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New gold-198 nanoparticle synthesis to be used in cancer treatment

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ABSTRACT

Gold nanoparticles (NPs) have been intriguing scientists for over 100 years. Recently, they have been studied for new applications such as cancer treatment. Although the synthesis of gold nanoparticles is extensively reported, in the majority of cases the methodology is confused and/or not clear. We describe a new synthesis methodology for radioactive gold-198 NPs. Gold-198 was activated in IPEN IEA-01 nuclear reactor. After that, chloroauric acid ($HAuCl_4$) was formed by dissolving the radioactive gold with aqua regia and performing repeated heating cycles. 0.1 mM $HAuCl_4$ containing 100 µL of 1 M NaOH was prepared in a flask equipped with a reflux condenser. The solution was brought to boil and stirred with a PTFE-coated magnetic stir-bar. Then 5 mL of sodium citrate was rapidly added. The reaction turns from light yellow to clear, black, dark purple until the solution attained a wine-red color (2–3 min). Dynamic light scattering (DLS) confirmed 8 nm particles. The presence of gold-198 (197.968 g/mol; half-life: 2.69517; decay mode: β-; average energy: 1.3723 MeV) was confirmed by an ORTEC HPGe detector. DLS was performed after complete decay confirming the 8 nm diameter maintenance. TEM analysis of the same solution yielded particles with 11 nm. We were able to achieve radioactive gold-198 NPs and are performing further studies such as: coating reactions, in-vitro and in-vivo studies.

Keywords: **Nanoparticles (J01.637.512.600), Brachytherapy (E02.815.150), Radiochemistry (H01.181.529.776).**

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1. INTRODUCTION

Nanoscience is the ramification of science that studies, produces and applies matter that are in the nanoscale dimensions. In nanomaterials, the energy levels of the electrons are not continuous as when compared to the bulk form. They are discrete due to the confinement of the electronic wave function in up to three physical dimensions. That results in a change in surface area and electron confinment, making the change in materials properties such as melting point, fluorescence, electrical conductivity, magnetic permeability, and chemical reactivity.[1-3]

Maybe the most important result of the nanoscale quantum effects is the concept of "tunability" of properties. It means that a researcher can change the proprieties behavior to serve a determined propose. For example, changes in fluorescence can be used to identify diseases. [1]

Adding to their importance, the size of nanomaterials is similar to most of molecules and structures in the human biological systems such as DNA (2nm). A majority of biological processes occur at the nanoscale giving scientists models and templates to imagine and construct new processes. This fact can enhance their work in medicine, imaging, computing, printing, chemical catalysis, materials synthesis, and many other fields. [1]

Gold nanoparticles are a special type among all the others. About 87,000 papers were published since 1996. The use of these particles dates back to the 9th century in Mesopotamia when artisans unknowingly used gold nanoparticle to generate a glittering effect on the surface of pots. [1]

Michael Faraday provided the first synthesis description, in scientific terms, of the optical properties of nanometer-scale metals in his 1857 paper describing the production of colloidal gold by the reduction of chloroauric acid by phosphorous. [4]

Gold nanoparticles (AuNPs) interaction with light is environment, size and physical dimensions dependent. Consistent with the Fermi liquid model, plasmons are explained as a negatively charged electron cloud coherently displaced from its equilibrium position around a lattice made of positively charged ions.[5] When a small spherical AuNP is exposed to light, the oscillating electric field causes the conduction electrons to oscillate coherently. Because of the displacement of the electron cloud, a restoring force arises from Coulomb attraction between electrons and nuclei resulting in oscillation of the electron cloud relative to the nuclear framework. [6] The reflection in NPs with

size much smaller than photon wavelength are non-propagating excitations, called localized surface plasmons (LSPs), due to the resulting plasmon oscillation being distributed over the entire particle volume. Such a coherent displacement of electrons from the positively charged lattice generates the restoring force that pulls the polarized electrons back to the lattice. When the wavelength is greater than the size of the NPs, a uniform and oscillating electric field is formed resulting in an in-phase electrons oscillation. Nevertheless, this collective oscillation is constrained by the reduced dimensions of the NP in which the electrons are confined, leading to a significant absorption of the wavelengths around green. That is why AuNPs appear with the complementary color, which is red. [2, 7-10] A few examples of gold nanoparticles being studied are:

- Therapeutic Agent Transport: The large ratio of surface area-volume of gold nanoparticles enables their surface to be coated with hundreds of molecules (including ligands, antibodies, and therapeutic, diagnostic and targeting agents). [11, 12]
- Photodynamic Therapy: Heat can be generated by gold nanoparticles when excited by light with 700 to 800 nm wavelengths. When positioned inside a tumor, the particles rapidly heat up, killing tumor cells. [13, 14]
- Sensors: Gold nanoparticles can be used in Raman spectroscopy as substrates to enable/improve measurements of vibrational energies of chemical bonds. This strategy can be used for proteins detection. [15]
- Probes: In dark-field microscopy, gold nanoparticles can produce an array of colors that can be used for biological imaging applications. [16]
- Diagnostics: Gold nanoparticles are also used to detect biomarkers in the diagnosis of heart diseases, cancers, and infectious agents. [17]
- Treatment: gold nanoparticle can be used to improve the radiation therapy dose delivery or can be used for treatment when activated to gold-198. [18]

1.1 Cancer

Cancer is a term used generically to represent a group of more than 100 illnesses, including malignant tumors from different locations. According to World Health Organization (WHO), it is a leading cause of death worldwide. Only in 2012, 14 million new cases of cancer were diagnosed

and a total of 8.2 million deaths were accounted, about 13% of worldwide deaths. Recent studies carried out by the International Agency for Research on Cancer (IARC) estimates that in 2030 will be 26.4 million new cases diagnosed, with 17 million deaths accounted worldwide [19, 20].

According with National Cancer Institute (INCA) in Brazil, 625,000 new cases of cancer will be diagnosed in 2020-2022. The most incidents, excluding non-melanoma skin cancer are prostate and lung cancer in males and breast and cervical cancer in females [21].

It is imperative that new and feasible forms of treatment be developed. Most people in countryside don't have access to linear accelerator radiation therapy and cancer surgery.

1.2 Nanobrachytherapy

The idea to combine nanotechnology and brachytherapy is extremilly new. It might be a good cancer treatment due to its effectiveness, portability, and simplicity. Brachytherapy is the type of radiation therapy that uses a radiation source in direct contact with the site of interest, might be interesting as a full or adjuvant treatment. In the new sub-cathegory called nano-brachytherpay, radioactive AuNPs can be injected directly onto the treatment site by a seringe. [22]

Gold-198 decays with a half- life of ca. 2.7 days to stable mercury-198 by emission of ß particles with 0.960 Mev maximum energy and γ rays of energies 0.412 (most abundant), 0.68 and 1.09 Mev. The energy is suited for internal irradiation of human organs [20, 21]. Non-radioactive gold can be easily activated by IPEN's IEA 01 research reactor (4.5 MeV).

Chanda et al. [17] published a gold-198 nanoparticle coated with arabic gum. The authors state that their new method is better than the classic ones that consisted in the reduction of Au^{3+} in $AuCl_4^-$ with $NaBH_4$ or citrate, compounds that the author claims are highly toxic. Instead of the traditional route, the researchers synthesized a novel reducing agent that was named THPAL-alanine trimeric with phosphines. $^{198}AuCl_4^-$ was activated in a nuclear reactor with a flow of $8x10^{13}$n /cm^2/s in acid solution of HCl. After activation, 50-100 μL of $H^{198}AuCl_4$ is added with 6 mL of arabic gum along with 20 μL / 0.0337 THPAL for each mL of solution. This reaction occurs in 5 minutes, although the synthesis of THPAL is complicated and expensive.

The analysis of the material, without the radioactive nucleus, was performed obtaining the following results:

- Mean diameter (without the gum arabic coating): 7 ± 3 nm;
- Average diameter (with gum arabic coating): 85 nm;
- Zeta potential: -24.5 ± 1.5 mV

Fortin et. al. [18] used a mixture of 1mL $^{103}PdCl_2$ (700 mCi) with 500 mL H_2PdCl_4. In another tube, 200mL of DMSA (2,3- dimercaptosuccinic acid) was mixed with 100mL of Ascorbic Acid (AA). When combining the two reactant containers, the solution changed color from yellow to brown (classic color change in nanoparticles) in 5 min.

After this process, 24 mL of ^{103}Pd: Pd NPs and 12.5 mL of nanopure water with 0.8 mL of $HAuCl_4$ (0.1 M) were mixed. Two successive additions of AA (0.1 M) mL and 0.4 mL were performed. After coating with gold, the underwent again through a coating reaction, but this time with polyethylene glycol (PEG) 1.875 mL with 10 mg / mL for 2 hours. The analysis of the material by DLS - Dynamic Light Scattering obtained was: 9.3 nm for PdNp and 20.2 nm for PEG-AuPdNP.

Understanding the gold chemistry is key for nanoparticle formation success. Common oxidation states of gold include Au^{+1} (Au[I] or aurous compounds), Au^{+3} (Au[III] or auric compounds), and its non-oxidized state Au^0 (Au [0]). The Au^0 is the final desirable state for nanoparticles. So, the major step involving the synthesis of AuNps is reducing Au^{+1} or Au^{+3} to Au^0 by adding and electron donor (reduction agent) in the reaction. The precursor of choice for the majority of researches is chloroauric acid, $HAuCl_4$ with gold in its Au^{+3} oxidation state. [2, 4]

Although the synthesis of gold nanoparticles is extensively reported, in the majority of cases the methodology is confuse and/or not clear. Besides that, the toxicity of the reactants must be taken into account when developing products for medical applications.

The classical synthesis method was presented by Turkevitch in 1951 [5] using sodium citrate (cited as Na_3citrate, Nacit or simply citrate) as a reducing agent. The publication resulted in several others with some differences to the basic method presented. Mainly, the variations involve $HAuCl_4$/Na_3citrate ratio, pH control and temperature influence in nanoparticle size and stabilization. Turkevitch method for sodium citrate are as follows: 95 mL of chloroauric acid solution (containing 5 mg Au) were heated to the boiling point and 5 mL of 1% sodium citrate solution was added to the boiling solution with good mechanical stirring. The reaction mixture was colorless for 12 s

after the addition of the citrate, and then it turned purpleish-blue within a fraction of a second. After 5 minutes the final color was deep wine red. The best results were obtained with 5-50 mg citrate addition.[5]

The current paper will present a new methodology for producing gold-198 nanoparticles for future evaluation as a nanobrachytherapy source. This methodology is described step-by-step with all the quantities of the materials properly described making it easy to be reproduced.

2. MATERIALS AND METHODS

All reactants were used without any further purification. All glassware and magnetic stir bars were first cleaned with aqua regia (HCl and HNO_3 in a 3:1 volumetric ratio) and thoroughly rinsed with nanopure water (Barnstead, 18.2 MΩ, Dubuque, USA) before use. The same nanopure water was used to prepare aqueous solutions. $HAuCl_4$ was only handled with plastic spatulas to avoid corrosion.

2.1 Nuclear Activation

Nuclear activation was performed in gold foils (Goodfellow AU004925. Disc thickness: 0,25 µm; specific density: 483 µg.cm^{-2}; purity: 99.99+ %) at IPEN's IEA-01 reactor. Final activity for 8 hours irradiation cycle was calculated by using equation 1 [23]. Confirmation of gold-198 was obtained by an ORTEC HPGe detector.

$$A = \frac{M \,.N \,.\theta \,.\sigma \,.\phi}{p} \left(1 - e^{-\lambda t}\right) \quad (1)$$

Table 1: Initials meaning for equation 1

Initial	Meaning	Unity
A	activity	becquerel
P	Atomic weight	g/mol
M	mass	g
N	Avogadro	6.02×1023
θ	Isotopic abundance	%
λ	decay	$time^{-1}$
ϕ	reactor flow	$n.cm^2/s^{-1}$
σ	cross section	cm^2 ****
t	Irradiation time	tempo

**** 1 barn = 10^{-24} cm^2

2.2 Synthesis

After the activation process, gold foils were transformed into $HAuCl_4$ by dissolution using aqua regia (HCl and HNO_3 – Sigma) following:

1. About 0.7 g of gold metal in disks are placed in a 250 ml beaker without being cut. Seventy ml of royal water (HCl and HNO_3 in a volume ratio of 3: 1) are added slowly;
2. The mixture is stirred and gradually heated to 50 °C. When gold dissolution is finished (about one minute), the temperature is gradually raised to 70-80 °C;
3. The solution is continuously heated until it is concentrated to 30 ml.
4. HCl is slowly added to the hot solution until the brown nitric vapors are completely elimi-nated. The final volume reached is about 40 ml;
5. The solution is kept warm until it is concentrated to 30 ml;
6. The procedure described in items 4 and 5 is repeated 3 times until no brown nitric vapor is formed. The presence of acid vapors is verified by a litmus paper (pH indicator);
7. The solution is concentrated (by heating) to 15 ml;
8. Chloroauric acid in liquid form is ready for use.

Fifty milliliters of freshly prepared 0.1 mM $HAuCl_4$ containing 100 μL of 1 M NaOH (Casa Americana, 99,99%) was prepared in a 100 mL three neck flask equipped with a reflux condenser (figure 1). The solution was brought to boil (80-90 °C) while being stirred with a PTFE-coated magnetic stir-bar. Then 5 mL of 34 mM Na_3Ctr was rapidly added. The reaction turns from light yellow to clear, black, dark purple until the solution attained a wine-red color (2-3 min). The reaction was allowed to proceed for 7 more minutes (completing 10 in total). The vial was removed from the heat plaque and allowed to cool down for 10 minutes still under reflux. After this period, the reflux system was shut down and dynamic light scattering (figure 2) analysis were performed.

Confirmation of gold-198 production was obtained by an ORTEC HPGe detector (GEM-65970-B). Dynamic light scattering (Anton Paar – Litesizer 500) analysis were performed after decay confirming size maintenance. Transmission electron microscopy (JEM-2100F) results were also performed.

3. RESULTS AND DISCUSSION

The final radioactive activity obtained was 1.7×10^{13} Bq (0.45 mCi) for a neutron flux of 8×10^{13} $n.cm^2/s^{-1}$. The radioactive foils were then transformed in $HAuCl_4$ by dissolution with aqua regia.

Aqua Regia dissolves gold, though neither HCl and HNO_3 have the power to dissolve it alone, because in combination, each acid performs a different task. Nitric acid is a powerful oxidizer, which dissolves virtually undetectable amount of gold, forming ions of gold (Au^{3+}). The hydrochloric acid provides chloride ions (Cl^-), which react with the ions gold to produce tetrachlorourate (III) anions, also in solution. The reaction with hydrochloric acid is an equilibrium reaction that favors the formation of chlorourate anions ($AuCl_4^-$). This results in the removal of gold ions from the solution allowing further oxidation of the remaining gold. The gold foil them became chloroauric acid.

Nanoparticle formation occurs due a multi-step coalescence process. The aggregation barrier (activation energy that two particles have to overcome to merge into one) increases to an optimum particle size allow colloidal stability to be reached. The steps are presented below [24]:

- Step 1: high reduction rate increases the number of particles. Clusters with 1–2 nm are formed;
- Step 2: reduction continues at a much lower rate. Since particles have weak stabilization ate this stage, coalescence processes take place (two or more droplets, bubbles or particles merge during contact to form a single daughter droplet, bubble or particle) resulting in a decrease in the number of particles. When the radius is around 2.5 nm, the number of particles is now constant, but they keep growing in size;
- Step 3: NPs grow due to the diffusion of the metal atoms reduced in solution;
- Step 4: When the particles reach a radius of around 4–5 nm, the growth rate increases drastically and the remaining of the metal salt consumed. Particle size increases to the final radius.

The reaction them was performed by using sodium citrate as an electron donor. Glassware scheme is shown in figure 1. The exit of the reflux condenser was connected to a trap system to prevent possible leakage of the radioactive material. Heat is necessary due to at low temperatures nucleation is not fast enough resulting in broad size distribution. As expected, the reaction color turned to light yellow, black-purple wine-red confirming all the consumption of gold salts. Gold-198 presence was confirmed by HPGe detector (figure 2).

Figure 1: *Glassware scheme.*

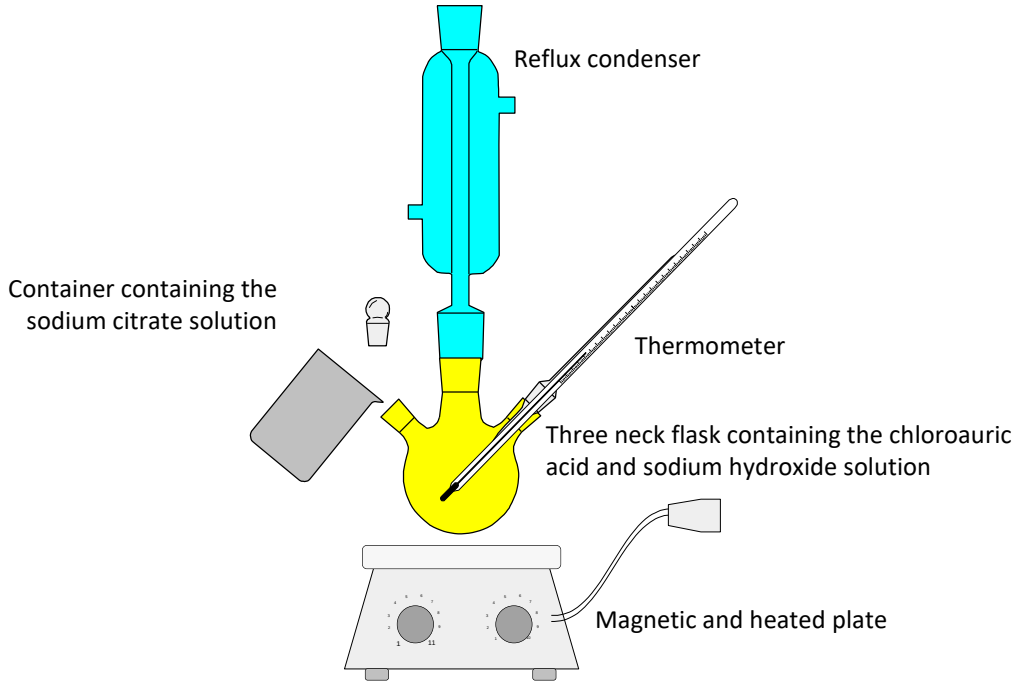
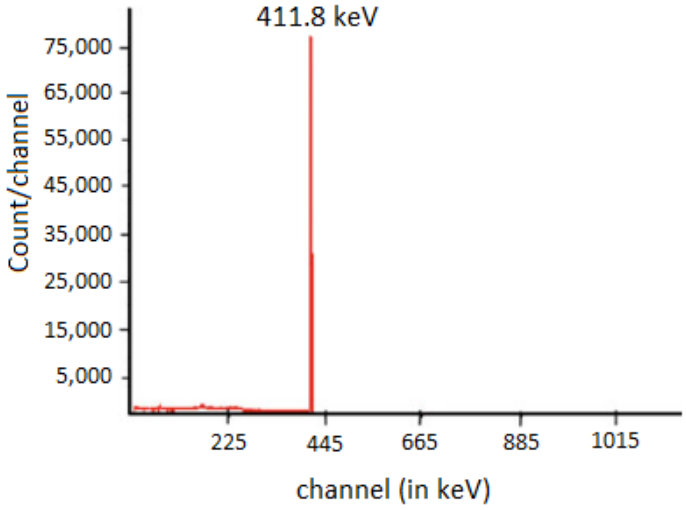


Figure 2: *HPGe detector confirming gold-198 presence.*



The reactants proportions deserve especial attention. The suitable amount of gold precursor and reducing agent must be placed in the reaction, otherwise excess gold might not reduce fast enough and/or citrate salt might not be enough to reduce all gold atoms. That is one of the reasons that reproducing literature methods might be difficult. Besides quantities, reaction, set up, temperature,

form of agitation, reactant and solvents purity, glassware cleaning procedures, might also influence results.

The best method of analyzing the reaction success is by measuring size. Mostly, DLS and TEM (Transmission electron microscopy) are used (other methods such as UV-vis and AFM are also used). It is always necessary to use two or more different methods for size measurement. Both methods, DLS and TEM use measure different parameters. DLS measure the hydrodynamic radius of the whole sample (it's the measurement of the core considering the electric dipole layer formed by any coating material or solvent layer moving under the influence of Brownian movement) when TEM is as estimation of the projected area diameter of the part of the sample being analyzed. While DLS depends of the correlation function (the calculation that is used to convert the Brownian movement in a size distribution) and the particle movement to estimate size, TEM allows larger or smaller particles to be visually accessed identifying shape and possible agglomeration. When the measurements of both are different, it means that particles are attached to the surface of the NPs altering the range of motion (detected by DLS) [6, 10, 25]. The difference among the DLS and TEM sizes can achieve differences up to 21 nm [25]. When there are a few nanometers apart, it means that the surface is free or have very small molecules in the surface [11, 14, 21]. Particle stability and shelf life can be easily accessed by repeating measurements from time to time.

To access the success of the present reaction, DLS analysis was then performed before and after decay (3 months after). Size was maintained (figure 3 and 4) and no agglomeration or smaller peaks were found.

Figure 3: *DLS Results. Average size: 8.721 nm. Mode size : 8 nm*
FWHM = 2.1 nm; Standard deviation = 2.034

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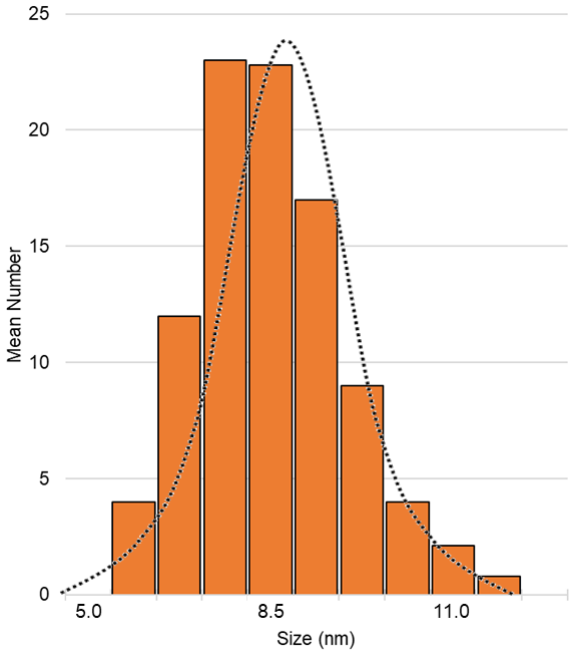

Figure 4: *DLS Results after decay. Average size: 8.95 nm. Mode size: 8.0 nm FWHM = 2.48 nm; Standard deviation = 2.051*

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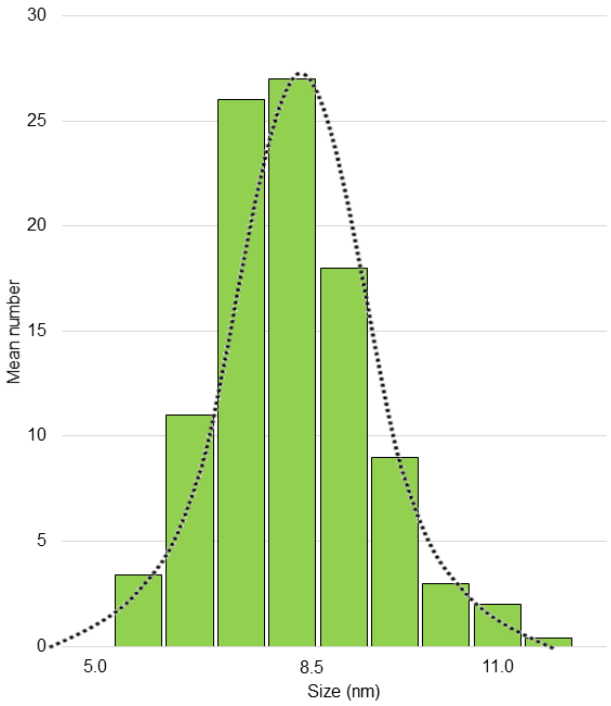


TEM was performed after radioactive decay (figure 5). Size was calculated by the ImageJ software. Two fields from each quadrant were selected and the number of nanoparticles were stipulated by the program and a graph was plotted. Figure 6 presents the mean plot of these results. Although there is a mean size difference when compared to DLS is within acceptable margins.

Figure 5: *TEM images. Results show a good distribution and size (11 nm average).*

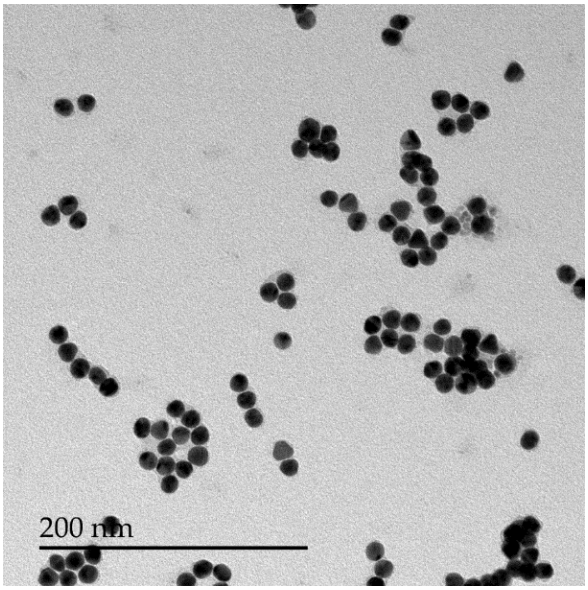
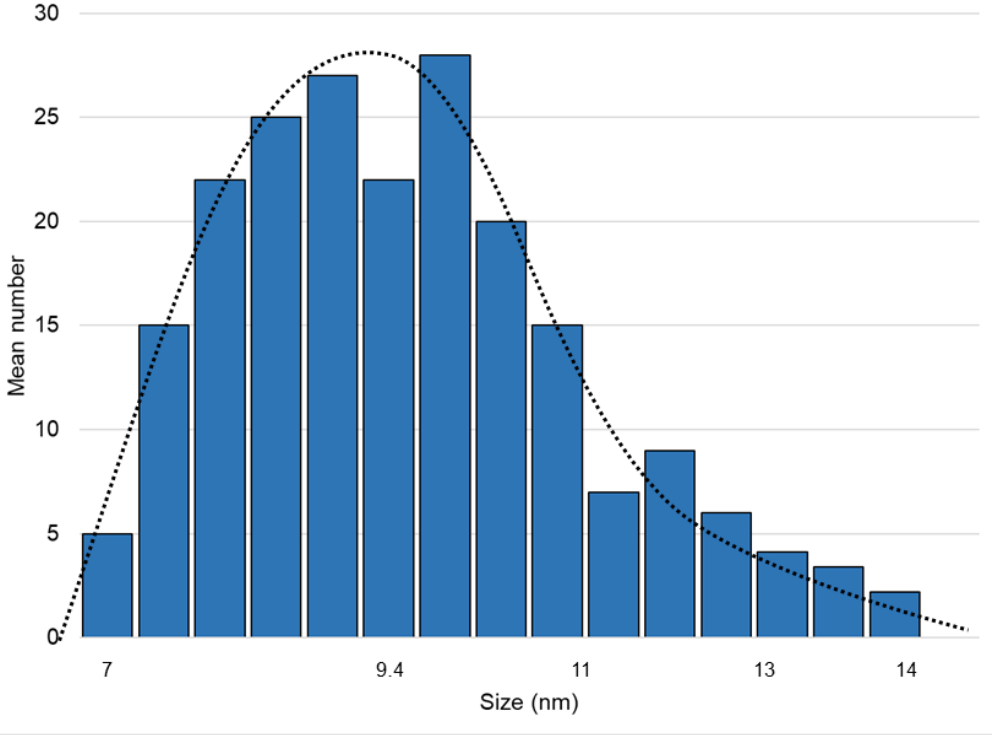


Figure 6: *Number x Size Histogram of TEM results of decayed gold nanoparticles. Average size: 11 nm. Mode size: 9.4 nmFWHM = 3.01 nm; Standard deviation = 2.256*



4. CONCLUSION

This paper presented a synthesis and evalutaion of radioactive gold-198 nanoparticles. Nuclear activation in IPEN IEA-R1 reactor, prepartion of $HAuCl_4$, and synthesis by using sodium citrate as a reducing agent were presented.

Evaluation were performed. Gold-198 presence was confirmed by a HPGe detector. The size of nanoparticles for the radioactive and decaied particles were measured by DLS and yielded, repectvelly, 8.721 nm and 8.95 nm. The results confirm size maintenance after the decay. TEM image of the decaied particles showed a good size distribuition and average size of 11 nm.

The next step of the project is: stabilization evaluation in biological fluids; coating assessments; DLS, TEM and Zeta Potential of all variants; in-vivo; and in-vitro studies to evaluate its use for cancer treatment.

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