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Silver nanoparticles in X-ray biomedical applications

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ABSTRACT

The fluorescence of silver nanoparticles or ions can be used for detection and dose enhancement purposes in X-ray irradiation applications. This study is focused on the full integration of the chemical synthesis of silver nanoparticles suitable for dosimetric and radiological purposes with characteristics that can be exploited in radiotherapy and radiodiagnostic. A narrow size distribution and a compatible stabilizing agent is often desired in order to obtain homogeneous behaviors in nanoparticle suspension. With the method proposed in this study, nanoparticles ranging from 5 to 20 nm were obtained. The fluorescence of aqueous suspensions of silver nanoparticles has been measured experimentally and simulated with the Monte Carlo PENELOPE code for different silver concentrations and geometrical configurations. Finally, the feasibility of using these nanoparticles for the elaboration of Fricke gel dosimeters has been tested obtaining a dose enhancement when compared with the same material irradiated below the silver K-edge.

1. Introduction

Particles in the size range 1–100 nm are commonly referred as nanoparticles (NPs) and have been gaining a great interest and application in many research areas, such as food industry (Pan and Zhong, 2016), material science (Linic et al., 2015; Wildgoose et al., 2006) and most of the current health applications (Barreto et al., 2011; Thakor et al., 2011; Weissleder et al., 2014; Yamada et al., 2015). These materials have unique characteristics (Mohanraj et al., 2006; Nie et al., 2010) and one of the great advantages of using NPs is the ability to vary these characteristics by modifying their size, size distribution, shape, and surface chemistry. Moreover, many physicochemical properties such as photochemical characteristics, magnetic properties or fluorescence can be changed by these variations and also by selecting a specific preparation method. Also, in most cases, it is possible to obtain materials which behave differently from their bulk version (Sau et al., 2010).

The first application of NPs in medicine and medical research took place in the early 1950s, which were based on liposomes and polymer systems for drug delivery, protecting the drugs and providing them with hydrophilic or hydrophobic functionality when needed (Petros and DeSimone, 2010). From that moment to the present great advances have been made in the use of NPs into medicine and at least 20 therapeutics with NPs have clinical use. In addition, numerous NPs platforms are currently under preclinical and clinical development including liposomes, polymeric micelles, dendrimers, quantum dots, gold and ceramic NPs (Schütz et al., 2013). One of the medical areas where NPs had a great impact is in treating complex diseases such as cancer. In most cases, a single approach or treatment is not sufficient and a combination of chemotherapy, radiotherapy, immunotherapy, gene therapy and thermotherapy is used to treat the disease. NPs are ideal platforms for a synergic combination of chemo and radiotherapy since they can act as contrast agents and drug carriers simultaneously (Puntes, 2016; Smith et al., 2012). Also, NPs of high Z number atoms like gold, gadolinium and iodine have been used for decades as radiological sensitizers and contrast agents (Rancoule et al., 2016). A key goal in radiotherapy is to increase the radiation dose deposited in the target tissue while minimizing the dose to surrounding healthy tissues. From a general point of view, absorbed dose is a consequence of primary beam, scattering particles and eventually –as happen in mixed field situations– secondary radiation produced by the primary beam. In this context, dose components associated with these secondary radiations may be considered as dosimetric reinforcement or dose enhancement. Actually, dose enhancement at interfaces between high

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and low atomic number materials has been largely studied (Botchway et al., 2015; Hainfeld et al., 2004). The presence of metallic NPs with high atomic number in biological tissues have proved a promising performance as radiosensitizers for both kilo-voltage and mega-voltage regimens (Guidelli and Baffa, 2014; Jones et al., 2010). In one of the first studies in the field Nath et al. (1990) incorporated iodine into cellular DNA with iododeoxyuridine in vitro, reporting an approximate radiation enhancement factor of 3 times, whereas Regulla et al. (1998) reported dose enhancement factors of about 50 times for fibroblast irradiated on a gold foil. Furthermore, it is possible to take advantage from the increased mass absorption coefficient of high atomic number NPs with the aim of enhancing radiation damage mainly due to secondary electrons and free radical species, which would yield appreciable factors for radiosensitization enhancement, even for modest or relatively low concentrations of NPs.

With a different approach, high atomic number materials like gadolinium and iodine have been used as contrast agents (Caschera et al., 2016; Taupin et al., 2015). There are several studies reporting that these agents are capable of in vitro and in vivo damage when are used combined with ionizing radiation (Coppola et al., 1984; McMahon et al., 2011; Sancey et al., 2014). Because of the high atomic number of metallic NPs, it appears obvious that they are candidates as potential contrast agents. These applications may become more relevant if targeting efficacy can be achieved, thereby limiting the cost implications while therapeutic outcome is improved due to a better target specificity. What is more, this capability has given place to new imaging techniques, such as X-ray fluorescence computed tomography (Kuang et al., 2013).

In this study silver NPs were synthesized to investigate the relationship between fluorescence signals with silver concentration and depth in a tissue equivalent phantom. To synthesize these particles two main approaches can be used, top down methods like milling or grinding and bottom-up approaches (Sau and Rogach, 2010) where the nanomaterials are synthesized from a solution by means of chemical reactions or precipitation techniques. The former approach usually renders poorly controlled properties with a behavior similar to the bulk material, while the latter approach could lead to completely new functionalities and physicochemical properties (Lee et al., 2016). Among the different synthesis methods available in literature a thermal reduction of silver nitrate within a gelatin matrix was used. The main idea of using gelatin as a stabilizing agent for the silver NPs suspension was to ensure a maximum compatibility with the matrix of most of the 3D dosimetric systems e.g. polymer or Fricke gel. The Fricke gel dosimeter is an acid solution doped with ferrous ions (Fe^{2+}) within a gelatin or agarose supporting matrix. The absorbed dose in this material can be correlated to the amount of ferrous ion oxidized by water radicals formed by radiolysis during an irradiation (Schreiner, 2004). The use of silver NPs in Fricke gel dosimeters has not been reported yet; however, there are some reports on gel dosimetry with NPs (Titus et al., 2016). Moreover, special precautions have to be taken into account when using silver ions as a dopant, since a redox reaction between silver and ferrous ions can take place.

The main goal of this study is the synthesis and use of silver NPs for dosimetry and radiological applications from a theoretical and experimental standpoint. For that purpose, the fluorescence signal of silver was used for the detection of volumes doped with silver NPs at different depths and Ag concentrations. Also, another specific objective was to develop a useful tool to simulate and predict the fluorescence of silver in tissue equivalent material. Finally, the feasibility of using these NPs in Fricke gel dosimeters for dose enhancement estimation was tested.

2. Materials and methods

2.1. Nanoparticle synthesis

Silver nitrate 99.9% acquired from Prodesa S.C.A. (Buenos Aires, Argentina) was thermally reduced against the amino groups present in porcine gelatin 300 Bloom purchased from Sigma Aldrich (Saint Louis, MO, USA) according to the reaction schemed in Fig. 1 in an aqueous media. In the presence of amino groups such as the ones in amino acids and proteins, silver ions form complexes ensuring their homogeneous distribution in the reaction media. Once temperature conditions provide the necessary energy, the reduction of silver ions takes place under isothermal conditions, where the growth of NPs is delayed by reducing the ion diffusion mainly given by the coordination between silver ions and the amino groups. For that purpose, gelatin and silver nitrate concentration and reaction time depicted in Table 1 were used at a temperature of 90 °C in closed vessels at a pressure of 0.6 atm.

2.2. Nanoparticle characterization

The size and morphology of the silver NPs were characterized by transmission electron microscopy (TEM) of the reaction products. After the reaction time was completed, a sample of each reaction product, a colloidal solution, was diluted 10 times with water, then 2 drops of the obtained solution were placed on a TEM grid and dried at room temperature. Afterwards, TEM micrographs of at least 10 different random regions of the grid were collected and analyzed using the procedure described elsewhere (Rice et al., 2013) with a Jeol - 1200 EXII TEM. Briefly, the procedure consists on using the open source software ImageJ, with a set of analysis routines (http://rsbweb.nih.gov/ij/download.html) following these steps: first setting the scale of the image to match the TEM micrograph scale. Secondly, cropping the image to remove additional information such as scale bars, correct contrast and brightness to ensure that all images have an centered histogram and wide enough to cover 80% of the possible grey levels. Then, performing a threshold operation and select the desired shape descriptors and finally analyzing the particles. In the present study. the Ferret's diameter and the diameter of a circle with equivalent area were used to represent the size distribution and morphology of the obtained NPs. Afterwards, the statistical analysis of the results was performed with the statistical toolbox in Matlab® version 7.11.0.584 (R2010b) 64 bit (MathWorks Inc, Natick, MA, USA).

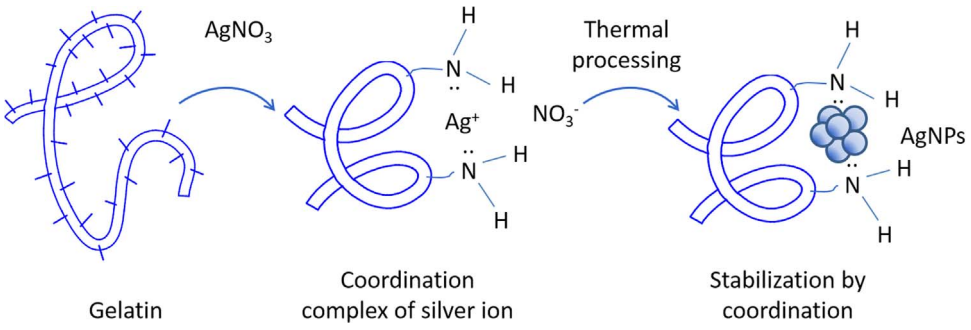

Fig. 1. Synthesis of silver NPs by a thermal reduction reaction of silver ions and gelatin.