancement for a better protection of the surrounding organs at risk. To this aim, suitable modifications may be necessary for the preparation protocol of standard Fricke gel in order to achieve a chemically stable and physically useful product. Moreover, synthesis of AgNPs may also require specific modifications or adaptations to obtain adequate AgNP suspensions for this specific application. Besides, dedicated X-ray detection system needs to be incorporated into the proposed configuration for further investigation about the potentiality of correlating the X-ray fluorescent signal with AgNPs spatial distribution and local absorbed dose, even at real-time level.

## 2. Materials and methods

### 2.1. Nanoparticle synthesis and characterization

In order to obtain silver nanoparticle suitable for gel dosimetry a synthesis process where particles are being formed and stabilized at the same time with a gel dosimetry compatible substance was used as described elsewhere (Vedelago et al., 2018). Briefly, a 300-mM aqueous solution of silver nitrate (99.9% acquired from Prodesa S.C.A., Buenos Aires, Argentina) and a 96-mM aqueous solution of gelatin (250 Bloom purchased from Sigma Aldrich, Saint Louis, MO, USA) were mixed and stirred for 60 min. The obtained solution was kept in a sealed reactor at 90 °C for at least 15 h. The synthesis product was then purified by a dialysis and freeze-drying process ensuring that no unreacted material was present in the final product. The obtained material was then characterized by transmission electron microscope (TEM) with a JEM-JOEL 1200-EX II TEM microscope (USA).

### 2.2. Gel dosimeters manufacture, irradiation and characterization

Two different Fricke gel dosimeters were prepared; on one hand, a sensitive material was manufactured based on the method described elsewhere (Valente et al., 2007), where a 250-bloom gelatin solution (3.00% w/w) was stirred for 20 min at 50 °C. Then, the resulting gel was mixed at 28 °C with sulfuric acid (1.38% w/w), xylenol orange (0.04% w/w) and ferrous sulfate (0.06% w/w). On the other hand, a AgNP-infused Fricke gel dosimeter was manufactured with a similar protocol but reducing the xylenol orange concentration to 70 ppm and with a AgNPs concertation of 1.00% w/w. Both materials were contained in poly(methyl methacrylate) (PMMA) cuvettes of $10 \times 10 \times 45\ mm^3$ and stored at 4 °C for at least 12 h before irradiation. Sulfuric acid and xylenol orange were provided by Sigma Aldrich (USA), and ferrous sulfate was purchased from Research AG, (Buenos Aires, Argentina).

For the X-ray beam irradiations, a conventional X-ray tube coupled with a W target was used with two different irradiation setups based on a previous study (Mattea et al., 2017). For the silver fluorescence detection study, the X-ray source generator was set to 50 kVp and the scattered spectrum was collected with an AMPTEK XR-100T Cd-Te γ/X-ray detector. A collimator with a 2 mm diameter window was used and the detector was perpendicularly placed to the incident beam and at 45° with respect to the phantom's surface. The distance between phantom's surface and detector's collimator was kept fixed at 50 mm and 1 mm water-equivalent slabs were used to emulate the desired target depth. Two different incident spectra were used for the dose enhancement study. The beams were configured by setting the X-ray generator at 50 kVp and 14.4 mA, and at 25 kVp and 34.5 mA. In both cases, the resulting dose rate was (25.9 ± 0.8) cGy/min, measured by a calibrated ionization chamber (TN 30013, PTW, Freiburg, Germany). The characterization of the dosimeters was carried out by means of optical methods. In particular, the absorbance change between the non-irradiated and the irradiated materials was measured with a Shimadzu UV-1800 spectrophotometer (Japan) at room temperature.

### 2.3. Nanoparticle detection and dose enhancement in AgNP-infused Fricke gel dosimeter

Ionization of Ag electrons is responsible of an appreciable part of the collective dose enhancement effect. Therefore, in order to study dose enhancement, X-rays beams capable or not of exciting silver K-edge (25.5 keV) were used, mentioned before as 25 kVp and 50 kVp. Irradiations were carried out with a $30 \times 30\ mm^2$ field size, a source-to-phantom distance of 930 mm and a collimator to sample distance of 135 mm.

### 2.4. Dose enhancement and nanoparticle detection by Monte Carlo simulations

There are numerous Monte Carlo codes properly benchmarked and currently used for different applications of radiation transport, like EGS4, GEANT4, MCNP, FLUKA and PENELOPE. Specifically,

PENELOPE (PENetration and Energy Loss Of Positrons and Electrons; photon simulation was introduced later) Monte Carlo code 2001 has demonstrated to provide excellent agreements with experimental data for the so called "low energy range", *i.e.* < 0.1 MeV, as it is the case of medical radiology. In this context, PENELOPE appears as a suitable option to simulate AgNP-infused Fricke gel dosimeters with the aim of characterizing some relevant physical properties as well as evaluating the absorbed dose distributions for different configurations.

PENELOPE main code provides a comprehensive database containing pure elements and some compounds commonly used during radiation-matter interaction processes, like biological tissues, some plastics and alloys. However, user-specific materials, such as AgNPs suspended in Fricke gel, require a proper definition by the user, which can be reasonably achieved by defining the weight fractions of the corresponding constituents and using the additivity rules incorporated in the *material.exe* module of PENELOPE, along with the corresponding mass density that was experimentally measured. Clearly, the validity of the obtained results is strongly dependent on this approach, which may be adequately applied for AgNPs in low concentration, uniformly distributed within the Fricke gel and with no significant differences in their dimensions. If all these conditions are satisfied, simulation may provide acceptable descriptions of absorbed dose distribution as well as emerging photon spectrum. In this study, an analogous setup to that of the experiments was designed by means of the *pengeom* module to sketch $10 \times 10 \times 45\,mm^3$ spectrophotometry vials containing AgNP-infused Fricke gel with different Ag concentrations. These vials, surrounded by air, were irradiated by X-rays with geometric properties defined exactly as the ones in the experimental configurations. The energy spectra were defined by means of typical piecewise approach in order to incorporate in the simulation the exact spectrum experimentally measured at sample position. Particle fluence was recorded at different positions by means of dedicated tallies, being the detector location the most relevant one. The Monte Carlo tally for photon detection was defined aimed at attaining energy binning according to the used in the experimental detector.

## 3. Results

Obtained results are presented with the following structure: Synthesized AgNPs characterization, AgNP-infused Fricke gel dose-response, AgNPs detection by X-ray fluorescence and estimation of local dose enhancement due to AgNPs.

Silver nanoparticles within a porcine skin gelatin matrix were successfully obtained with mean sizes ranging from 2 to 20 nm. A TEM image of the synthesized NPs is shown in Fig. 1, along with the nanoparticle area-equivalent-diameter (AED) histogram and its fitted log-normal distribution. The materials used in the AgNP-infused Fricke gel dosimetry study had a mean AED of 7.8 nm with a standard deviation of 3.1 nm. Also, their incorporation on the dosimeters didn't caused any

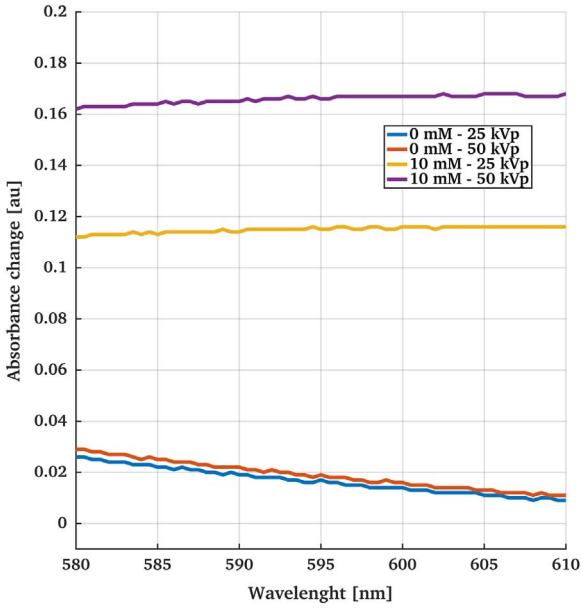


**Fig. 2.** Absorption change curves for silver AgNP-infused Fricke gel samples and standard Fricke gel samples.

modification to their or severe changes to their optical properties, as reported in previous studies when a silver salt was used as modifier (Mattea et al., 2017).

In order to evaluate the dose enhancement effects due to the presence of silver nanoparticles, AgNP-infused Fricke gel dosimeters were irradiated with X-ray beams with kVp energies below and above silver K-edge and a total absorbed dose of 12 Gy. The obtained absorption spectra are shown in Fig. 2.

An increase in the absorbance change was observed when the dosimeters were irradiated above silver K-edge, thus proving a dose enhancement because of their presence. For comparison purposes, absorption spectra of Fricke gel dosimeters without nanoparticles and irradiated under the same conditions are included in Fig. 2. From these results, it becomes clear that nanoparticles are increasing the base absorbance value in the material, but if a proper concentration of xylenol orange and nanoparticles are used a clear dose enhancement can be measured with the proposed method.

Silver characteristic X-ray fluorescence was detected in a water equivalent phantom placing a nanoparticle-doped volume at different depths from the surface of the phantom. The measured spectra are shown in Fig. 3 together with the background spectra in the samples with no AgNPs. The intensities of the experimental and simulated K-alpha lines are depicted in Fig. 4, where both curves were normalized to their respective result at the minimum used depth of 1 mm. Dotted lines

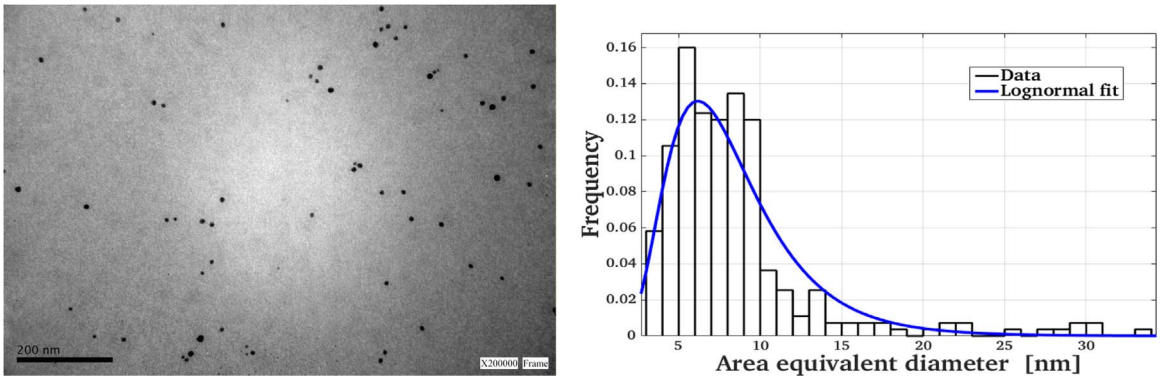


**Fig. 1.** TEM image of the silver nanoparticle synthesis product (left) and particle size distribution (right).

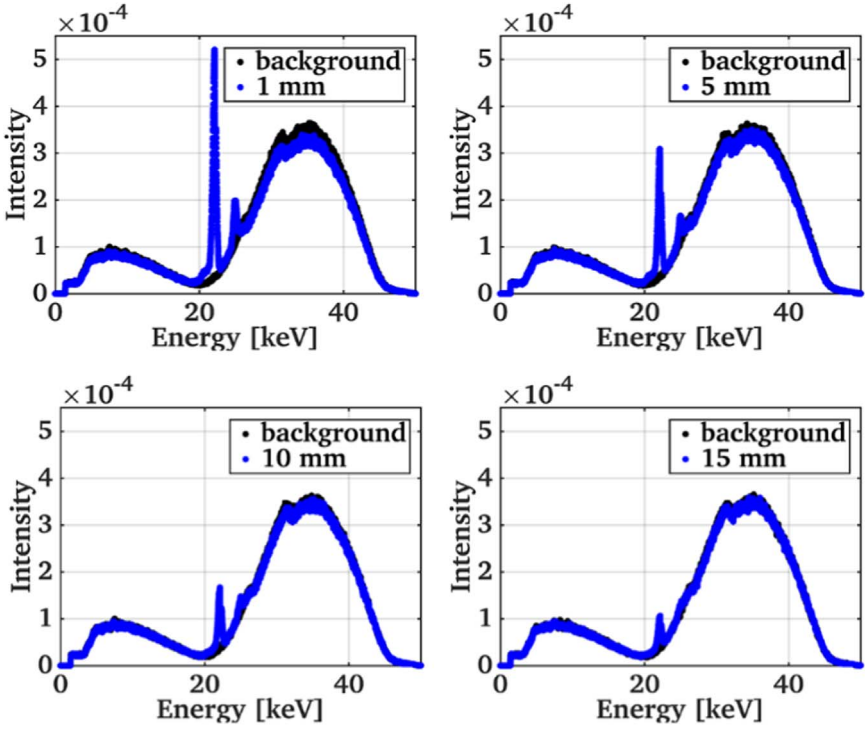


**Fig. 3.** Measured scattered spectra at different depths with and without AgNPs.

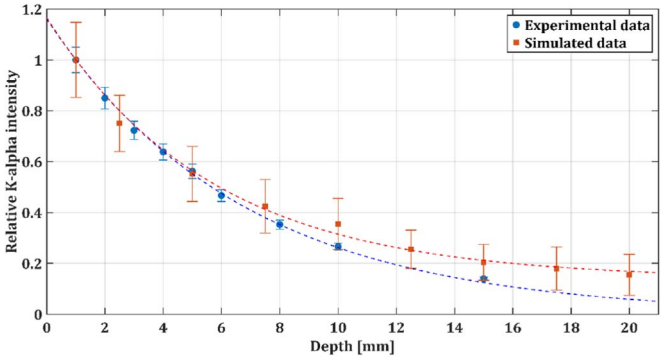


**Fig. 4.** Silver K-alpha intensities at different depths (normalized to 1 mm depth) for AgNP-infused Fricke gel dosimeter at different water-equivalent depths.

were included only as a guideline.

Similarly, total absorbed dose was calculated for AgNP-infused samples for different AgNP concentrations, and the obtained results were normalized to the case of standard Fricke gel dosimeter. The obtained results are summarized in Table 1.

## 4. Discussion

During the first phases of this work, AgNPs synthesis represented one of the main limitations and required an exhaustive study and the implementation of several techniques to overcome the implications of using silver as a modifier for Fricke gel dosimetry. Also, because of the high demanding requirements in the final product, AgNPs with minimal ionic $Ag^+$ concentration was mandatory and essential for the appropriate further implementation on Fricke gel dosimetry. Successive dialysis processes demonstrated to be a suitable solution without affecting significantly the properties of AgNPs, like their average size descriptors and their size distribution. It is worthwhile mentioning, that the use of other elements different from gold may involve secondary reactions with other species in the dosimeters and must be considered in the manufacturing methods.

X-ray fluorescence was proposed for real-time external monitoring, because it is a well-known robust technique capable of being easily integrated or adapted to typical irradiation setups involving nanoparticle-infused materials. Moreover, the dose enhancement due to the presence of AgNPs was proved by measuring the difference in the absorbance of dosimeters irradiated above and below the silver K-edge.

Monte Carlo simulations results of in-depth silver K-alpha intensity were found to be in good agreement with measured data within corresponding uncertainties, thus supporting the possibility of using the Monte Carlo tool as a first approach in the design and characterization of AgNP-infused Fricke gel experiments. As reported in Fig. 4, in-depth exponential trends were observed in both simulated and experimental results, with similar relative intensities at different depths. However, differences between Monte Carlo simulations and experimental data appear to increase with increases in depth, which may be attributed to minor discrepancies between user-defined Monte Carlo material and actual AgNP-infused Fricke gel. Although the additivity rules for estimating properties of the mixtures in terms of the ones of the constituents might be reliable for practical purposes, it should be considered that minor differences may be obtained, especially in the low energy range. Besides, it should be pointed out that mixtures and compounds modelling in Monte Carlo is based on homogeneity, uniformity, and constant density approaches; while experimental cases may involve effective larger attenuation due to the presence of clusters or nanoparticles that may diminish fluorescence emerging from the sample. This effect should be increased with depth, as suggested by the

**Table 1**
Dosimetry effect due to AgNP presence in Fricke gel dosimeters.

| AgNP concentration [ %w/w] | Norm. total dose [a.u.] |
|---|---|
| 0 | 1.000 ± 0.001 |
| 0.5 | 1.008 ± 0.005 |
| 1.0 | 1.019 ± 0.009 |
| 1.5 | 1.05 ± 0.01 |
| 2.0 | 1.09 ± 0.01 |
| 10.0 | 1.02 ± 0.01 |

results depicted in Fig. 4. In this framework, there should be more discrepancies between Monte Carlo modelling and experimental data for larger depths due to the larger attenuation paths, which increase the number of interaction processes, thus becoming more sensitive to the mentioned differences in the implemented model. Finally, dose enhancement effects due to AgNPs presence was calculated for different concentrations of silver in an aqueous solution system. Local dose enhancement increases with higher AgNPs concentration in the range of 0–2% w/w. However, for a concentration of 10% w/w the effect of the increase in the effective atomic number of the simulated AgNP-infused Fricke gel dosimeter material produces a decrease in the dose enhancement. These fact suggest that an optimal concentration of AgNPs could be defined in terms of the maximum enhance of absorbed dose.

## 5. Conclusions

To the authors' knowledge, this is the first study of Fricke gel dosimetry with silver nanoparticles. What is more, very scarce published material is available on the use of nanoparticles with gel dosimetry and most of them are on the use of polymer gels and gold nanoparticles. AgNPs and gel dosimetry were integrated by means of the AgNP-infused Fricke gel dosimeter, which maintained a reasonable useful response, comparable to that of standard gel dosimeters. Modifications proposed for adapting existing elaboration protocols for AgNP-infused Fricke gels proved to achieve good results in terms of feasibility and AgNPs characterization. Experimental X-ray fluorescence demonstrated to be a robust technique for the characterization of emerging photons making possible further correlations with AgNPs presence, concentration and location. Experimental results and Monte Carlo predictions exhibited very good agreements, as reported in Fig. 4, for the monitoring of emerging X-rays and its correlation with AgNP location. Additionally, dose enhancement was satisfactorily described by means of Monte Carlo simulations. These results might constitute a valuable contribution for current and further investigations and developments in the field.

## Acknowledgments

This study was partially financed by CONICET (Argentina) project ESPORA I - PIP 112–20130100658CO, SeCyT-UNC (Argentina) project DOSCOM I and 30720150101410CB, and DI-UFRO (Chile) projects DI-16-6008 and DI-17–1003.

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