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1. **Draft manuskrip sebelum proses submission**

# Cover Letter

Ali Khumaeni
Faculty of Science and Mathematics, Diponegoro University, Indonesia
Jl. Prof. H. Soedarto, S.H. – Tembalang Semarang, Indonesia 50275.

August 31, 2020
Dear Prof. Mohammad Taghi Bahreyni Toossi
Mashhad University of Medical Sciences

I wish to submit an original research article entitled "Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography" for consideration by Iranian Journal of Medical Physics.

I confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

We believe that this manuscript is appropriate for publication by Iranian Journal of Medical Physics, because it consider reviews about professional preparation (the university's counselors) and organizational and professional issues that occur in a higher education.

We have no conflicts of interest to disclose.
Please address all correspondence concerning this manuscript to me at khumaeni@fisika.fsm.undip.ac.id.
Thank you for your consideration of this manuscript.

Sincerely,
Ali Khumaeni

# Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography

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# Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography

**Abstract**

**Introduction** : Syntheses of colloidal silver nanoparticles (Ag NPs), platinum nanoparticles (Pt NPs), and silver-platinum nanoparticles (Ag-Pt NPs) have been successfully performed using pulsed laser ablation method in deionized water media.

**Materials and Methods** :Experimentally, an Nd:YAG laser (1064 nm, 45 mJ, 10 Hz) was focused on a metal plate including Ag and Pt, placed in deionized water medium. Colloidal Ag nanoparticles has been succesfully produced with a dark brownish-yellow color and the averaged diameter of 24 nm. For colloidal Pt, the nanoparticles have transparent color with aan averaged diameter of 20 nm. Both colloidal nanoparticles of Ag and Pt were then mixed to obtain a mixture composition of Ag and Pt with ratios of Ag:Pt of 75:25%, 50:50%, 25:75%, respectively, with a concentration of 10 ppm. The Ag-Pt mixture were then examined as an contrast agent in computed tomography (CT) scan.

**Results**: The imaging results of these agents were measured in *Hounsfield Unit* (HU), showing 13.5, 17.3, 12.8, 13.3, and 14.1 HUs respectively for the above order.

**Conclusion:** These findings confirmed that the greater amount of Platinum in the colloidal solution would result in the greater value of image, as magnitude of atomic number correlates positively to attenuation value of a particle.

**Keywords:** Pulsed laser ablation, colloidal silver nanoparticles, colloidal platinum nanoparticles, colloidal silver-platinum nanoparticles, contrast agent for CT Scan**.**

## INTRODUCTION

X-ray based imaging technique has been widely used in medicine (cormodeet. al.,2014), Computed Tomography (CT) has been superior in terms of imaging and cost efficiencies and yet non-optimal in soft tissues detection. In this regard, attempts to enhace CT diagnostic qualities has used clinically standard contrast agents, such as the small molecular iodinated agent and barium suspension. These have only led to other essential problems in the medical imagings, including high osmolality, contrast agent's low longevity, kidneys toxicity, and poor contrasts in patients with large body volumes (Hainfeld et al. 2006). Over the last seven years the development of nanoparticles as CT'scontrast agents has increased. Nanoparticles have several advantages compared to the micro-sized, molecular contrast agents, such as lower osmolality, longer longevity, potentials for cell tracking and targeted imaging applications (Cormode et al., 2014).

The syntheses of metal nanoparticlesare generally achieved either chemically or physically. A typical, chemical process begins with thermal decomposition of precursors into atoms, followed by aggregation into nanoparticles (Yonezawa et al., 1998). During this process, additives like surfactants or molecular ligans are commonly used to avoid aggregation and to control the nanoparticles shapes (Corma et al., 2008). However, these treatments result in unrefined products that require multiple purifications before they can be applied in subsequent nanoparticle processes. This has been deemed to be the adverse effect of chemically synthesized nanoparticles (Warner et al., 2000), and persisted including in the stabilizations using dendrimer (Liu et al. 2010) and Polyol (Chou et al., 2010).

On the other hand, physical syntheses rely on grouping precursors to be made into nanoparticles and involves condensation of vapors, which result from the corresponding physical interactions. Laser becomes one of the most representative physical approaches for synthesis of nanoparticles. An example of laser applications is pulsed laser ablation (PLA) in gas or liquid vacuum. Invented by Maiman (1960), the technique has become a focal point of more intensive researches. With results differ from the most chemical synthesis methods, PLA offers manufacture of high purity nanoparticles, simpler methods, and mass productions (Elder et al., 2007). Simply by permuting the combinations of target solid and choice fluid (Zeng et al., 2012), one can produce a variety of colloidal nanoparticles including metals, alloys, oxides, and semiconductors for many applications including medical applications (Amendola et al., 2013).

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In body tissue imaging, one factor responsible for a substance's contrast property is the atomic number, which is described physically by the number of interacting photons. The larger the atomic number means the more photons interact with the atom. In addition, thickness and density also play an important roles in contrast differences (Shilo et al., 2012). Attenuation coefficient increases accordingly to augmentation of atomic number and density (Hainfeld et al., 2006). It greatly affects X-rays attenuation value measured in Hounsfield units (HU).

Silver (Ag; Z = 47), an elastic, easily forged metal, posseses ions which remain neutral under water, acid, and salt environments. Ag shows stability under heat and light (Dwandaru et al., 2016), and the nanoparticle form has a unique, optical scattering property of plasmon-resonances which allows applications in bio-sensing and imaging (Schrand et al., 2008). The nano-size bestows it properties to penetrate several biological cell membranes like in bacteria, enhancing the contact surfaces and allowing direct penetration (Navarro et al., 2008). In this experiment, contrast properties of Silver's Dendrimer Stabilized NPs (DSNPs) in CT Scan were tested. Although Ag's atomic number is relatively low, its DSNPs mode is able to approach the contrast intensity of conventional agents (Liu et al., 2010). It is accessible to be produced within reasonable price range as compared to other metals.

Another metal, which is possible to be used as an contrast agent is platinum (Pt; Z = 78), which is often found naturally in alluvium sands throughout various rivers. Owing to its high durability against corrosion, which renders it less toxic than some other metals (WHO, 2000), platinum has been adopted in catalytic modifiers, laboratory equipment, electrical contacts and electrode, resistance thermometers, dentistry equipment, and jewellery. In medicine, the nanoform has shown promises such as in the combination of sinotherapy and radiotherapy, acting simultaneously both as a contrast agent and a drug carrier (Ferretti et al., 2017). A Pt NPs-based contrast agent synthesized in the form of Fe-Pt NPs using Polyol method has also been used in CT Scan. Intravenal injection of the nanoparticles in an animal's tail increased active cells contrast from cancer lesions in scanning for tumor carrier (Chou et al., 2010).

To develop medicinal potentials of Ag NPs and Pt NPs as contrast agents, this research attempts to formulate a combo-solution of the two where it best suits CT Scan demands. The use of PLA method is expected to improve the quality of Ag-Pt NPs as contrast agent, in the hope to find a reliable alternative in CT Scan modalities. Characteristics of Ag-Pt NPs produced in the research was examined using Ultraviolet-Visible Spectroscopy (UV-Vis), Scanning Electron Microscopy (SEM), and X-ray diffraction (XRD). Thr produced Ag and Pt NPs were then applied as an contrast agent via in vitro.

### MATERIALS AND METHODS

Pulsed laser ablation was employed to form silver-platinum nanoparticles (Ag-Pt NPs). The decontamination of 99.95%-pure Ag plate with alcohol was followed with incorporation into a petri dish of 25 mL deionized water. To produce a colloidal nanoparticle with a minimum concentration of 20 ppm, the Ag metal plate was bombarded by an Nd: YAG laser beam at 1064 nm with 45 mJ at a frequency of 10 Hz. During the process, the petri dish was rotated slowly and continuously to obtain a homogeneous nanoparticle fluid. Figure 1 shows the setup of an ablation experiment using anNd: YAG laser at 1064 nm.

**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

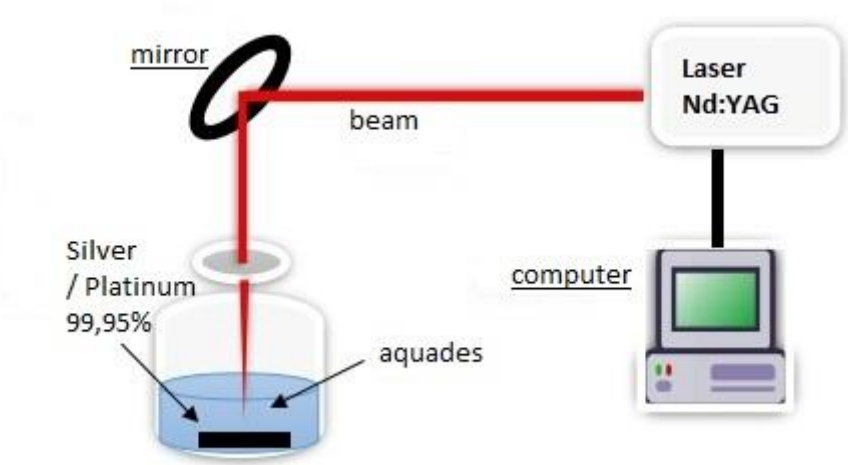


**Fig. 1.** Setup for an Nd: YAG 1064 nm laser ablation experiment

After treatment of the Ag plate, the laser bombardment was made on the Pt plate using the same method. The Ag and Pt NPs produced from PLA method were then mixed and stirred into uniformity with variations of compositions: 25:75%, 75:25% and 50:50% of Ag-Pt NPs. An additional radiation of Nd: YAG 1064 nm laser was applied to the Ag-Pt NPs mixtures with parameters equal to those of previous synthezing processes.

Sequential tests were performed to the synthesized colloidal Ag, Pt, and Ag-Pt NPs. Using UV-Vis Spectroscopy, the plasma surface resonances was determined, while the NPs' morphology and average sizewas derived from SEM examination. These were followed with *X-ray Diffraction* (XRD) to extract information on the structure type, grid parameters, and different atomic arrangement of the NPs crystals. Analysis on the diameter of the NPs sizes was performed using *ImageJ* software.

The CT Scan contrast tests began with preparing various mixtures of the NPs into the 10-ml tubes at equal concentrations each and placed them on the holder. The CT Scan was set at 80 kV and 100 mAs. In addition, *CT Reader* software was employed to process the resulting images. Comparative analyses were performed on the HU values of the variations.

## RESULTS

The colloidal synthesis of Ag and Pt nanoparticles using PLA has been performed successfully by focusing the Nd: YAG Laser at 45 mJ and 10 Hz frequency onto 99, 95% pure Ag and Pt targets immersed in deionized water medium placed in the petri dishes. The interaction between the laser and the target were followed with plasma formations resulting in the targets atomic breakdowns. Simultaneous blasts occurred, followed by shock wave expansions to the surrounding area. With the surrounding temperatures much lower than those of the plasmas, the cooling-downs may result in losses of explosive effects, leaving a mixture of fluid and nanoparticle-sized material referred to as colloidal nanoparticles (Dell'aglio et al., 2015). The target in the petri dish was moved slowly to avoid a spot being bombarded sequentially, as this affects the quality of nanoparticle formation. The result shown in Fig. 2(a) is the dark, brownish-yellow Ag NPs colloid after 13 hours of pulsed-laser bombardment. By contrast, Fig. 2(b) shows a clear, brown Pt NPs colloid after 10 hours of PLA bombardment to the platinum sample. The shades also indicates different levels of NPs concentrations: 30 ppm versus 20 ppm, respectively for Ag NPs and Pt NPs colloids. The colloidal concentrations were diluted using deionized water to achieve equalization before CT Scan tests could be performed.

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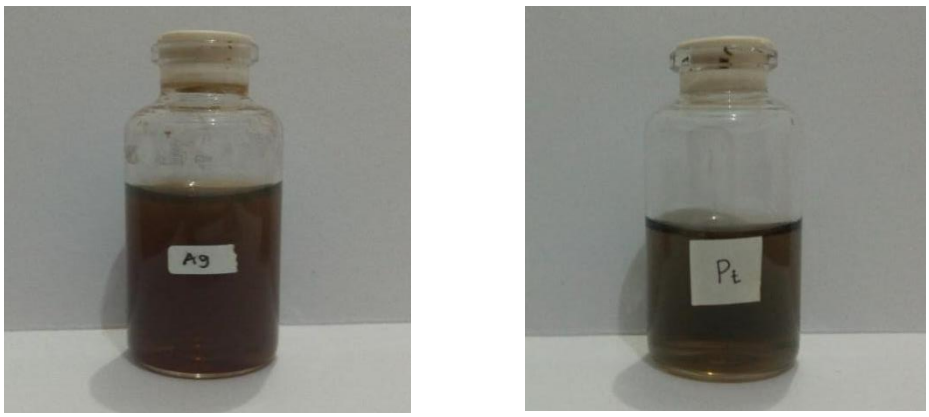


**A** **B**

**Fig. 2.** (a) AgNPs and (b) PtNPs colloids

Further verifications of these visual observations involved characterization testings using *Ultraviolet-Visible spectroscopy* (UV-Vis), *Scanning Electron Microscope* (SEM), and *X-ray diffraction* (XRD).

**UV-Vis Examination**

UV-Vis examines the object quality in terms of absorbance of UV and visible lights wavelengths, in which acquired parameters indicatethe object particles'types and numbers (Dwandaru, 2016). The characterization of Ag and Pt NPs by UV – Vis spectrum test results as follows.

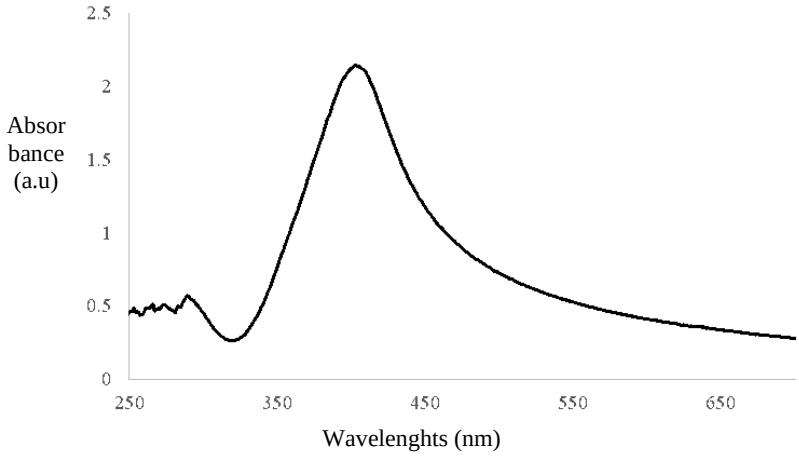


**Fig. 3.** UV– Vis Spectrum of colloidal Ag NPs

Fig.3 shows the highest absorbance value of the bombarded sample by 2.146 a.u at a wavelength of 403 nm. The value specifically confirms the sample as silver, since the spectral image matched the obtained data of previous research (Panacek, 2009).

**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

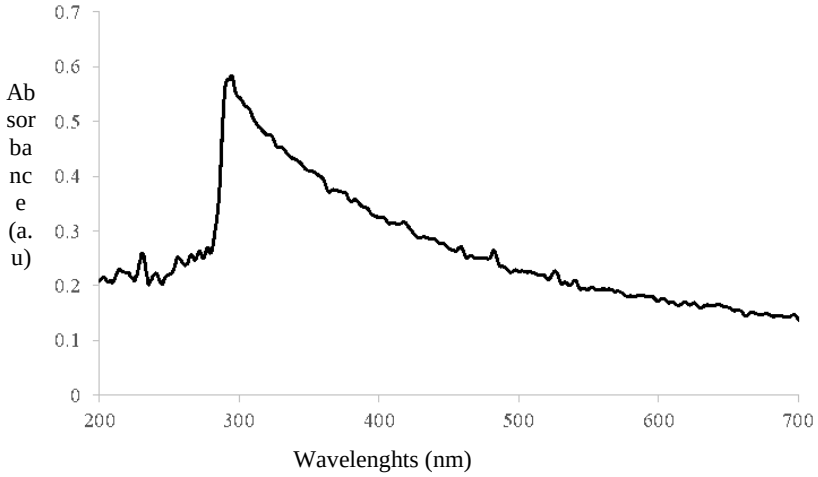


**Fig. 4.** UV– Vis Spectrum of Colloidal Pt NPs

Fig. 4. specifically confirms the sample as platinum sample, since the spectral image matched the obtained data of previous study (Nellore, 2013).

After achieving colloidal mixture of Ag-Pt NPs from the seperated results of the colloidal syntheses of Ag and Pt NPs, UV-Vis test was performed for the colloidal mixture. Figure 5 shows the result of UV-Vis examination of the mixture, revealing multiple peaks of Ag and PtNPs wavelengths.

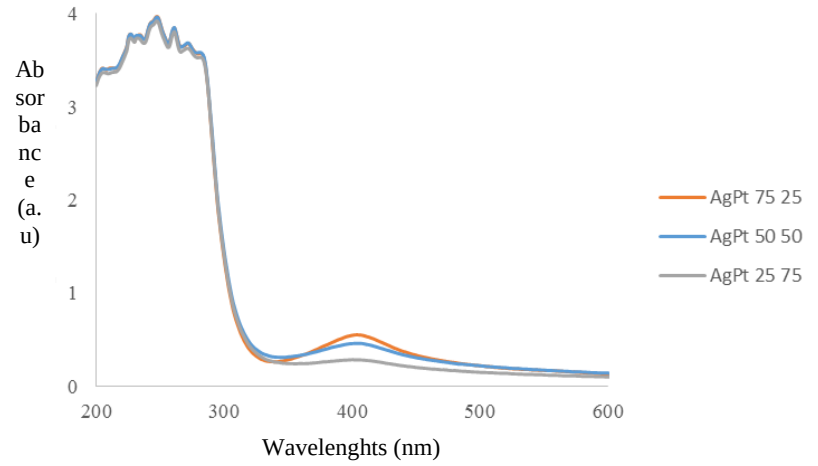


**Fig . 5.**UV– Vis Spectrum of the Ag-Pt NPs colloidal mixture with variations of compositions

The degree of absorbance indicates the compositions of Ag and Pt. In this case, greater absorbance signifies greater percentage of the AgNPs in the mixture. Magnification of the Fig. 5 spectrum image (shown in Fig.6) clarifies different peaks resulting from variations of the NPs blends. The highest Ag NPs level in the mixture (75%Ag-25%Pt) is depicted by absorbancelevel of 0.55 a.u at a wavelength of 403 nm. On the other hand, the balanced compositions of Ag-PtNPs in the mixture (50%Ag-50%Pt) results in an absorbance level of 0.458 a.u at a wavelength of 402 nm while the lowest Ag NPs percentage (25%Ag-75%Pt) shows the absorbance level of 0.282 a.u at a wavelength of 401 nm.

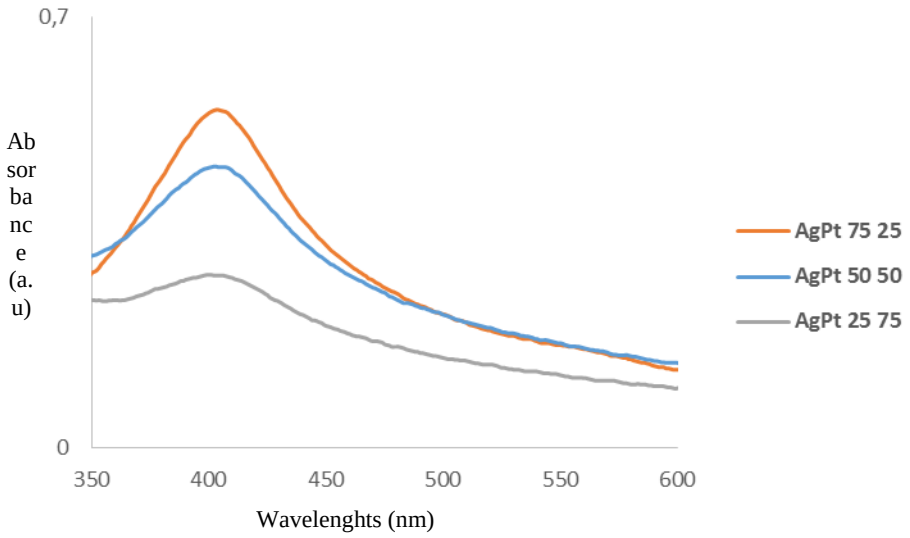


**Fig.6.**Magnification of UV– Vis Spectrum of the Ag-Pt NPs colloidal mixture with variations of compositions

**XRD Examination**

The most frequently used among recent methods for material characterization, X ray diffraction spectroscopy (XRD) identifies material crystalline phase by parameters specification of the lattice structure and obtains the particle sizes of nanocrystals. It is very handy for studying the crystal structure, chemical composition, and physical properties of nanomaterials (Sharma et al., 2012). The spectrum patterns of Ag NPs, Pt NPs, and Ag-Pt NPs produced from XRD analysis of the sample colloids have matched with the data from previous study (Umar, 2014). The XRD spectographs below reveals elemental and compound existences of the NPs in the colloids. For the Ag sample, the diffraction peaks showed at 38.0328 (111), 44.2745 (200), and 64.6473 (220) as shown in Fig. 7.

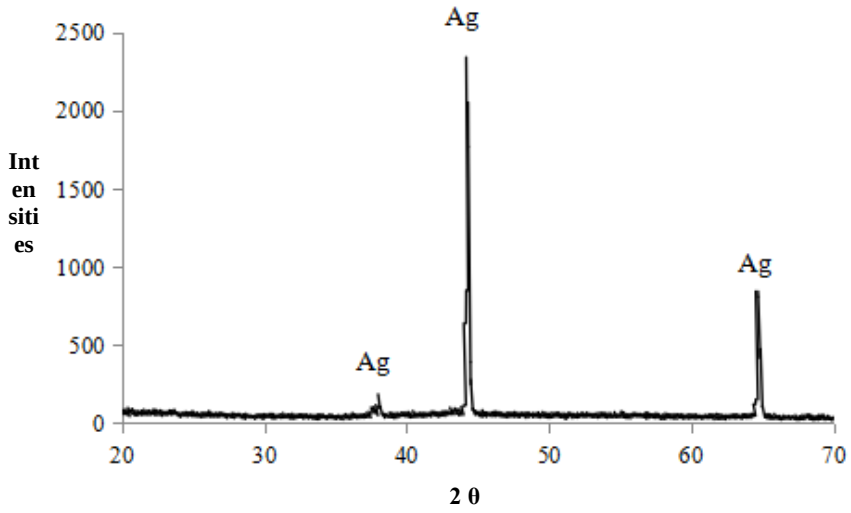


**Fig . 7.**XRD Spectrum of Ag Sample

The Pt NPs sample shows the diffraction peaks at 33.01 (111) and 66.4 (220) as shown in Fig. 8.

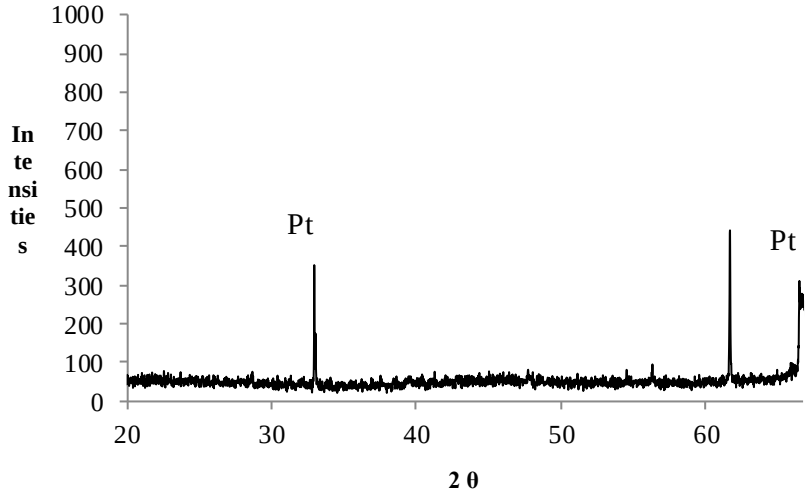


**Fig. 8.** XRD Spectrum of Pt Sample

Meanwhile, Ag-Pt NPs sample shows the diffraction peaks at 32.9 (111), 47.6 (200), 67.3 (220) as shown in Fig. 9.

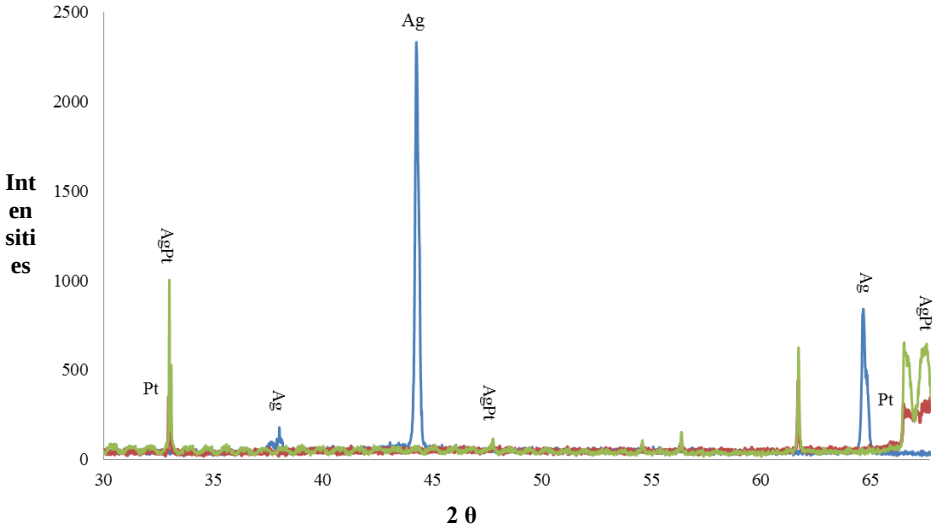


**Fig. 9.** XRD Spectrum of Silver – Platinum Sample

**SEM Examination**

Scanning Electron Microscope (SEM) observedthe morphology and determined the size of the NPs. SEM is an efficient method for specimens surfaceimaging. In this study SEM processing was used with 2000 times magnification. In case of platinum sample, preparation was performed using colloidal Pt NPs derived from PLA bombardment at 10 Hz and 45 mJ. A total of 1 ml PtNPs colloid was dripped on ± 0.5 x 0.5cm$^2$ plate of *silica carbide* (SIC), followed by drying with Oven Toaster at 100°C for 30 minutes. SEM-EDX result of the colloidal PtNPs is shown in Fig. 10.

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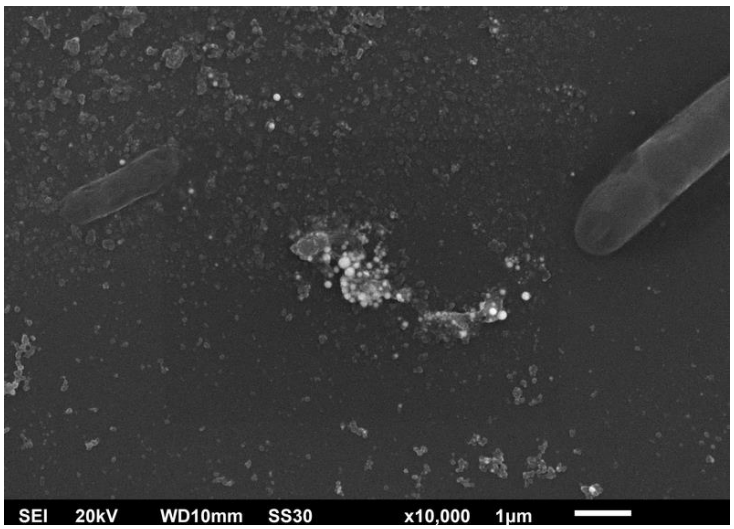


**Fig. 10.** SEM-EDX Spectrum result for colloidal PtNPs

Fig. 10 shows the average colloidal size of Pt NPs 20 nm with a standard deviation of 7 nm, morphologically in the form of brownish spheres. Meanwhile, the following is the SEM-EDX result for the Ag NPs colloid.

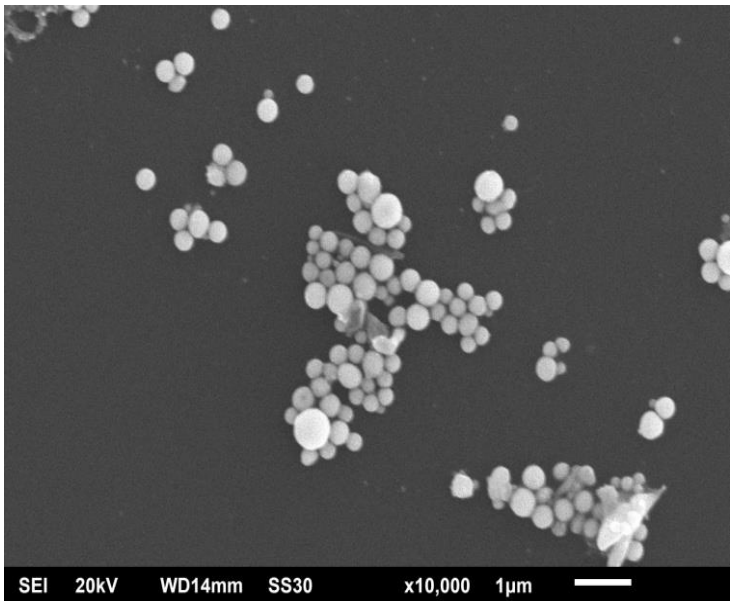


**Fig.11.**SEM-EDX spectrum result for colloidal AgNPs

Fig.11 shows the mean size of the Colloidal Ag NPS by 24 nm with a standard deviation of 5 nm, morphologically in the form of brownish spheres. After achieving colloids of AgNPs and PtNPs, both were blended and synthesized using the PLA method at 10 Hz and 45 mJ. Five variations of colloidal NPs were produced in the experiment: 100%-Pure AgNPs, 100%-Pure PtNPs, 75%:25% Ag-Pt NPs, 25%:75% Ag-Pt NPs, and 50%:50% Ag-Pt NPs colloids, each with a concentration of 10 ppm. All of the colloids achieved were inserted into 10ml-sized cylindrical vials.

**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

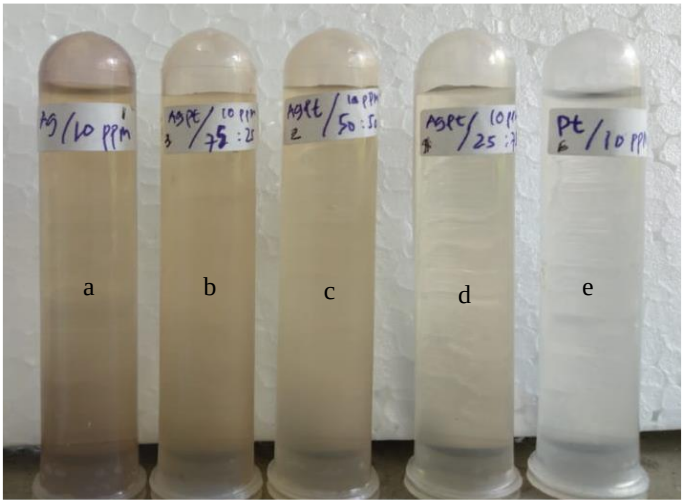


**Fig.12.**Sample Preparationsof (a) 100% AgNPs colloid (b) 75%:25% Ag-PtNPs colloid (c) 25%:75% Ag-PtNPs colloid (d) 50%:50% Ag-PtNPs colloid and (e) 100% PtNPs colloid in 10ml-sized cylindrical vials

## DISCUSSION

Different shades of the colloids in the tubes imply different NPs compositions. In the left end in Fig.12, the 100%-pure AgNPs colloid has the darkest, brownish-yellow shade, and in the other end, the 100%-pure PtNPs colloid has the most contrastive, transparent, bright shade. The shades were gradually fading and becoming brighter and transparent with the lowering of AgNPs concentration and the raising of PtNPs concentration in the colloid compositions. Hence, the darker the shade means the more AgNPs and the less PtNPs in the composition and, vice versa, the brighter the shade means the lessAgNPs and the more PtNPs in it. In this phase colloidal syntheses of AgNPs, PtNPs, and Ag-Pt NPs have been successfully performed and the samples were readily prepared as contrast agentsin CT Scan testings.

The samples were then aligned and scanned by CT-scan simultaneously using a voltage of 80 kV and a current of 100 mAs. The image results depicted in Fig.13 indicate the colloidal NPs' contrast property qualities in HU measurement, represented in the greyish shades. Darker greyish shades represent lower HU values, and vice-versa. The shades are associated with the number of X-ray photons passing through the body tissues which determine the variations of the dark and bright areas in the CT images. The dark areas are called the low-attenuated areas, while the bright areas the high attenuated (Shilo et al., 2012).

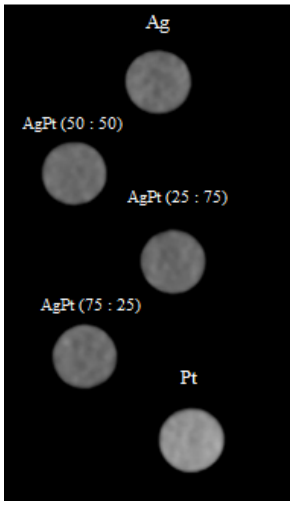

**Fig. 13.** Image results of AgNPs, PtNPs and Ag-PtNPs with variations of compositions as CT Scan contrast agents

The CT Scan contrast properties of 100%-pure AgNPs colloid, 100%-pure PtNPs colloid, 75%:25% Ag-PtNPs colloid, 50%:50% Ag-PtNPs colloid, and 25%:75% Ag-PtNPs colloid were measured by 13.5 HU, 17.3 HU, 12.8 HU, 13.3 HU, and 14.1 HU, respectively. The presentation chartis shown in Fig.14.


**Fig. 14.** CT Scan tests on contrast properties of Ag, Pt, and Ag-Pt NPs with variations of compositions

It is shown in Fig. 14 that colloidal contrast agent Pt NPs has a higher absorption power compared to that of AgNPs, and thereby affecting the absorptions of any predetermined composition of colloidal Ag-Pt NPs, with the highest in 25:75% Ag-Pt NPs composition and continue to decrease in the direction of vice-versa composition (75:25% Ag-Pt NPs). This phenomena refers to the concept of mass attenuation coefficient (Shilo et al., 2012),which states high atomic numbers as the one factor responsible for determining better contrasts on scanned tissues. This is explained in physics from the number of photons interacting with a structure, which are influenced by its thickness, density, and atomic numbers. The coefficient of attenuation will increase if the atomic number and density are increased (Hainfeld et al., 2006). The coefficient of attenuation greatly affects the attenuation value of X-rays measured in the units of Hounsfield units (HU). With the NIST data of mass attenuation coefficients indicating by 2.6 for silver (Z = 47) and 8.7 for platinum (Z = 78), the results of HU values for the colloidal NPs in this study have been appropriate.

## CONCLUSION

The syntheses of Silver, Platinum, and Silver – Platinum NanoParticles using Pulsed Laser Ablation have been successfully carried out and produced spherical, colloidal nanoparticles (NPs). Comparative analysis among the NPs colloids' shades confirmed the higher AgNPs concentrations to be responsible for darker tones in the colloids, while the higher PtNPs for the brighter. The characteristics of Ag NPs, Pt NPs, and Ag-Pt NPs have been successfully demonstrated by UV Vis test which shows wavelengths of 403 nm and 294 nm respectively for Ag and Pt NPs. In addition, double waves appeared in the imaging graph of colloidal nanoparticle Ag-Pt NPs with wavelength values equal to those of individual UV-Vis testings of Ag and Pt NPs. The XRD analysis on the synthesized colloidal NPs characteristics confirms the essential NPs compositions in the colloids.In addition, SEM examinations complete the information on the morphology and dimensions of the

formed Ag and Pt NPs (each spherical with average size of 24 nm and 20 nm). Contrast testings for the Ag, Pt, and variations of Ag-Pt NPs compositions have been performed *in vitro*in a CT – Scan machine, involving five colloidal variations at a concentration of 10 ppm each: 100%-pure AgNPs, 100%-pure PtNPs, 50:50% Ag-PtNPs, 75:25%Ag-PtNPs, and 25:75% Ag-Pt NPs.Results reveal the highest absorbent power was found in the colloidal contrast agent of Pt NPs, followed by the 25:75%Ag-Pt NPs.

## ACKNOWLEDGMENTS

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**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

**ALL TABLES, FIGURES, & CHARTS**

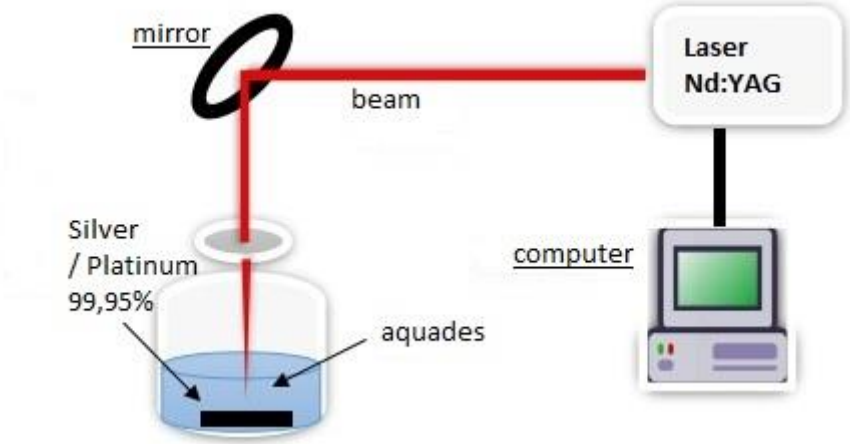
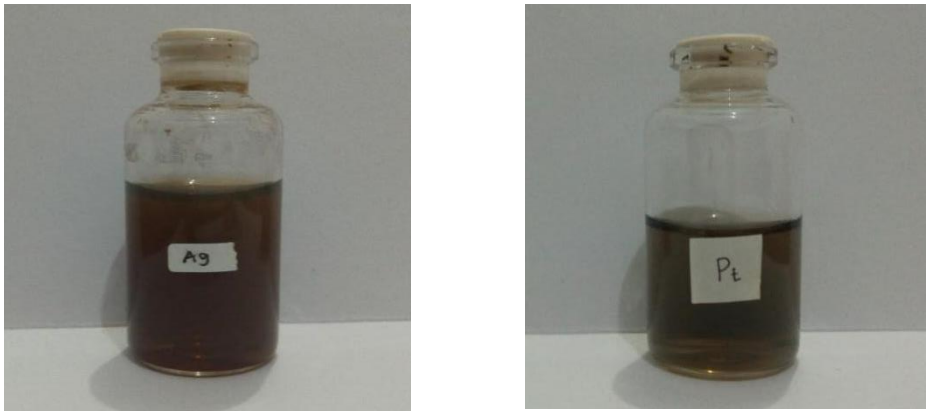



**Fig. 1.** Setup for an Nd: YAG 1064 nm laser ablation experiment




**A** **B**

**Fig. 2.** (a) AgNPs and (b) PtNPs colloids

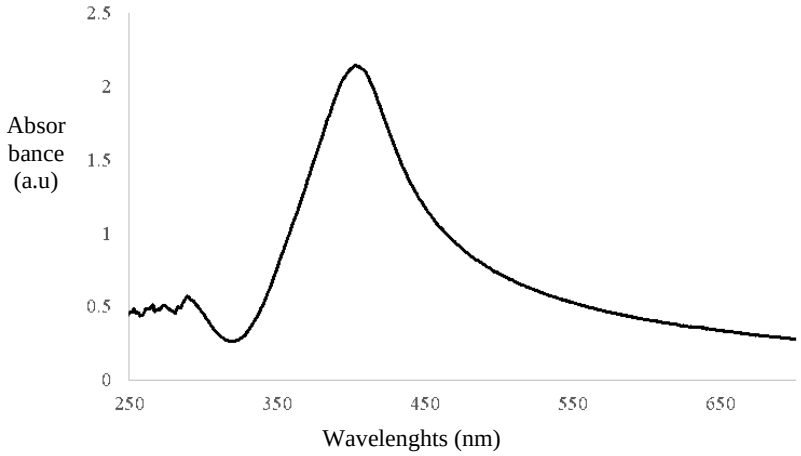



**Fig. 3.** UV– Vis Spectrum of colloidal Ag NPs

**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

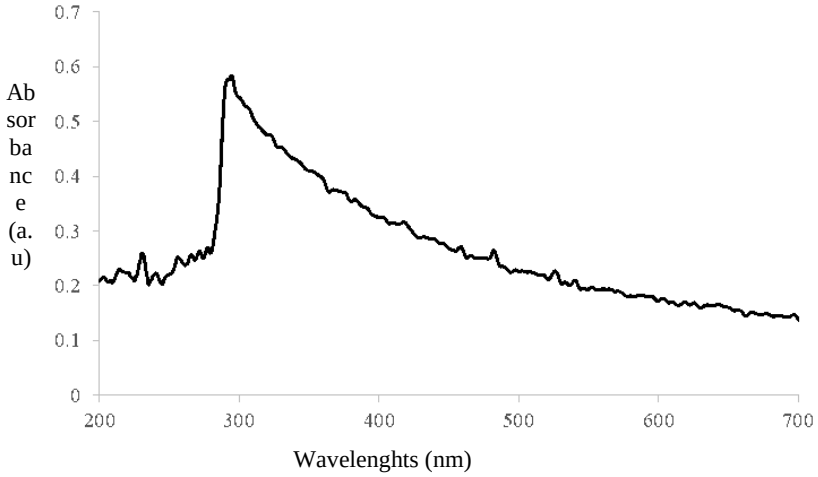



**Fig. 4.** UV– Vis Spectrum of Colloidal Pt NPs

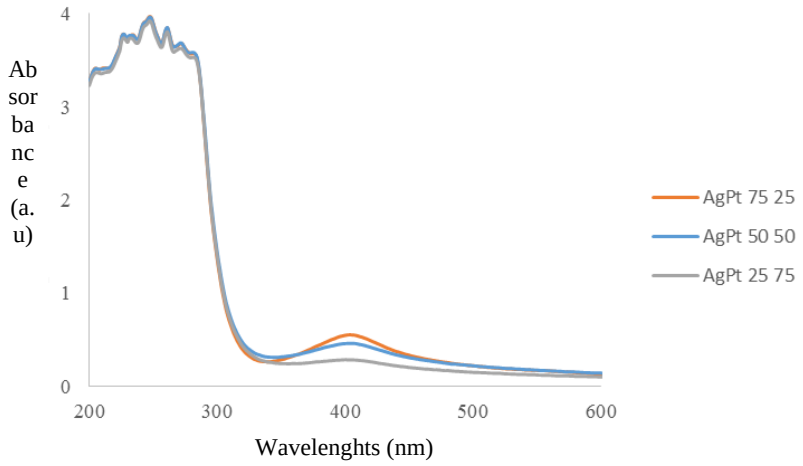



**Fig . 5.**UV– Vis Spectrum of the Ag-Pt NPs colloidal mixture with variations of compositions

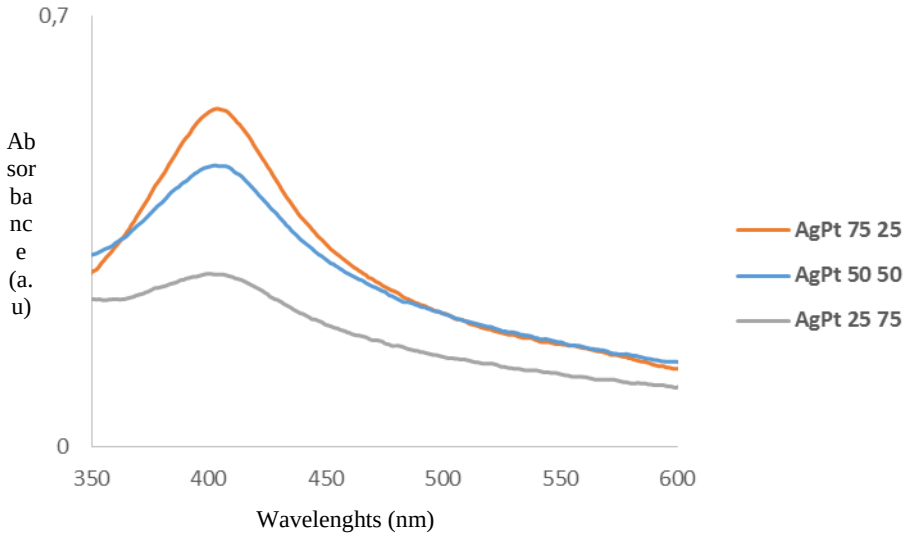



**Fig.6.**Magnification of UV– Vis Spectrum of the Ag-Pt NPs colloidal mixture with variations of compositions

**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

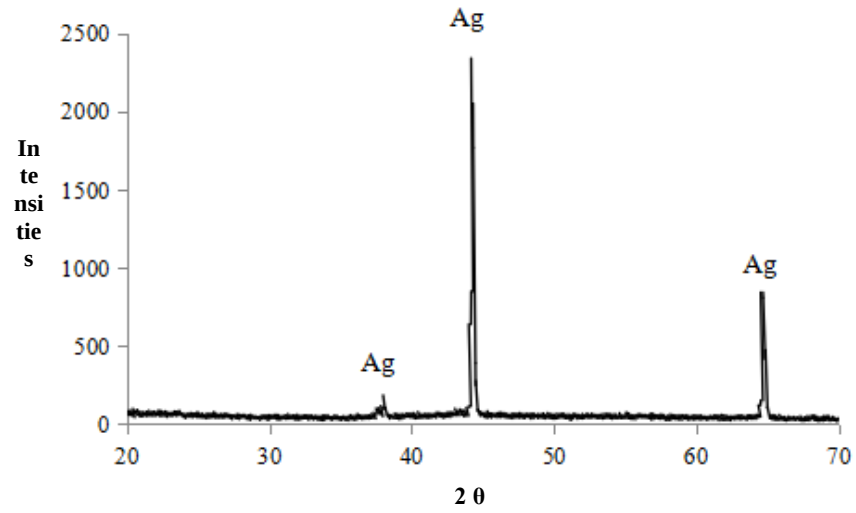



**Fig . 7.**XRD Spectrum of Ag Sample

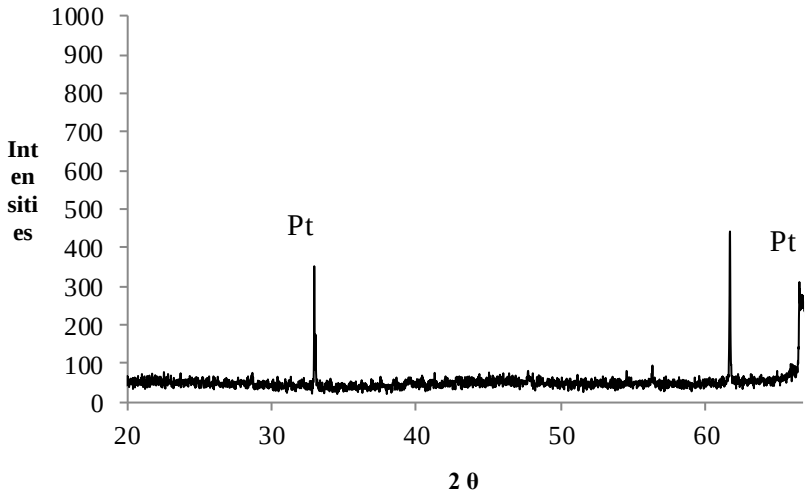



**Fig. 8.** XRD Spectrum of Pt Sample

**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

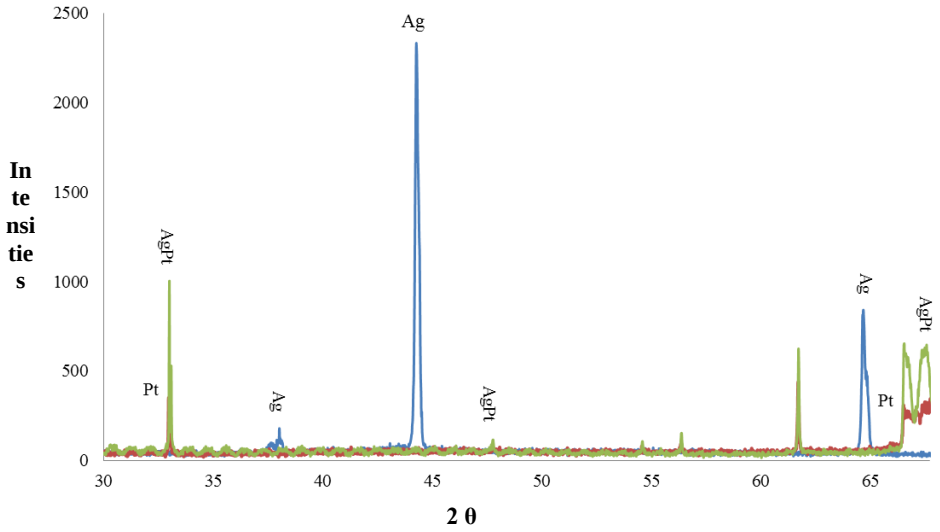



**Fig. 9.** XRD Spectrum of Silver – Platinum Sample

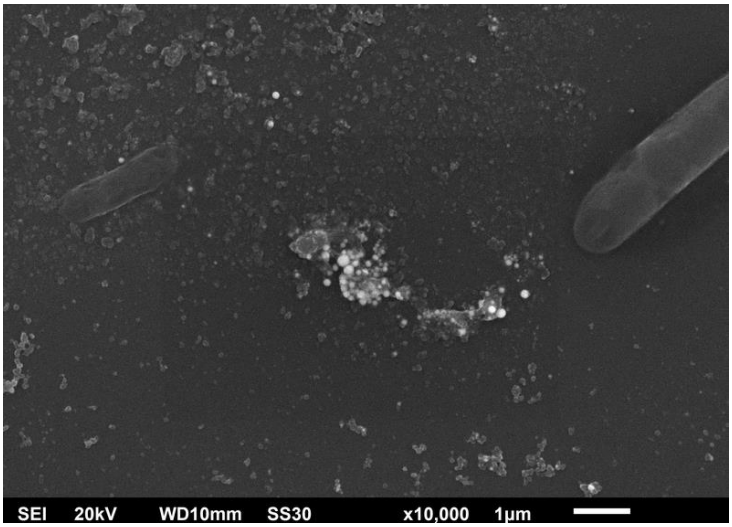



**Fig. 10.** SEM-EDX Spectrum result for colloidal PtNPs

**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

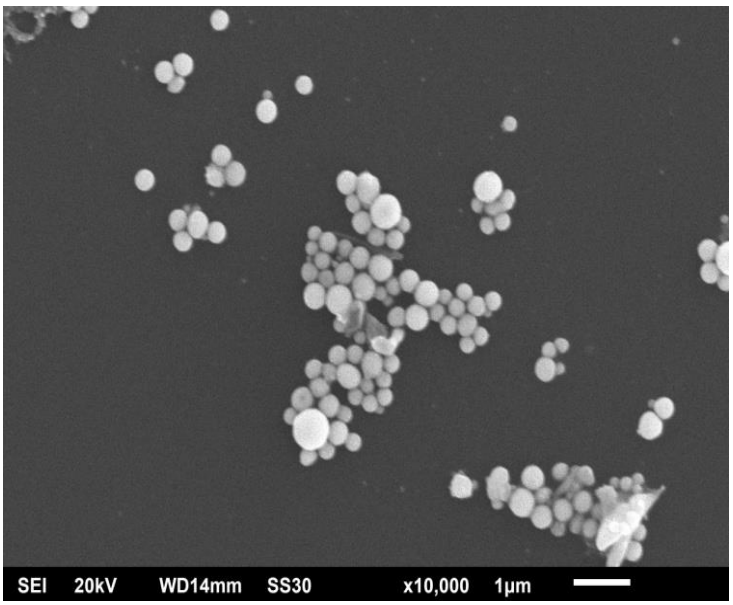



**Fig.11.**SEM-EDX spectrum result for colloidal AgNPs


**Fig.12.**Sample Preparationsof (a) 100% AgNPs colloid (b) 75%:25% Ag-PtNPs colloid (c) 25%:75% Ag-PtNPs colloid (d) 50%:50% Ag-PtNPs colloid and (e) 100% PtNPs colloid in 10ml-sized cylindrical vials

**Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

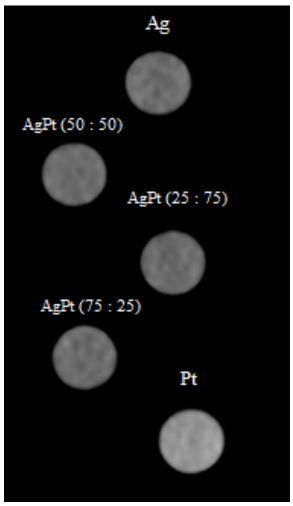



**Fig. 13.** Image results of AgNPs, PtNPs and Ag-PtNPs with variations of compositions as CT Scan contrast agents


**Fig. 14.** CT Scan tests on contrast properties of Ag, Pt, and Ag-Pt NPs with variations of compositions

2. **Submission acknowledgment dari Iranian Journal of Medical Physics (30 Oktober 2020)**

webmail FISIKA universitas diponegoro

**Ali Khumaeni <khumaeni@fisika.fsm.undip.ac.id>**

# Acknowledgement of Submission (#IJMP-2009-1849)

1 message

**Iranian Journal of Medical Physics** <medical.physics.ir@mums.ac.ir> Fri, Oct 30, 2020 at 5:20 AM
To: khumaeni@fisika.fsm.undip.ac.id

Manuscript ID: IJMP-2009-1849

Manuscript Title: **Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

Authors: Ali Khumaeni,Mohammad Zamakhsari Alhamid,Choirul Anam,Ari Budiono

Dear **Dr. Ali Khumaeni**

I wish to acknowledge receiving the above mentioned manuscript.

It should be noted that the manuscript will be reviewed for possible publication in the **Iranian Journal of Medical Physics**.

Please be sure that the submitted manuscript has not been published previously and will not be submitted elsewhere prior to our decision.

Our editorial board's decision will be brought to your attention once the paper has been reviewed due the referees consideration.

**You can track the status of the manuscript by logging into the system.**

**Attention**: Immediately after submitting the manuscript, all authors must complete and sign **The Licence to publish, Authorship Responsibility & Financial Disclosure form** and then the completed form should be faxed (both pages) to +98 (0)51- 38002320 or scanned and sent by Email to medical.physics.ir@mums.ac.ir. Submissions remain pending until submitting author send the form.

I wish to take this opportunity to thank you for sharing your work with us.

Sincerely yours,

Executive managing Editor of **Iranian Journal of Medical Physics**

## 3. Editor and reviewers' comments (6 Desember 2020)

webmail FISIKA universitas diponegoro

Ali Khumaeni <khumaeni@fisika.fsm.undip.ac.id>

# Manuscript Needs Major Revision (#IJMP-2009-1849 (R1))

1 message

**Iranian Journal of Medical Physics** <medical.physics.ir@mums.ac.ir> Sun, Dec 6, 2020 at 5:17 PM
To: khumaeni@fisika.fsm.undip.ac.id
Cc: loekmono@generalhospital.co.id, anam@fisika.fsm.undip.ac.id, alhamid@student.fisika.fsm.undip.ac.id

Manuscript ID: IJMP-2009-1849

Manuscript Title: **Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

Authors: Ali Khumaeni,Mohammad Zamakhsari Alhamid,Choirul Anam,Ari Budiono

Dear **Dr. Ali Khumaeni**

Your manuscript is still requiring major corrections. Please download and read carefully the attached file(s) prepared by reviewer(s) (if any) and manuscript evaluation forms.

However, if all corrections pointed out by reviewers could be addressed and the manuscript is re-written again it may be reconsidered for publication. The final decision depends on the opinion of reviewers on the revised manuscript.

I invite you to respond to the reviewer(s) comments and revise your manuscript until **2020-12-21**.

**Instructions to Submit a Revised Manuscript:**

Ensure you have all the revised files ready before you begin submitting your revision (Revised Manuscript, Response to Reviewers, …).

**1- Preparing your revised manuscript:**

In revised manuscript, all changes that have been made to the submission in response to the reviewers' comments and also any other changes must be simply Underlined.

**2- Preparing Response to Reviewers:**

If you do not agree with any of the reviewers' comments, give reasons for disagreeing with them. If reviewers need more detailed information for re-review your manuscript, please add them in the response file.

**3- To resubmit your manuscript please:**

- Log into https://ijmp.mums.ac.ir/ and enter as "Author".
- DO NOT CLICK "Submit a New Manuscript".
- You will find your manuscript title listed under "Submissions Needing Revision".
- Click on the "Manuscript ID".
- You will see a similar interface to that you used when submitting the original manuscript. You can revise any of the data (i.e. Manuscript Type, Manuscript Title, etc.) and you can attach revised files. You may either click through each page using the 'Next' button to decide whether any changes are required, or you can navigate more quickly by clicking the relevant menu item on the left-hand side of the screen, i.e. if no other data require changing, you can quickly move to 'Attach Files' by clicking this item on the left-hand menu.
- Upload any new or revised files in the same way that you attached your original files. Click the item in the drop-down box, browse for your revised/new file and click 'Attach File'. Please name all your revised files with the suffix 'revised', e.g. Manuscript revised.doc, Figure 1 - revised.tiff, Figure 3 revised.jpeg.
- In the last page, click on "Submit Revision".

Because we are trying to facilitate timely publication of manuscripts submitted to journal, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to this journal and I look forward to receiving your revision.

Sincerely yours,

Editorial Office of **Iranian Journal of Medical Physics**

Reviewers Recommendation:

**Reviewer 1:**

File Sent by Reviewer:
https://ijmp.mums.ac.ir/jufile?__file=c6T6K2uW295jmcLp05rvG7AppNV4JI_9S8_sWbXUQo1g8Jf2B73_P9MYuSmrTojobxuicG7ox.X1A3K.ZZB3.XpSo8wcr8p1tG_QE_HqrlZfJffzvKjheqY.a5Q4Rgjd7TXD.1RzWvGRsytXnD3mJBc1ztWAh1vVOPBVvPVw7W10mekk.Y0Sjw9M4ya.mpeb
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**Reviewer 2:**

Reviewer Comment For Author:

1. How are made silver and platinum nanoparticles ? How are they connected (exact method with reference)?
2. Why is not done the nanoparticles size with other standard methods like DLS (Dynamic Light Scattering)?
3. What measures have been taken to prevent from coagulate of the nanoparticles?
4. By SEM method, the desired nanoparticles are analyzed superficially. Why was not determine their

morphology by TEM method?
5. Why was used only a laser with a wavelength of 1064 nm ? Please explain your reasons with reference.

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**Reviewer 3:**

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**Reviewer 4:**

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https://ijmp.mums.ac.ir/jufile?__file=.bOjsJVnwp4xccwt3CNo4GxrtTCHZj6TgyHQKh2fN_vdeU0K1aI6xoPC43NL0UQtMor8kErxNN3S6rAsmuA.xVk9pSdnNSVQGPFk7T7eVY9Ibda1njVc2D8bOM8uurBXvOAPIPvtWsZ92YbNupqbmLaWL4DBy4yp_LBTlwJAPZA-
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https://ijmp.mums.ac.ir/jufile?__file=bpKKdbG7zaSh_TM2Rqk7fgbbIV9WFk6Pzmb3bdOmbbGl_EMT0AzADBwU6cJ5jl8MkKMY2NNc.GPjtqQFkKrYnL89szqTqvmRFVxik9u2OdJjobXiE7V3Lt29gW0IT_fgfyJuwtMCLfJXT5lVO1UddBOxTInhtgr8jvwtAM_El.A-

Reviewer Comment For Author:

Dear Author/Authors
Thank you very much for selecting an interesting subject "using nano-particles as a contrast agent in CT scanning". In my opinion this study can be accepted for publication in the Iranian Journal of Medical Physics after major revision. I have put my comments inside the text and highlighted them by yellow color. Also, I have typed them here as well.
The re-written paper must have the following points:
1- In which area of medical physics will these nan-particles will be useful
2- As a contrast material in HU, how are these better than iodine based contrast
3- Ag and Pt are expensive materials so what are the special purpose for using such expensive materials
4- We find that in the concentrations of NPs that I used the changes of HU values are too little. For iodine contrast the HU at 80kVp is about 250. We must know the weight/weight composition of Pt or Ag with that of water. I believe that to have a high HU value comparable to iodine contrast the weight/weight concentration of the metals should be increased by a factor of 250/16=15.6 times.
5- What would be the physiological effects of injecting such high concentration of metals into the body. We do not know but it should be stated.
6- As of now, these NPs system with low level metal content cannot be useful as a contrast material for CT but the authors can try with higher concentration of metallic particles.
7- The authors appear to have carefully prepare the NPs and carefully characterize them. These colloids are found to have interesting optical properties in the visible range. The authors should look for and comment about usefulness for diagnosis by using visible light. I hope they can identify some such cases.
8- This paper can be accepted by introducing a modified perspective as given in the above comments. For rewriting by detailed observations given below may be useful.
Abstract:
Introduction: The aim of this study is not clear to me? Why was the author/authors selected colloidal silver nanoparticles (Ag NPs), platinum nanoparticles (Pt NPs), and silver-platinum nanoparticles (Ag-Pt NPs) as contrast agent in diagnostic imaging (Computed Tomography enhancement)?
Materials and methods: The full form of the abbreviations has to be written (with abbreviation in the bracket in front of the full form) for the first time (e.g. ppm). The scanning method and exposure parameters of experimental work is missing.
Results: In abstract, the author gave the results of HU values of different concentrations of colloidal nano-particles while there is no explanation for the experimental method on the materials and methods section.
Conclusion: the author did not write about their finding and conclusion properly. For example, " These findings confirmed that the greater amount of Platinum in the colloidal solution would result in the greater value of image, as magnitude of atomic number correlates positively to attenuation value of a particle", the greater values of image does not have meaning. It has to be greater or higher HU values. The higher HU value for platinium can be attributed to its higher density since (refer to the main text of the manuscript) the effective energy of 80 kVp (excitation voltage) is about 42 keV which is much less than the k-edge (binding energy of electron in k-shell) of Pt (k-edge≈78 keV). It means that the attenuation of x-ray in Pt is due to compton scattering dominantely.
Keywords: Keywords have to be rewritten on the basis of journal instruction
Introduction:
In the sentence, "Invented by [8], the technique has become a focal point of more intensive researches", please write the name of the scientist or mention Ref (reference) before [8].
What is the superiority of Ag-Pt over Iodine contrast in enhaced CT? For patient or for image quality? Please write the aim of the study more clearly.
Materials and methods:
Please write the full form followed by abbreviation inside the braket for the first time, e.g mJ and ppm.
Why the authors did not used Ag or Pt without making mixture of these two metals?

The readers of the medical physics journal are medical physicists. It is better you explained the details of the method of scanning, reconstruction algorithm, reconstructed slice thickness. Please use an image of your experimental scanning set up. Show a typical image of the scanned samples with ROI inside one of the sample.
Results:
The first 5 sentences in the results part have to be transfered to the materials and methods.
Please define the unit a.u
I am not expert on nano-technology but it seems that the results part is the method of preparation of the nano-particles and the method of testing of purity and concentration measurements which should be shiftted to the materials and methods.
I have expected to read the results of the scanning samples contain different concentrations of the mentioned nano-particles. Thereore, I am not able to follow the results of this study.

Discusion:The authors explanation is, "The image results depicted in Fig.13 indicate the colloidal NPs' contrast property qualities in HU measurement, represented in the greyish shades. Darker greyish shades represent lower HU values, and vice-versa. The shades are associated with the number of X-ray photons passing through the body tissues which determine the variations of the dark and bright areas in the CT images." Shade of gray simply determines the attenuation coefficients of the material in the path of the x-ray beam.
This figure has to be shiftted to the results part. The Fig caption " Fig. 14. CT Scan tests on contrast properties of Ag, Pt, and Ag-Pt NPs with variations of compositions." should be re-written since this bar chart shows the HU value or CT-number of different nano-particles in the colloidal forms.
The higher attenuation coefficient in the nano-colidal Pt compound may be attributed to its higher electron density. The attenuation coefficient has a direct proprtional relationship with density or electron density of the materials in the path of the x-ray beam. This is Pt with higher density have higher attenuation coefficient compared to Ag. Density of Pt is 21.45 gm/cc and density of Ag is 10.49 gm/cc.
I have a question from the authors of this study, you have proven that Pt in a form of colloidal nano-particle has higher attenuation coefficient therefore has higher HU value and can be considered as a suitable contrast agent. Then why we have to use the mixture of (Pt and Ag colloidal form) nano-particles.
The discussion part is very similar to the result section and does not contain enough and satisfactory physical explanation of research finding.

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4. **Balasan komentar Editor dan Reviewers**

Dear Editor in Chief
Iranian Journal of Medical Physics

We are so sorry to revise the submitted manuscript very late. We are very pleased to know that our submitted manuscript entitled *Synthesis of colloidal silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography* is publishable to Iranian Journal of Medical Physics.

We are also very pleased that most reviewers have positive comments to our submitted manuscript. In this regard, we would like to respond the comments from the reviewers as below. We have included the responds of reviewer's comments in the revised manuscript with a red letter.

Again, we would like to thank you very much for your kindness and we are looking forward to your positive response.

Best regards
Ali Khumaeni
Department of Physics
Faculty of Science and Mathematics
Diponegoro University
Semarang 50275, Indonesia

**Reviewer 1:**

1. **Please compare this study with another study that used silver or platinum in CT in the discussion section.**

We have added the other studies made by other researchers using silver and platinum nanoparticles as contrast agents. This following additional explanation has been added in the revised manuscript.

It is shown in Fig. 14 that colloidal contrast agent Pt NPs has a higher absorption power compared to that of AgNPs, and thereby affecting the absorptions of any predetermined composition of colloidal Ag-Pt NPs, with the highest in 25:75% Ag-Pt NPs composition and continue to decrease in the direction of vice-versa composition (75:25% Ag-Pt NPs). This phenomena refers to the concept of mass attenuation coefficient (Shilo et al., 2012), which states high atomic numbers as the one factor responsible for determining better contrasts on scanned tissues. This is explained in physics from the number of photons interacting with a structure, which are influenced by its thickness, density, and atomic numbers. The coefficient of attenuation will increase if the atomic number and density are increased (Hainfeld et al., 2006). The coefficient of attenuation greatly affects the attenuation value of X-rays measured in the units of Hounsfield units (HU). With the NIST data of mass attenuation coefficients indicating by 2.6 for silver ($Z = 47$) and 8.7 for platinum ($Z = 78$), the results of HU values for the colloidal NPs in this study have been appropriate. As reported by Jakhmola et al., elements with high atomic number such as gold, silver, platinum, and other heavy metals (Thorium, bismuth, and tantalum) have high possibility to be

employed to enhance the image in CT scan. Lui et al. reported that silver nanoparticles having averaged diameter size of 16 nm displayed X-ray attenuation properties similar to that of iodine based contrasting agent. For platinum nanoparticles, Chen et al. demonstrated that Pt nanoparticles mixed with Fe can be employed as a dual modal contrast agent of MRI and CT scan. The Pt NPs with averaged sizes ranging from 42-52 nm have higher HU value compared to the case of commercial iodinated contrast agent with the same concentration of 1 mM.

**2. Please more explain about the parameters of CT and CT devices.**

We have added detail explanation about parameters of CT and CT devices in the revised manuscript. The additional explanation is as follows:

The CT scan used in this work was commercial CT Philips with a model of ingenuity core 128 and name product of multiscale CT scan 128 slice. This modality has anode effective heat capacity of 30 MHU, anode heat storage capacity of 8 MHU and anode cooling rate of 1,608 KHU/min. This CT is generally used in hospitals in Indonesia. The CT Scan contrast tests began with preparingvarious mixtures of the NPs into the 10-ml tubes at equal concentrations each and placed them on the holder. In addition, *CT Reader* software was employed to process the resulting images. Comparative analyses were performed on the HU valuesof the variations. Philips multiscale CT scan 128 slice (model of ingenuity core 128, United States) was used in this study as the imaging modality. The polystyrene box was strapped on CT table couch and positioned so that the centre of the box is aligned with the gantry isocenter. The irradiation was performed with tube energy and effective tube current of 80 kV and 100 mAs, respectively, while the slice thickness was set at 0.6 mm.

**Reviewer 2:**

**1. How are made silver and platinum nanoparticles ? How are they connected (exact method with reference)?**

Silver, platinum, and silver-platinum nanoparticles were synthesized by using pulse laser ablation technique, similar with the technique used by Shukri et al. for synthesized Au-Ag nanoparticles in deionized water (Shukri et al., 2018). First, Ag nanoparticles were produced by focusing a pulse Nd:YAG laser on a high-purity Au metal plate, which was immersed at the bottom of the petri dish and filled with 10 ml water. After that, synthesis was made for Pt nanoparticles using the same procedure as in the case of Ag nanoparticles. Finally, mixture of Ag-Pt was produced by mixing Ag and Pt nanoparticles with a various volume ratio. Afterwards, the mixture nanoparticles were irradiated with a laser beam.

**2. Why is not done the nanoparticles size with other standard methods like DLS (Dynamic Light Scattering)?**

Based on our literature study, there are various standard methods for measuring nanoparticle sizes including dynamic light scattering and ImageJ software. Bothum reported that analysis on the diameter of the NPs sizes can be performed by using *ImageJ* software, which is one of the technique used for analysis of nanoparticle diameter (Bothun, 2008). In this present work, we used imageJ software for measuring a diameter of produced nanoparticles. The analysis was made from the SEM image obtained in the study.

**3. What measures have been taken to prevent from coagulate of the nanoparticles?**

For measuring the coagulation, we usually use TEM or SEM technique to qualitatively see the morphology difference after several days due to particle agglomeration. Quantitative measurement was made by analysis of TEM or SEM image using imageJ software to know the change of particle size due to agglomeration.

**4. By SEM method, the desired nanoparticles are analyzed superficially. Why was not determine their morphology by TEM method?**

In this present work, we used SEM method because we only want to analyze the morphology and composition of produced nanoparticles, and we did not study in detail about crystal structure and others. By knowing the particle size and composition of produced particle, we can apply the particles as a contrast agent in CT scan.

**5. Why was used only a laser with a wavelength of 1064 nm? Please explain your reasons with reference.**

Some studies on silver nanoparticles synthesis were performed using Nd:YAG laser 1064 nm such as a report by Zamiri et al. In the study, they produced silver nanoparticles in virgin coconut oil medium. The result certified that various diameter sizes of nanoparticles are produced depending on laser bombardment time. The averaged sizes are from 4-6 nm, which is applicable for medical applications such as a contrast agent of CT scan. Therefore, in this present work, we used an Nd:YAG laser with a wavelength of 1064 nm as an irradiation source.

**Reviewer 3:**

Manuscript Evaluation Form:

**1. In the last figure you should use "contrast agent" also error bars for CT numbers indicating standard deviation and average number are required.**

We have revised Fig. 14 in the revised manuscript following your suggestion.

**2. The concentration of nano-agent have been too low to give strong HU changes in solution. So Thus of 10-15 is very close to water and considering the noise of 5-10 HU in normal CT images, the results do not seen reliable to me.**

Thank you very much for your kind suggestion. In this present study, we used low concentration of Ag and Pt nanoparticles to demonstrate the ability of the nanoparticles for application as a contrast agent in CT scan. Even the concentration is low, we can clearly distinguish the HU value for Ag only, PT only, and mixture of Ag-Pt with various concentration ratio. Based on this result, we obtained the Pt nanoparticles only have highest CT number (HU). Therefore, for next study, we will perform in-vivo study using Ag and Pt nanoparticles with high concentration of around 15-20 times higher than those in this present work as contrast agents in CT scan following your recommendation.

**Reviewer 4:**

Thank you very much for selecting an interesting subject "using nano-particles as a contrast agent in CT scanning". In my opinion this study can be accepted for publication in the Iranian Journal of Medical Physics after major revision. I have put my comments inside the text and highlighted them by yellow color. Also, I have typed them here as well.

The re-written paper must have the following points:

**1- In which area of medical physics will these nan-particles will be useful**

In our present study, the nanoparticles produced were used as a contrast agent in CT scan. The application of these nanoparticles includes the area of diagnostic field in medical physics. The use of Ag and Pt nanoparticles is for the enhancement of CT diagnostic qualities.

**2- As a contrast material in HU, how are these better than iodine based contrast**

Based on our literature study, current agents including iodinated based contrast materials impose serious limitations on medical imaging, namely, short imaging times, the need for catheterization in many cases, occasional renal toxicity, and poor contrast in large patients. Nanoparticles have higher absorption than iodine with less bone and tissue interference achieving better contrast with lower X-ray dose. Nanoparticles clear the blood more slowly than iodine agents, permitting longer imaging times (Hainfeld et al., 2006)

**3- Ag and Pt are expensive materials so what are the special purpose for using such expensive materials**

Current contrast agents usually applied in CT scan are molecules based on iodine, barium, and gadolinium. However, those agents have many drawbacks including short blood half life, nonspecific biodistribution, fast clearance, slight renal toxicity and poor contrast in fat patients.

Metal nanoparticles are intensively exploited as a future candidate of contrast agent in CT scan because (a) they have a surface, which can be functionalized with one or more targeting molecules at a wide range of densities; (b) their plasma circulation time can be turned over several orders of magnitude based on their physico-chemico properties and (c) contrast agents and drugs can be included at predetermined ratios either in the interior or on the surfaces. Furthermore, metals have high X-ray attenuation and high density. However, few papers have been reported on Ag and Pt nanoparticles synthesized by using pulse laser ablation. Researchers generally explore gold nanoparticles functionalized with another material to reduce toxicity. In this present work, we examine a potential Ag and Pt nanoparticles as contrast agent in CT scan.

**4- We find that in the concentrations of NPs that I used the changes of HU values are too little. For iodine contrast the HU at 80kVp is about 250. We must know the weight/weight composition of Pt or Ag with that of water. I believe that to have a high HU value comparable to iodine contrast the weight/weight concentration of the metals should be increased by a factor of 250/16=15.6 times.**

In this present work, we used quiet low concentration of 10 ppm for ratio of Ag and Pt nanoparticles with that of water. This comparative study between Ag and Pt was made to evaluate which metal between them is suitable as a contrast agent in CT scan. For next study, we will perform in-vivo study using Ag and Pt nanoparticles

with high concentration of around 15-20 times higher than those in this present work as contrast agents in CT scan following your recommendation.

**5- What would be the physiological effects of injecting such high concentration of metals into the body. We do not know but it should be stated.**

Many reports have been published about the toxicity of metal nanoparticles when being injected into the body. As reported by Jamuna Bai et al., metal nanoparticles with a various concentration level can induce toxicity for human health (Jamuna Bai et al., 2014). Korani et al. reviewed effect of silver nanoparticles to human body. He found that the toxicity of silver nanoparticles in the human body depends on concentrations, shapes, and sizes of nanoparticles (Korani et al., 2015), e.g. silver nanoparticles with a concentration of 10,000 ppm can induce necrosis for liver toxicity.

**6- As of now, these NPs system with low level metal content cannot be useful as a contrast material for CT but the authors can try with higher concentration of metallic particles.**

In this present work, we used quiet low concentration of 10 ppm for ratio of Ag and Pt nanoparticles with that of water. This comparative study between Ag and Pt was made to evaluate which metal between them is suitable as a contrast agent in CT scan. For next study, we will perform in-vivo study using Ag and Pt nanoparticles with high concentration of around 15-20 times higher than those in this present work as contrast agents in CT scan following your recommendation.

**7- The authors appear to have carefully prepared the NPs and carefully characterize them. These colloids are found to have interesting optical properties in the visible range. The authors should look for and comment about usefulness for diagnosis by using visible light. I hope they can identify some such cases.**

Early diagnosis of diseases is urgently imperative to prevent and screen the diseases in the human body. Various techniques have been commercially established to perform diagnosis of disease; one of them is visible light spectroscopy, which is commonly used for diagnosis of chronic mesenteric ischemia (Friedland et al., 2007). The other technique is x-ray based imaging technique, which is recently employed as a diagnostic technique of cancer in the human body. We have included this additional information in the revised manuscript.

**8- This paper can be accepted by introducing a modified perspective as given in the above comments. For rewriting by detailed observations given below may be useful.**

**Abstract:**

**Introduction: The aim of this study is not clear to me? Why was the author/authors selected colloidal silver nanoparticles (Ag NPs), platinum nanoparticles (Pt NPs), and silver-platinum nanoparticles (Ag-Pt NPs) as contrast agent in diagnostic imaging (Computed Tomography enhancement)?**

We have revised the introduction in Abstract as follows: Over the last seven years the development of nanoparticles as CT's contrast agents has increased. However, few reports have been published on the use silver and platinum nanoparticles as a contrast agent. These nanomaterials are a good candidate for contrast agent because of high atomic number and high durability against corrosion. In this present work, syntheses of colloidal silver nanoparticles (Ag NPs), platinum nanoparticles (Pt NPs),

and silver-platinum nanoparticles (Ag-Pt NPs) have been successfully performed using pulsed laser ablation method in deionized water media.

**Materials and methods: The full form of the abbreviations has to be written (with abbreviation in the bracket in front of the full form) for the first time (e.g. ppm). The scanning method and exposure parameters of experimental work is missing.**

Experimentally, an neodymium-doped yttrium aluminum garnet (Nd:YAG) laser (1064 nm, 45 mJ, 10 Hz) was focused on a metal plate including Ag and Pt, placed in deionized water medium. Colloidal Ag nanoparticles has been succesfully produced with a dark brownish-yellow color and the averaged diameter of 24 nm. For colloidal Pt, the nanoparticles have transparent color with aan averaged diameter of 20 nm. Both colloidal nanoparticles of Ag and Pt were then mixed to obtain a mixture composition of Ag and Pt with ratios of Ag:Pt of 75:25%, 50:50%, 25:75%, respectively, with a concentration of 10 part per million (ppm). The Ag-Pt mixture were then examined as an contrast agent in computed tomography (CT) scan. The CT Scan contrast tests began with preparing various mixtures of the NPs into the 10-ml tubes at equal concentrations each and placed them on the holder. The CT Scan was set at 80 kV and 100 mAs. In addition, *CT* Reader software was employed to process the resulting images. Comparative analyses were performed on the HU valuesof the variations.

**Results: In abstract, the author gave the results of HU values of different concentrations of colloidal nano-particles while there is no explanation for the experimental method on the materials and methods section.**

We have added explanation in Materials and methods about the use of CT scan to obtain the image from the Ag, Pt, and Ag-Pt nanoparticles.

**Conclusion: the author did not write about their finding and conclusion properly. For example, " These findings confirmed that the greater amount of Platinum in the colloidal solution would result in the greater value of image, as magnitude of atomic number correlates positively to attenuation value of a particle",** the greater values of image does not have meaning. It has to be greater or higher HU values. The higher HU value for platinium can be attributed to its higher density since (refer to the main text of the manuscript) the effective energy of 80 kVp (excitation voltage) is about 42 keV which is much less than the k-edge (binding energy of electron in k-shell) of Pt (k-edge≈78 keV). It means that the attenuation of x-ray in Pt is due to compton scattering dominantely.

We have revised the conclusion following your suggestion as follows; These findings confirmed that for colloidal solution with high concentration of platinum has higher HU values compared to the case of silver. The higher HU value for platinium can be attributed to its higher density since the effective energy of 80 kVp (excitation voltage) is about 42 keV, which is much less than the k-edge (binding energy of electron in k-shell) of Pt (k-edge≈78 keV). It means that the attenuation of x-ray in Pt is due to compton scattering dominantely.

**Keywords: Keywords have to be rewritten on the basis of journal instruction**

We have revised the keywords following the instruction for authors of Iranian Journal of Medical Physics.

**Introduction:**

**In the sentence, "Invented by [8], the technique has become a focal point of more intensive researches", please write the name of the scientist or mention Ref (reference) before [8].**

We have added the name of scientist in introduction.

**What is the superiority of Ag-Pt over Iodine contrast in enhaced CT?**

We have added information about the superiority of Pt NPs compared to commercial iodinate contrast agent in the revised manuscript. Also, we have added clear aim of the study as in the revised manuscript. The aim of this study is to develop potential candidate of Ag NPs and Pt NPs as contrast agents, this research attempts to look for which NPs among them have best suits for improvement CT Scan imaging. Furthermore, the mixture of Ag and Pt NPs was also examined to know the best suitable candidate for contrast agent in CT scan. The use of PLA method is expected to improve the quality of Ag-Pt NPs as contrast agent, in the hope to find a reliable alternative in CT Scan modalities. Characteristics of Ag-Pt NPs produced in the research was examined using Ultraviolet-Visible Spectroscopy (UV-Vis), Scanning Electron Microscopy (SEM), and X-ray diffraction (XRD). The produced Ag NPs, Pt NPs, and mixture of Ag-Pt NPs were then applied as a contrast agent via in vitro. The results certified that the colloidal solution having higher concentration of Pt has higher HU value compared to that of Ag NPs, indicating that Pt NPs is better candidate of contrast agent compared to the Ag NPs case.

We included this explanation in the revised manuscript.

**Please write the full form followed by abbreviation inside the braket for the first time, e.g mJ and ppm.**

We have added the full form in the revised manuscript.

**Why the authors did not used Ag or Pt without making mixture of these two metals?**

In the present work, we used not only mixture of Ag-Pt NPs, but also we used Ag NPs only and Pt NPs only as a candidate of contrast agent. We make a comparative study between Ag only, Pt only, and mixture of Ag-Pt with various concentration ratios as stated in all sections of revised manuscript.

**The readers of the medical physics journal are medical physicists. It is better you explained the details of the method of scanning, reconstruction algorithm, reconstructed slice thickness.**

We have added detail explanation of the method of scanning as in the revised manuscript. Philips multiscale CT scan 128 slice (model of ingenuity core 128, United States) was used in this study as the imaging modality. The polystyrene box was strapped on CT table couch and positioned so that the centre of the box is aligned with the gantry isocenter. The irradiation was performed with tube energy and effective tube current of 80 kV and 100 mAs, respectively, while the slice thickness was set at 0.6 mm.

**Results:**

**The first 5 sentences in the results part have to be transfered to the materials and methods.**

We have moved the first 5 sentence in the results section to the materials and methods section.

**Please define the unit a.u**
We have written full abbreviation to arbitrary unit (a.u.)

**I am not expert on nano-technology but it seems that the results part is the method of preparation of the nano-particles and the method of testing of purity and concentration measurements which should be shiftted to the materials and methods.**
We have moved some results part to the materials section as in the revised manuscript.

**I have expected to read the results of the scanning samples contain different concentrations of the mentioned nano-particles. Thereore, I am not able to follow the results of this study.**
We have moved the result of CT image obtained from Ag only, Pt only, and mixture of Ag-Pt with various concentration ratios in the results sectionas shown in the revised manuscript.

**Discusion:The authors explanation is, "The image results depicted in Fig.13 indicate the colloidal NPs' contrast property qualities in HU measurement, represented in the greyish shades. Darker greyish shades represent lower HU values, and vice-versa. The shades are associated with the number of X-ray photons passing through the body tissues which determine the variations of the dark and bright areas in the CT images." Shade of gray simply determines the attenuation coefficients of the material in the path of the x-ray beam. This figure has to be shiftted to the results part.**
We have moved Fig. 13 in the results part

**The Fig caption " Fig. 14. CT Scan tests on contrast properties of Ag, Pt, and Ag-Pt NPs with variations of compositions." should be re-written since this bar chart shows the HU value or CT-number of different nano-particles in the colloidal forms.**
We have revised the figure as shown in the revised manuscript.

**The higher attenuation coefficient in the nano-colidal Pt compound may be attributed to its higher electron density. The attenuation coefficient has a direct proprtional relationship with density or electron density of the materials in the path of the x-ray beam. This is Pt with higher density have higher attenuation coefficient compared to Ag. Density of Pt is 21.45 gm/cc and density of Ag is 10.49 gm/cc. I have a question from the authors of this study, you have proven that Pt in a form of colloidal nano-particle has higher attenuation coefficient therefore has higher HU value and can be considered as a suitable contrast agent. Then why we have to use the mixture of (Pt and Ag colloidal form) nano-particles.**
The mixture of Ag-Pt nanoparticles was studied to know which NPs most contributed to HU value are. Best on our results, composition of Ag-Pt mixture having high concentration of Pt gain higher HU value. Therefore, we concluded that the Pt NPs are better candidate for contrast agent compared to the case of Ag NPs.

**The discussion part is very similar to the result section and does not contain enough and satisfactory physical explanation of research finding.**

We have made a major revision in the part of results and discussions as in the revised manuscript.

5. **Paper setelah proses revisi mempertimbangkan masukan Editor dan Reviewers**

# Synthesis of colloidal silver, platinum, and mixture of silver-platinum nanoparticles using pulsed laser ablation as a contrast agent in computed tomography

Running title: Silver-platinum nanoparticles for contrast agent

**Abstract**

**Introduction**: The development of nanoparticles as computed tomography contrast agents has increased significantly. However, few reports have been published on the use of silver and platinum nanoparticles as contrast agents. These nanomaterials are a good candidatefor contrast agents because of their high atomic number and high durability against corrosion.
**Materials and Methods**: Experimentally, a Nd:YAG laser (1064 nm, 45 mJ, 10 Hz) was focused on a high-purity metal plate including Ag and Pt plates, which are placed in deionized water medium. Colloidal nanoparticles of Ag and Pt were then mixed to obtain a mixture composition of Ag and Pt with ratios of Ag:Pt of 75:25%, 50:50%, 25:75%, respectively.The Ag, Pt, and Ag-Pt NPs mixture were then examined as contrast agents in CT scan.
**Results**: The imaging results of the quantitative analysiswere measured in the Hounsfield Unit(HU), showing 13.5, 12.8, 13.3, 14.1, and 17.3 HU for colloidal 100% AgNPs, colloidal Ag and Pt NPs with volume ratios of Ag:Pt of 75:25%, 50:50%, 25:75%, and colloidal 100%Pt NPs, respectively.
**Conclusion:** Results reveal the highest absorbent power was found in the colloidal contrast agent of Pt NPs 100% is 17.3 HU, followed by the 25:75% Ag-Pt NPs is 14.1 HU. The higher HU value for platinum can be attributed to its higher density since the effective energy of 80 kVp is about 42 keV, which is lower than the K-edge of Pt (K-edge ≈ 78 keV), which means that the attenuation of X-ray in Pt is due to Compton scattering dominantly.

**Keywords:** Diagnosis; metal nanoparticles; contrast agent; CT scan.

## INTRODUCTION

Early diagnosis of diseases is urgently imperative to prevent and screen the diseases in the human body. Various techniques have been commercially established to perform diagnosis of disease; one of them is visible spectrometry, which is commonly used for chronic diagnosis [1]. The other technique is x-ray based imaging technique, which is recently employed as a diagnostic technique of cancer in the human body.

Imaging technique based on X-ray has been employed in the medical field [2], Computed Tomography (CT) has been superior in terms of imaging and cost efficiencies and yet non-optimal in soft tissues detection. In this regard, attempts to enhance CT diagnostic qualities have used clinically standard contrast agents, such as the small molecular iodinated agent and barium suspension. These have only led to other essential problems in the medical imaging's, including high osmolality, contrast agent's low longevity, kidneys toxicity, and poor contrasts in patients with large body volumes [3]. Over the last seven years, the development of nanoparticles as CT'scontrast agents has increased significantly. Nanoparticles have several advantages compared to the micro-sized, molecular contrast agents, such as lower osmolality, longer longevity, potentials for cell tracking and targeted imaging applications [2]. Also, compared to iodine that is commonly employed as a contrast agent in CT scans, the absorption of nanoparticles is much higher with low tissue and bone interference, resulting in better contrast. Furthermore, the nanoparticles have a longer circulation time in the blood than the iodine case, yielding longer imaging times [3]. Metal nanoparticles are intensively exploited as a future candidate of contrast agent in CT scan because (a) their wide surface can be modified with the much more targeting molecules; (b) their plasma dissemination time can be turned north of a few significant degrees dependent on their physicochemical properties; and (c) drugs and contrast agent can be incorporated at foreordained proportions either in the inside or on the surfaces.

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**Synthesis of colloidal silver, platinum, and mix..**

The syntheses of metal nanoparticlesare generally achieved either chemically or physically. A typical, chemical process begins with the thermal decomposition of precursors into atoms, followed by aggregation into nanoparticles [4]. During this process, additives like surfactants or molecular ligands are commonly used to avoid the aggregation and to control the nanoparticles' shapes [5]. However, these treatments result in unrefined products that require multiple purifications before they can be applied in subsequent nanoparticle processes. This has been deemed to be the adverse effect of chemically synthesized nanoparticles [6], and persisted including in the stabilizations using dendrimer [7] and Polyol [8].

On the other hand, physical syntheses rely on grouping precursors to be made into nanoparticles and involves condensation of vapors, which result from the corresponding physical interactions. Laser becomes one of the most representative physical approaches for synthesis of nanoparticles. An example of laser applications is pulsed laser ablation (PLA) in gas or liquid medium. Invented by Maiman (1960), the technique has become a focal point of more intensive researches. With results differ from the most chemical synthesis methods, PLA offers manufacture of high purity nanoparticles, simpler methods, and mass productions [9]. Simply by permuting the combinations of target solid and choice fluid [10], one can produce a variety of colloidal nanoparticles including metals, alloys, oxides, and semiconductors for many applications including medical applications [11].

In body tissue imaging, one factor responsible for a substance's contrast property is the atomic number, which is described physically by the number of interacting photons. The larger the atomic number means the more photons interact with the atom. In addition, thickness and density also play an important roles in contrast differences [12]. Attenuation coefficient increases accordingly to augmentation of atomic number and density [3]. It greatly affects X-rays attenuation value measured in Hounsfield units (HU).

Silver (Ag; Z = 47), an elastic, easily forged metal, posseses ions which remain neutral under water, acid, and salt environments. Ag shows stability under heat and light [13], and the nanoparticle form has a unique, optical scattering property of plasmon-resonances which allows applications in bio-sensing and imaging [14]. The nano-size bestows it properties to penetrate several biological cell membranes like in bacteria, enhancing the contact surfaces and allowing direct penetration [15]. In this experiment, contrast properties of Silver's Dendrimer Stabilized NPs (DSNPs) in CT Scan were tested. Although Ag's atomic number is relatively low, its DSNPs mode is able to approach the contrast intensity of conventional agents [7]. It is accessible to be produced within reasonable price range as compared to other metals.

Another metal, which is possible to be used as an contrast agent is platinum (Pt; Z = 78), which is often found naturally in alluvium sands throughout various rivers. Owing to its high durability against corrosion, which renders it less toxic than some other metals [16], platinum has been adopted in catalytic modifiers, laboratory equipment, electrical contacts and electrode, resistance thermometers, dentistry equipment, and jewellery. In medicine, the nanoform has shown promises such as in the combination of sinotherapy and radiotherapy, acting simultaneously both as a contrast agent and a drug carrier [17]. A Pt NPs-based contrast agent synthesized in the form of Fe-Pt NPs using Polyol method has also been used in CT Scan. Intravenal injection of the nanoparticles in an animal's tail increased active cells contrast from cancer lesions in scanning for tumor carrier [8]. Comparative study between the use of Pt NPs and commercial iodinate contrast agent has been reported by Anuar et al. [18]. They obtained that the Pt NPs with diameters of 42 nm and 52 nm have higher CT number compared to that of commercial iodinated contrast agents at the same concentration of 1 M. However, still few papers have been reported on Ag and Pt nanoparticles synthesized by using pulse laser ablation for application of contrast agent in CT scan. Researchers generally explore gold nanoparticles functionalized with another material to reduce toxicity. In this present work, we examine a potential Ag and Pt nanoparticles as a candidate of contrast agent in CT scan.

To develop potential candidate of Ag NPs and Pt NPs as contrast agents, this research attempts to look for whichNPs among them have best suits for improvement CT Scan imaging. Furthermore, the mixture of Ag and Pt NPs was also examined to know the best suitable candidate for contrast agent in CT scan. The use of PLA method is expected to improve the quality of Ag NPs, Pt NPs, and Ag-Pt NPs as contrast agent, in the hope to find a reliable alternative in CT Scan modalities. Characteristics of Ag-Pt NPs produced in the research was examined using Ultraviolet-Visible Spectroscopy (UV-

Vis), Scanning Electron Microscopy (SEM), and X-Ray diffraction (XRD). The produced Ag NPs, Pt NPs, and mixture of Ag-Pt NPs were then applied as a contrast agent via in vitro. The results certified that the colloidal solution having higher concentration of Pt has higher HU value compared to that of Ag NPs, indicating that Pt NPs is better candidate as a contrast agent compared to the Ag NPs case.

## MATERIALS AND METHODS

The pulsed laser ablation method was employed to produce silver (Ag) nanoparticles (NPs), platinum (Pt) nanoparticles (NPs), and a mixture of silver-platinum nanoparticles (Ag-Pt NPs) from the high-purity metal plates of Ag and Pt (The Nilaco Corporation, Japan), respectively. For synthesis Ag NPs, the decontamination of 99.95%-pure Ag plate with alcohol was followed with incorporation into a petri dish of 25 mL deionized water. To produce a colloidal nanoparticle with a minimum concentration of 20 ppm, the Ag metal plate was bombarded by an Nd: YAG laser beam at a wavelength of 1064 nm with an energy of 45 mJ at a frequency of 10 Hz. During the process, the petri dish was rotated slowly and continuously to obtain a homogeneous nanoparticle fluid. Figure 1 shows the setup of an ablation experiment using a Nd: YAG laser at 1064 nm. In this present work, we used an Nd:YAG laser 1064 nm (New Wave Research Model Polaris II 20 Hz, 7 ns, USA) as an energy source to ablate a material. Some studies on silver nanoparticles synthesis were performed using Nd:YAG laser 1064 nm such as a report by Zamiri et al. [19]. In the study, they produced silver nanoparticles in a virgin coconut oil medium. The result certified that various diameter sizes of nanoparticles are produced depending on laser bombardment time. The averaged sizes are from 4-6 nm, which is applicable for medical applications such as a contrast agent of CT scan.

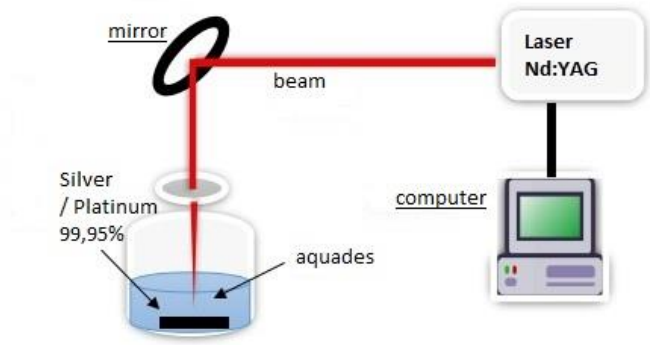


**Fig. 1.** Setup for an Nd: YAG 1064 nm laser ablation experiment

The interaction between the laser and the target was followed with plasma formations resulting in the target's atomic breakdowns. Simultaneous blastsoccurred, followed by shockwave expansions to the surrounding area. With the surrounding temperatures much lower than those of the plasmas, the cooling-downs may result in losses of explosive effects, leaving a mixture of fluid and nanoparticle-sized material referred to as colloidal nanoparticles [20]. The target in the petri dish was moved slowly to avoid a spot being bombarded sequentially, as this affects the quality of nanoparticle formation.

After the treatment of the Ag plate, the laser bombardment was made on the Pt plate using the same method with Ag NPs production. Forthe Ag-Pt mixture nanoparticles, the experiment was made by following the method described in the paper prepared by Shukri et al. [21]. Namely, the Ag and Pt NPs produced from PLA method were then mixed and stirred into uniformity with variations of compositions: 25:75%, 75:25% and 50:50% of Ag-Pt NPs. The total volume for each composition is 10 ml; e.g., for making a composition of Ag-Pt NPs with mixture composition of 25:75% for Ag-Pt NPs, 2.5 ml colloidal AgNPs (AgNPs concentration of 10 ppm) were mixed with 7.5 ml colloidal PtNPs (PtNPs concentration of 10 ppm). Additional radiation of Nd: YAG 1064 nm laser was applied

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to the Ag-Pt NPs mixtures for 2 hours laser bombardment to convince that the homogeneous mixture of Ag-Pt NPs was produced.

Sequential tests were performed onthe synthesized colloidal Ag NPs, Pt NPs, and Ag-Pt NPs. Using UV-Vis Spectroscopy, the plasma surfaceresonances were determined, while the NPs' morphology and the average size were derived from the SEM examination.In this present work, we used the SEM method because we only want to analyze the morphology and composition of produced nanoparticles, and we did not study in detail crystal structure and others. These were followed with *X-Ray Diffraction* (XRD) to extract information on the structure type, grid parameters, and different atomic arrangements of the NPs crystals.Analysis on the diameter of the NPs sizeswas performed using *ImageJ* software, which is one of the techniques used for the analysis of nanoparticle diameter [22].

The produced Ag NPs, Pt NPs, and Ag-Pt NPs mixture were examined as a potential contrast agents in CT scans. The CT scan used in this work was commercial CT Philips with a model of ingenuity core 128 and name product of multiscale CT scan 128 slice. This modality has anode effective heat capacity of 30 MHU, anode heat storage capacity of 8 MHU and anode cooling rate of 1,608 KHU/min. This CT is generally used in hospitals in Indonesia. The CT Scan contrast tests began with preparing various mixtures of the NPs into the 10-ml tubesat equal concentrations each and placing them on the holder. In addition, CT Reader software was employed to process the resulting images. Comparative analyses were performed on the HU valuesof the variations. The modality used was Philips multiscale CT scan 128 slices (model of ingenuity core 128, United States). A polystyrene box was placed just on the CT table where the box center is parallel with the gantry isocenter. During the irradiation, the tube voltage and effective current were set at 80 kV and 100 mAs, separately, and the thickness of the slice was 0.6 mm.

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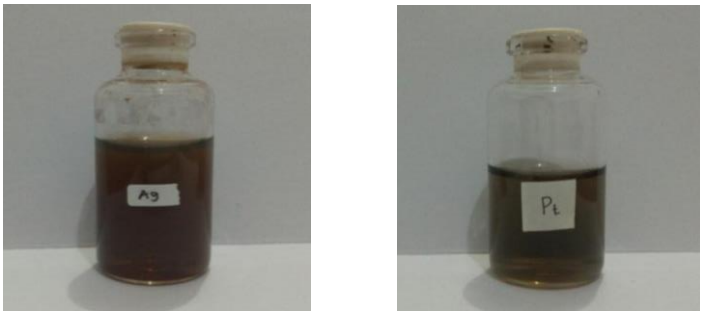
## RESULTS

The result shown in Fig. 2(a) is the dark, brownish-yellow Ag NPs colloid after 13 hours of pulsed-laser bombardment. By contrast, Fig. 2(b) shows a clear, brown Pt NPs colloid after10 hours of pulse laserbombardment onthe platinum sample.The shades also indicate the different levels of NPs concentrations: 30 ppm versus 20 ppm, respectively for Ag NPs and Pt NPs colloids. The colloidal concentrations were diluted using deionized water to achieve equalization before CT Scan tests could be performed.




**A** **b**

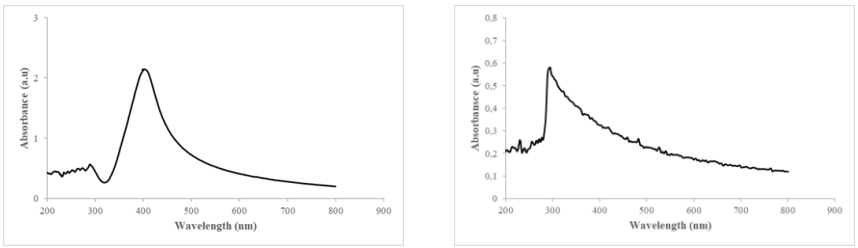
**Fig. 2.** (a) AgNPs and (b) PtNPs colloids

To obtain detailed information of produced colloidal Ag and Pt nanoparticles above, characterization of the produced Ag and Pt nanoparticles were further made using Ultraviolet-Visible spectroscopy (UV-Vis), Scanning Electron Microscope (SEM), and X-Ray Diffraction (XRD) methods.

### UV-Vis Examination

**Synthesis of colloidal silver, platinum, and mix..**

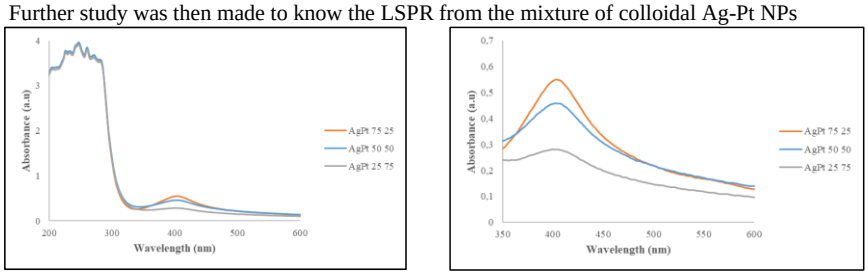
UV-Vis examines the optical characteristics of the object in terms of absorbance of UV and visible lights wavelengths, in which acquired parameters indicatethe object particlestypes and numbers [13]. First, optical characteristics of pure colloidal Ag and pure colloidal Pt NPs were examined. Figures 3 show UV-Vis absorption spectra obtained from (a) Ag and (b) Pt nanoparticles. It can be seen that for AgNPs, a high absorbance peak of 2.146 arbitrary units occurs at the wavelength of 403 nm. This peak is defined as the peak of localized surface plasmon resonance LSPR, which is an important parameter to identify the type of particles contained in a solution. As is known that silver has an LSPR peak of around 380 nm – 425 nm as reported here [23]. Figure 3(b) specifically confirms the sample as platinum material with an absorbance value of 0.6 a.u. The spectrum shows a structureless broadband extending toward the visible-ultraviolet wavelength range because Pt does not have any wavelength at UV-Vis region. The absorbance spectral image has a similar pattern with the spectrum obtained by Nellore et al [24].




**(a)** **(b)**

**Fig. 3.**UV-Vis spectra obtained from(a) colloidalAgNPs and (b) Pt NPs

Further study was then made to know the LSPR from the mixture of colloidal Ag-Pt NPs




**(a)** **(b)**

**Fig. 4.**(a)UV– Visspectraand (b) magnification of the spectra of a mixture of the Ag-Pt NPs colloidal with various volume ratio between Ag and Pt of 75:25% (red curve), 50:50% (blue curve), and 25:75% (grey curve)

The absorption peak at the wavelength of around 401-403 nm belongs to AgNPs as reported by Panacek et al. [23]. Therefore, with various concentration of AgNPs in the mixture of Ag-Pt NPs, the absorption intensity of AgNPs vary as shown in Fig. 4(b).

**XRD Examination**

The most frequently used among recent methods for material characterization, X-ray diffraction spectroscopy (XRD) identifies material crystalline phase by parameters specification of the lattice structure and obtains the particle sizesof nanocrystals. It is very handy for studying the crystal structure, chemical composition, and physical properties of nanomaterials [25].

**Synthesis of colloidal silver, platinum, and mix..**

Figure 5 shows the XRD spectra taken from (a) AgNPs, (b) PtNPs, and (d) Ag-Pt NPs. The spectral patterns of AgNPs, PtNPs, and Ag-Pt NPs produced from XRD method of the sample colloids have matched with the data from the previous study [26]. The XRD spectrographs below reveal the elemental and compound existences of the NPs in the colloids. For the Ag sample, the diffraction peaksshowed at 38.0328 (111), 44.2745 (200), and 64.6473 (220) as shown in Fig. 5(a), while for the Pt NPs, the diffraction peaks at 33.01 (111) and 66.4 (220) as shown in Fig. 5(b). Meanwhile, Ag-Pt NPs sample shows the diffraction peaks at 32.9 (111), 47.6 (200), 67.3 (220) as shown in Fig. 5(c). It can be seen in the spectrum that for Ag-Pt NPs mixture, other emission lines of Ag-Pt occurs, which indicated that the Ag-Pt NPs alloys are produced in this present work.

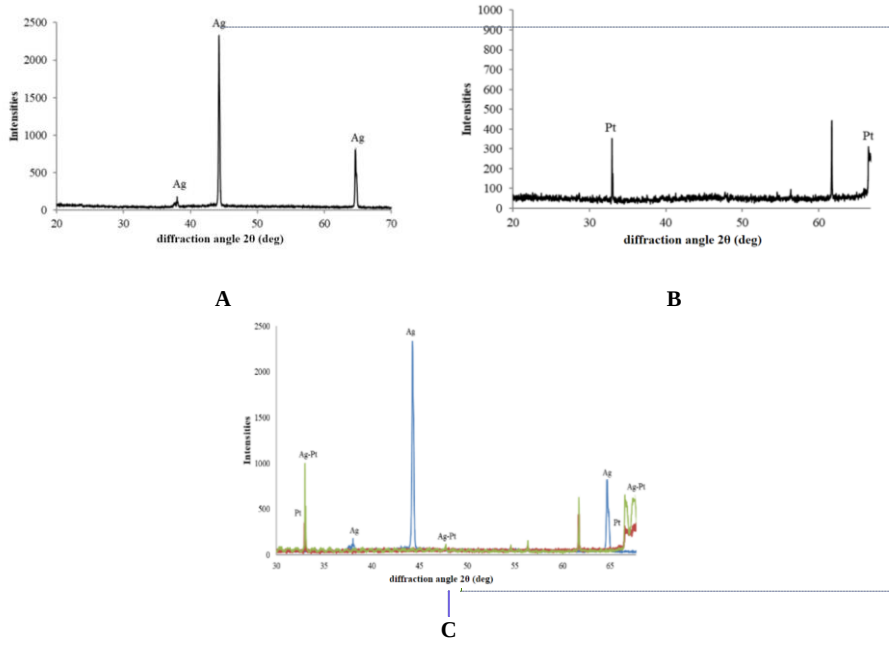



**Fig . 5.** XRD Spectra obtained from (a) AgNPs Sample (b) PtNPs Sample, and (c) Ag-Pt NPs Sample

**SEM Examination**

Scanning Electron Microscope (SEM) observed the morphology and determined the size of the NPs. SEM is an efficient method for specimens surfaceimaging. In this study, SEM processing was used with 2000 times magnification. In the case of platinum samples, preparation was performed using colloidal PtNPs produced bypulse laserbombardment at 10 Hz and 45 mJ for repetition rate and laser energy, respectively. A total of 1 ml PtNPs colloid was dripped on ± 0.5x0.5 $cm^2$ plate of *silica carbide* (SIC), followed by drying with Ovenat 100°C for 30 minutes. Scanning Electron Microscope-Energy Dispersive X-ray (SEM-Energy Dispersive X-ray) result of the colloidal PtNPs is shown in Fig.6(a).

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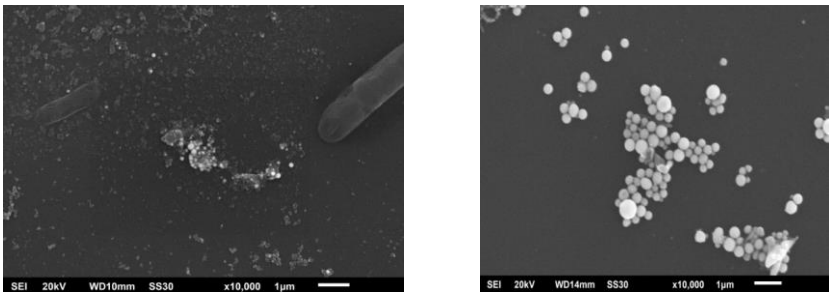
**Synthesis of colloidal silver, platinum, and mix..**




**a** **b**

**Fig. 6.** SEM-EDX images obtained from (a) colloidal PtNPs and (b) colloidal AgNPs

By using an imageJ processing, the averaged size of PtNPs is 20 nm with a standard deviation of 7 nm, morphologically in the form of brownish spheres as shown in Fig. 6(a). Figure 6(b) shows SEM-EDX image from the AgNPs colloid. The AgNPs have a spherical shape. Using an imageJ software, the diameter of AgNPsis estimated to be24 nm with a standard deviation of 5 nm, morphologically in the form of brownish spheres.After achieving colloids of AgNPs and PtNPs, both were homogeneously mixed and synthesized using the pulse laser ablation method at 10 Hz and 45 mJ to obtain a mixture of Ag-Pt NPs. Five variations of colloidal NPs were produced in the experiment with a volume ratio as follows; 100% AgNPs, 75%:25% Ag-PtNPs, 50%:50% Ag-PtNPs, 25%:75% Ag-Pt NPs, and100% PtNPs, each with a concentration of 10 ppm. All of the colloids achieved were inserted into 10ml-sized cylindrical vials.

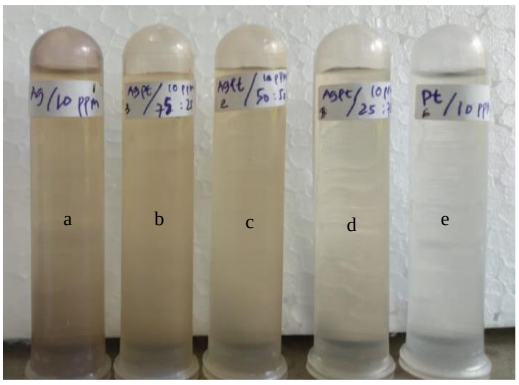



**Fig.7.**Sample Preparations of (a) 100% AgNPs colloid, (b) 75%:25% Ag-PtNPs colloid, (c) 50%:50% Ag-PtNPs colloid, (d) 25%:75% Ag-PtNPs colloid, and (e) 100% PtNPs colloid in 10ml-sized cylindrical vials

Different shades of the colloids in the tubes imply different NPs compositions. In the left end in Fig. 7, the 100% AgNPs colloid has the darkest, brownish-yellow shade, and in the other end, the 100% PtNPs colloid has the most contrastive, transparent, and bright shade. The shadeswere gradually fading and becoming brighter and transparent with the lowering of AgNPs concentration and the raising of PtNPs concentration in the colloid compositions. Hence, the darker the shade means the more AgNPs and the less PtNPs in the composition and, vice versa, the brighter the shade means the fewer AgNPs and the more PtNPs in it. In this phase, colloidal syntheses of AgNPs, PtNPs, and Ag-Pt NPs have been

successfully performed and the samples were readily prepared as contrast agents in CT Scan examination.

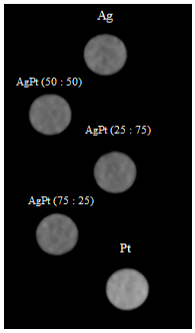



**Fig. 8.** Image results of AgNPs, PtNPs and Ag-PtNPs with variations of compositions as CT Scan contrast agents

The samples were then aligned and scanned by CT-scan simultaneously using a voltage of 80 kV and a current of 100 mAs. The image results depicted in Fig. 8 indicate the colloidal NPs' contrast property qualities in HU measurement, represented in the greyish shades. Darker greyish shades represent lower HU values, and vice-versa. The shades are associated with the number of X-ray photons passing through the body tissues which determine the variations of the dark and bright areas in the CT images. The dark areas are called the low-attenuated areas,while the bright areas are the high attenuated [12].

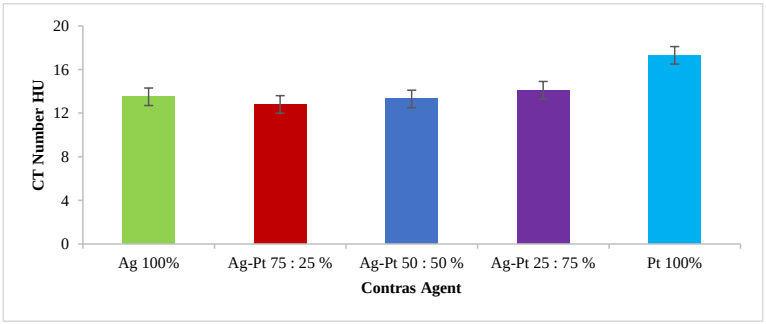



**Fig. 9.** CT Scan tests on contrast properties of 100% AgNPs, 75%:25% Ag-PtNPs, 50%:50% Ag-PtNPs, 25%:75% Ag-Pt NPs, and 100% PtNPs

Figure 9 shows HU values of 100% AgNPs, 75%:25% Ag-PtNPs, 50%:50% Ag-PtNPs, 25%:75% Ag-PtNPs, and 100% PtNPs. The CT Scan contrast properties for 100% AgNPs, 75%:25% Ag-PtNPs, 50%:50% Ag-PtNPs, 25%:75% Ag-Pt NPs, and 100% PtNPs colloid were measured by 13.5 HU, 12.8 HU,13.3 HU, 14.1 HU, and 17.3 HU, respectively. This result shows that the 100% PtNPs have the highest CT number is 17.3 HU compared to the case 100% AgNPs and other Ag-Pt NPs mixture with various volume ratios of Ag and Pt with P-value of 0.06. However, it has to be mentioned that the HU values of different NPs reported in this study are not considerably different. As a result, the shades of gray in CT image in Fig. 8 are looking similar.

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**Synthesis of colloidal silver, platinum, and mix..**

## DISCUSSION

Metal nanoparticles have recently been developed for specific applications of contrast agents in CT scans [3]. This is because nanoparticles have higher absorption than iodine with less bone and tissue interference achieving better contrast with lower X-ray dose. In this present work, we demonstrated the possibility of colloidal AgNPs, PtNPs, and Ag-Pt NPs mixture for contrast agent in CT scan. For this purpose, we have successfully synthesized those nanoparticles by using the pulse laser ablation technique. All colloidal AgNPs, PtNPs, and Ag-Pt NPs have spherical shapes (Fig. 6) with averaged diameters of 24 nm and 20 nm for AgNPs and PtNPs, respectively. The produced nanoparticles of AgNPs, PtNPs, and various volume ratios of Ag-Pt NPs mixture were then examined as CT contrast agents.

It is shown in Fig. 9 that colloidal PtNPs (PtNPs 100%) gain the highest CT number (HU) is 17.3 HU compared to the case of AgNPs 100% is 13.5 HU and Ag-Pt NPs with various volume ratios with a P-value of 0.06. Also, it should be noticed that the Ag-Pt NPs mixture containing a higher concentration of PtNPs (25%:75% Ag-Pt NPs) has higher CT number compared to the case of Ag-Pt NPs mixture containing higher AgNPs (75%:25% Ag-PtNPs). These findings confirmed that for a colloidal solution containing a high concentration of platinum (PtNPs only and colloidal Ag-Pt NPs mixture with a ratio of 25:75%) has higher x-ray absorbance compared to the case of AgNPs. The higher HU value for Platinium can be attributed to its higher density since the effective energy of 80 kVp (excitation voltage) is about 42 keV, which is much less than the K-edge (binding energy of an electron in K-shell) of Pt (K-edge ≈ 78 keV), which means that the attenuation of X-ray in Pt is due to Compton scattering dominantly.This phenomenon refers to the concept of attenuation coefficient [12], which states high atomic numbers as the one factor responsible for determining better contrasts on scanned tissues. This is explained in physics from the number of photons interacting with a structure, which are influenced by its thickness, density, and atomic numbers. The coefficient of attenuation will increase if the atomic number and density are increased [3]. The coefficient of attenuation greatly affects the attenuation value of X-rays measured in the units of Hounsfield Units (HU). With the NIST data of mass attenuation coefficients indicating 2.6 for silver (Z = 47) and 8.7 for platinum (Z = 78), the results of HU values for the colloidal NPs in this study have been appropriate. As reported by Jakhmola et al., elements with a high atomic number such as gold, silver, platinum, and other heavy metals (Thorium, bismuth, and tantalum) have a high possibility to be employed to enhance the image in CT scan. Lui et al. reported that silver nanoparticles having averaged diameter size of 16 nm displayed X-ray attenuation properties similar to that of iodine-based contrasting agents. For platinum nanoparticles, Chen et al. demonstrated that Pt nanoparticles mixed with Fe can be employed as a dual modal contrast agent of MRI and CT scan. The Pt NPs with averaged sizes ranging from 42-52 nm have higher HU value compared to the case of commercial iodinated contrast agent with the same concentration of 1 mM. In this present work, we used quiet low concentration of 10 ppm for ratio of Ag and Pt nanoparticles with that of water. This comparative study between Ag and Pt was made to evaluate which metal between them is suitable as a contrast agent in CT scan. For next study, we will perform in-vivo study using Ag and Pt nanoparticles with high concentration of around 15-20 times higher than those in this present work as contrast agents in CT scan.

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## CONCLUSION

The syntheses of Ag, Pt, and Ag-Pt NPs using pulsed laser ablation technique have been successfully carried out and produced spherical, colloidal nanoparticles (NPs). Comparative analysis among the NPs colloids' shades confirmed the higher AgNPs concentrations to be responsible for darker tones in the colloids, while the higher PtNPs for the brighter.The characteristics of Ag NPs, Pt NPs, and Ag-Pt NPs have been successfully demonstrated by UV Vis spectroscopy,which shows wavelengths of 403 nm and 294 nm respectively for Ag and Pt NPs. In addition, double waves appeared in the imaging graph of colloidal nanoparticle Ag-Pt NPs with wavelength values equal to those of individual UV-Vis testings of Ag and Pt NPs. The XRD analysis on the synthesized colloidal NPs

characteristics confirms the essential NPs compositions in the colloids.In addition, SEM examinations complete the information on the morphology and dimensions of the formed Ag and Pt NPs (each spherical with the average size of 24 nm and 20 nm). Contrast agent testings for the Ag, Pt, and variations of Ag-Pt NPs compositions have been performed *in vitro* in a CT Scan machine, involving five colloidal variations at a concentration of 10 ppm each: 100% AgNPs, 75%:25% Ag-PtNPs, 50%:50% Ag-PtNPs, 25%:75% Ag-Pt NPs, and 100% PtNPs. Results reveal the highest absorbent power was found in the colloidal contrast agent of Pt NPs, followed by the 25:75% Ag-Pt NPs. The higher HU value for Platinum can be attributed to its higher density since the effective energy of 80 kVp (excitation voltage) is about 42 keV, which is much less than the K-edge (binding energy of an electron in K-shell) of Pt (K-edge ≈ 78 keV), which means that the attenuation of X-ray in Pt is due to Compton scattering dominantly.

**ACKNOWLEDGMENTS**

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6. **Acknowledgment dari jurnal setelah mengirim balasan (22 Desember 2020)**

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Manuscript ID: IJMP-2009-1849 (R1)

Manuscript Title: **Synthesis of colloidal silver, platinum, and mixture of silver-platinum nanoparticles using pulsed laser ablation as contrast agent in computed tomography**

Authors: Ali Khumaeni,Mohammad Zamakhsari Alhamid,Choirul Anam,Ari Budiono

Date: 2020-09-06

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