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# Synthesis and characterization of PVP coated gadolinium oxide nanoparticles for imaging applications

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**Abstract.** In this work, we present the synthesis and applications of $Gd_2O_3$@PVP nanoparticles as an efficient contrast agent for MRI and CT techniques. $Gd_2O_3$@PVP nanoparticles have been successfully synthesized by the polyol method using ethylene glycol and poly(vinylpyrrolidone) as solvent and surfactant, respectively. The structure, morphology and characteristic properties of the materials are thoroughly investigated by SEM, TEM, UV-Vis, XRD, FTIR and DLS measurements. As an important result, NPs synthetized under optimized conditions have a diameter in the range of 12 nm and exhibit a good contrast signal in magnetic resonance imaging and computed tomography at relatively low concentration ([NPs] = 0.1 mM for MRI and 1.25 $mg.mL^{-1}$ for CT). In particular, the concentration of $Gd_2O_3$@PVP nanoparticles used in CT is 10 times lower than that of the commercial Iobitridol product (i.e., 12.5 mg.mL-1) to achieve similar signal intensity. This result has an important implication for reducing the dose of contrast agent introduced into the body. The obtained results suggest that PVP-coated $Gd_2O_3$ nanoparticles can be applied as multifunctional contrast agents for imaging diagnostic applications in the near future.

*Keywords:* $Gd_2O_3$ magnetic nanoparticles, MRI and CT, magnetic contrast, biocompatibility.

*Classification numbers*: 2.2.1, 2.4.3, 2.7.1.

## 1. INTRODUCTION

Among different medical imaging techniques, Magnetic Resonance Imaging (MRI) appears as one of the best candidates to visualize bio-target inside human body by means of magnetic

relaxation of proton measurement. However, one of the drawbacks of this technique is the low kinetic of magnetic relaxation process that could lead to a burden on patients. Thus, an urgent need in accelerating the magnetic relaxation is mandatory which allows to shorten the diagnosis time and to increase the applicability of the MRI [1]. Accordingly, contrast agents possessing large spin magnetic moments (e.g. 7.9 μB for $Gd^{3+)}$ have attracted widespread attention because their strong magnetic interaction with protons in the human body leads to the significant acceleration of the magnetic relaxation of these protons, thus defines and increases the magnetic contrast [2]. Commonly used contrast agents are based on gadolinium (Gd) complexes with linear or cyclic structures such as gadopentetate (trade name Magnevist), gadobenate (Multihance), gadodiamide (Omniscan), gadoteridole (Prohance) or gadobutrol (Gadovist). These are paramagnetic substances with small sizes, so they have the effect of increasing the speed of $R_1$ vertical recovery. The biggest disadvantage of $Gd^{3+}$ complexes is the release of toxic $Gd^{3+}$ ions due to weak chelates binding between $Gd^{3+}$ centers and surrounding organic particles. In addition, the number of paramagnetic centers in each complex molecule is limited (usually 1 $Gd^{3+}$ ion/complex molecule), in order to increase contrast, the amount of sample used will have a rather high concentration [3 - 5].

Recently, $Gd_2O_3$ nanoparticles have been of particular interest, for example in MRI application research due to their ability to improve positive contrast and less toxicity compared to the complex state. Possibly, this is because the number of $Gd^{3+}$paramagnetic centers (the positive contrast factor) per unit mass of the nanosized $Gd_2O_3$ (Gd content is about 60 %) is much larger than in the complex form (Gd accounts for about 10 - 16 %). Studies also show that nano-sized $Gd_2O_3$ is more chemically stable than $Gd^{3+}$ complexes [5].

The research has initially been successfully implemented; the positive contrast material system for MRI imaging has a large $R_1$ vertical recovery rate. It is biocompatible, stable in physiological environment. The practical applications based on the combination of $Gd_2O_3$ nanomaterials and biomedical molecules will be possibly potential. The obtained results are not only limited to basic research in the field of diagnostic imaging, such as MRI, computed tomorgraphy (CT), but also become a premise for realizing the application of nanotechnology in treatment (leading to drug delivery, thermotherapy) and diagnostic imaging [6-8].

Currently, there are many methods of synthesizing nanoparticles in general and $Gd_2O_3$ in particular. They are co-precipitation, microemulsion, polyol and thermal decomposition methods in organic solvents. Each method has advantages and disadvantages [7 - 9]. Among them, the polyol method is a relatively effective approach to synthesize nanoparticles with sizes from 2 to 15 nm, in which the formation and size growth of nanoparticles is easily controlled by controlling the factors affecting the chemical reaction such as temperature and reaction time [10-12]. Besides, the solvents commonly used in the polyol method are multifunctional alcohols such as ethylene glycol, diethylene glycol or polyethylene glycol which in some cases act as metal ion reducing agents. At the same time, they also act as the surface coating to protect the nanoparticles from agglomeration and prevent the formation of hydroxides.

In this study, polyol method is used to study the fabrication of $Gd_2O_3$ nanoparticles for MRI and CT imaging applications. The obtained $Gd_2O_3$ nanoparticle surfaces were then encapsulated with polyvinylpyrrolidone (PVP) polymer as a bio-responsive shell. This hydrophobic encapsulation controls surface charge and cytocompatibility of NPs *in vivo*. PVP is known as an inert, non-poisonous, heat-resistant, stable to pH, biocompatible and biodegradable polymer. It contains a hydrophilic component (pyrrolidone base) and a significantly hydrophobic group (alkyl group). There are highly polar amide groups in the pyrrolidone ring, apolar methylene and methane groups along its backbone. It is well known to be a stabilizer to prevent the aggregation

of nanoparticles because of steric hindrance effect. The characterizations of the $Gd_2O_3$@PVP sample such as size, morphology and surface properties were investigated using scanning electron microscopy (SEM), transmission electron microscopy (TEM), X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FT-IR), dynamic light scattering (DLS) and Zeta potential measurements. The ability to increase contrast of nanofluids obtained in MRI and CT imaging techniques is investigated.

## 2. MATERIALS AND METHODS

### 2.1. Materials

Gadolinium (III) acetate (99.9 %), sodium hydroxide (NaOH), ethylene glycol (EG), polyvinylpyrrolidone (PVP) were purchased from Sigma-Aldrich (Singapore) and were used as received without any further treatments.

### 2.2. Preparation of $Gd_2O_3$@PVP nanoparticles

In a round flask, 8 mmol (3.25 g) of gadolinium acetate ($Gd(CH_3CO_2)_3.4H_2O$) was poured into 50 mL of ethylene glycol (EG) solvent. The mixture was rigorously stirred until the precursor was completely dissolved. Then, 10 mL of an aqueous solution containing 0.8 g of NaOH and 2.0 g of PVP was added. The mixture was heated at 140 $^oC$ for 1 hour. Then the entire product was transferred to a Teflon lined stainless steel autoclave followed by a second heating step at a fixed temperature, ranging from 150 $^oC$ to 240 $^oC$ for 4 - 8 hours. Afterwards, the mixture was cooled down to room temperature and $Gd_2O_3$ nanoparticles were collected by centrifugation at 10,000 rpm for 8 minutes and washed 3 - 4 times with distilled water.

### 2.3. Characterization

The $Gd_2O_3$ nanoparticle morphology was studied by Transmission Electron microscopy (TEM, JEM1010-JEOL) and Scanning Electron Microscopy (SEM, Hitachi S-4800). X-ray diffraction method was used to investigate the crystal structure and phase composition of $Gd_2O_3$ nanoparticles. The UV-Vis spectra of the samples were recorded on a Jasco V-670 spectrometer. Fourier transform infrared (FT-IR) spectra were recorded using a Nicolet 6700 spectrometer. Dynamic light scattering (DLS) and zeta potential measurement were used to investigate the distribution and stability of $Gd_2O_3$ nanoparticles in aqueous medium.

The clinical 1.5T MRI scanner (Siemens Magnetom, Germany) and 128-Somatom Perspective CT scanner (Siemens, Germany) were used to measure longitudinal relaxation ($r_1$) and CT images of the $Gd_2O_3$@PVP sample, respectively.

## 3. RESULTS AND DISCUSSION

### 3.1. Characterization of PVP coated $Gd_2O_3$ nanoparticles

The reaction temperature is an important factor affecting the shape and the size development of nanoparticles. The reactions were conducted at 150 ºC, 180 ºC, 200 ºC, and 240 ºC. Figure 1 shows the SEM images of the obtained samples. From these SEM images, it can be seen that the nanoparticles obtained by the polyol method in ethylene glycol are spherical, at 150 ºC, the obtained particles are large in size and stick together (Figure 1a). The

nanoparticles become smaller at 180 $^{o}$C, but the size is still quite large (Figure 1b). When the reaction temperature is increased to 200 $^{o}$C, the particles are much smaller with a fairly uniform size of about 10 nm. The decrease in particle size with reaction temperature can be explained that at a high temperature, the diffusion rate of $Gd^{3+}$ ions increases leading to the formation of many small nuclei in solution and reduces the $Gd^{3+}$ source to feed up for the growth stage of nanoparticles and thus smaller nanoparticles are obtained. However, when the temperature continues to increase to 240 $^{o}$C, the size of $Gd_2O_3$ nanoparticles is larger, but the obtained particles still have a spherical shape with a size of about 20 - 30 nm. This can be explained that for temperatures higher than 200 $^{o}$C, the decomposition of $Gd(CH_3COO)_3$ precursors takes place faster, leading to the formation of a large number of $Gd^{3+}$ cations in solution, and as a result, this abundant source of $Gd^{3+}$ is available for further growth of nanoparticles. The result is the formation of larger sized particles.

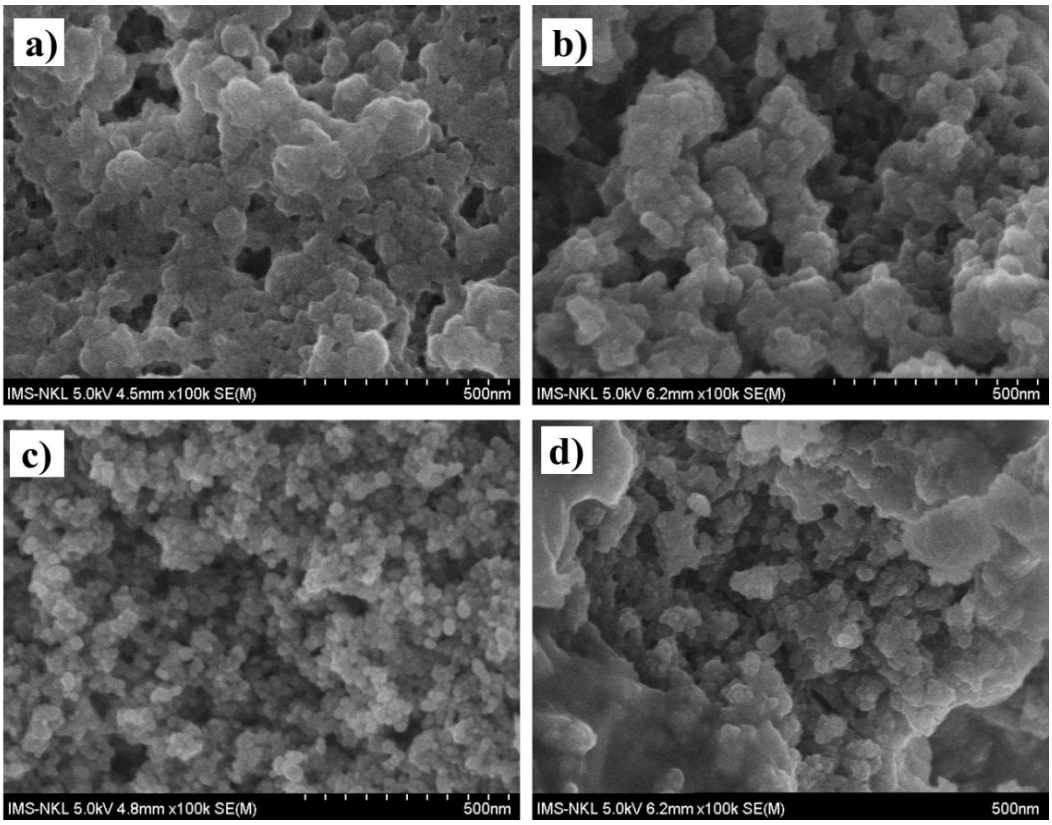


*Figure 1.* SEM images of $Gd_2O_3$ nanoparticles synthesized at (a) 150 ºC, (b) 180 ºC, (c) 200 ºC, and (d) 240 ºC for 6 hours.

After choosing the suitable temperature of 200 $^{o}$C for the synthesis of $Gd_2O_3$ nanoparticles, the reaction time is the subject of further investigation. The reaction time is varied to be 4 hours, 6 hours and 8 hours. The SEM images of the $Gd_2O_3$ samples are shown in Figure 2. From the results obtained, after a reaction time of 4 hours (Figure 2a), the particle size is still large, some large clusters exist, the morphology is uneven, and these clusters seem to be complex, not yet reacted. For a reaction time of 6 hours, the nanoparticles are smaller in size (about less than 10 nm) and have a uniform spherical shape (Figure 2b). Possibly, the short reaction time (4 hours)

is not long enough for a complete reaction. It can be seen that the duration of 6 hours is the optimal reaction time for the formation, division, and crystallization of $Gd_2O_3$ nanoparticles at the reaction temperature of 200 $^oC$. However, as can be seen in Figure 2c, for longer reaction time (8 hours), the particles collide with each other, then stick together to form large particles.

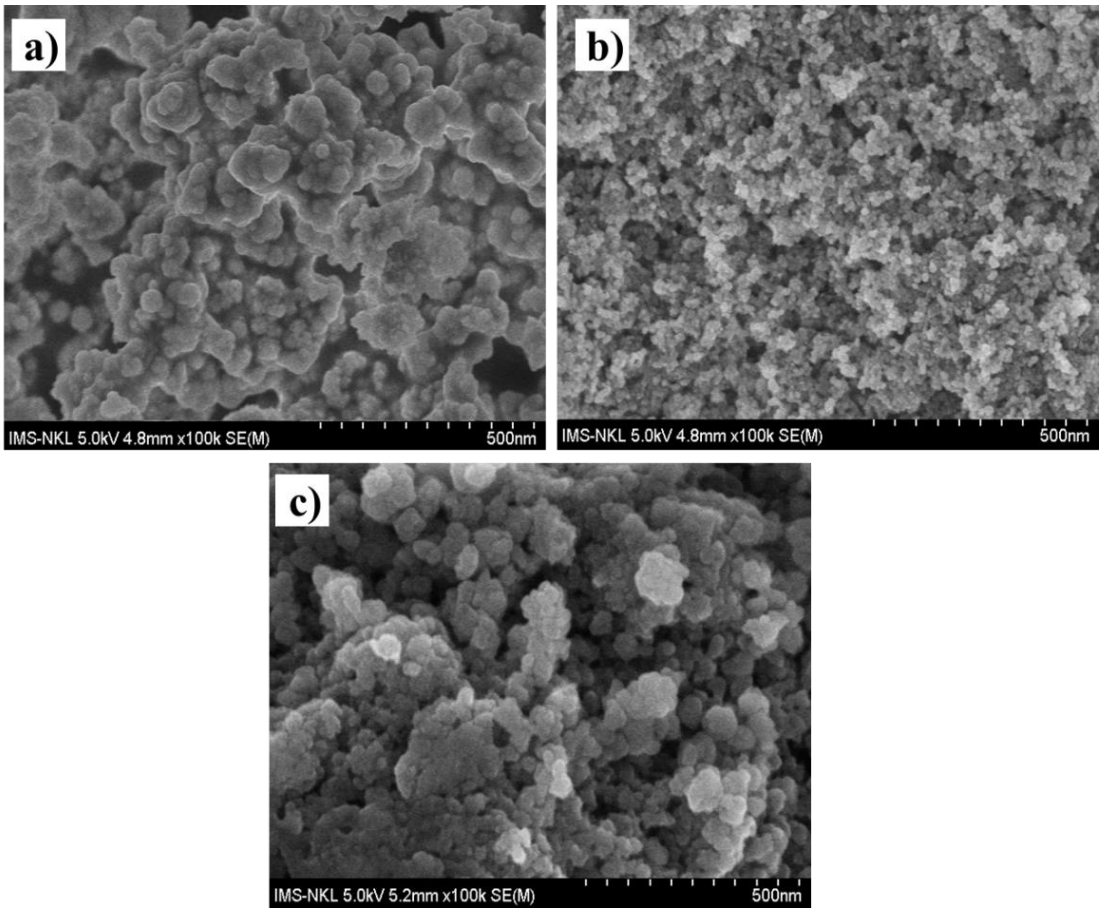


*Figure 2.* SEM images of $Gd_2O_3$ nanoparticles synthesized at a temperature of 200 $^oC$ with reaction times of 4 hours (a), 6 hours (b), and 8 hours (c).

For application as a contrast agent in MRI and CT scanning techniques, the surface of $Gd_2O_3$ nanoparticles is encapsulated with polyvinylpyrrolidone (PVP) polymer as a biocompatible shell. This shell not only prevents the release of harmful $Gd^{+3}$ ions into the body and regulates the interaction of water molecules with $Gd^{+3}$ ions on the particle surface, but also protects the nanoparticles from the agglomeration. Figure 3 shows the TEM images and size distribution diagram of the $Gd_2O_3$ nanoparticles with and without using PVP under the same synthesis conditions. From Figure 3a, it can be observed that in the absence of PVP, the $Gd_2O_3$ nanoparticles are clustered together to form large clusters with a size of approximately 100 nm. In contrast, in the presence of PVP, the shape of the obtained $Gd_2O_3$ nanoparticles is almost spherical. They are relatively small and highly uniform. Besides, it can be found that each $Gd_2O_3$ nanoparticle has an organic shell on its surface and the average size of each $Gd_2O_3$@PVP nanoparticle is about 12.5 nm (Figures 3b, 3c).

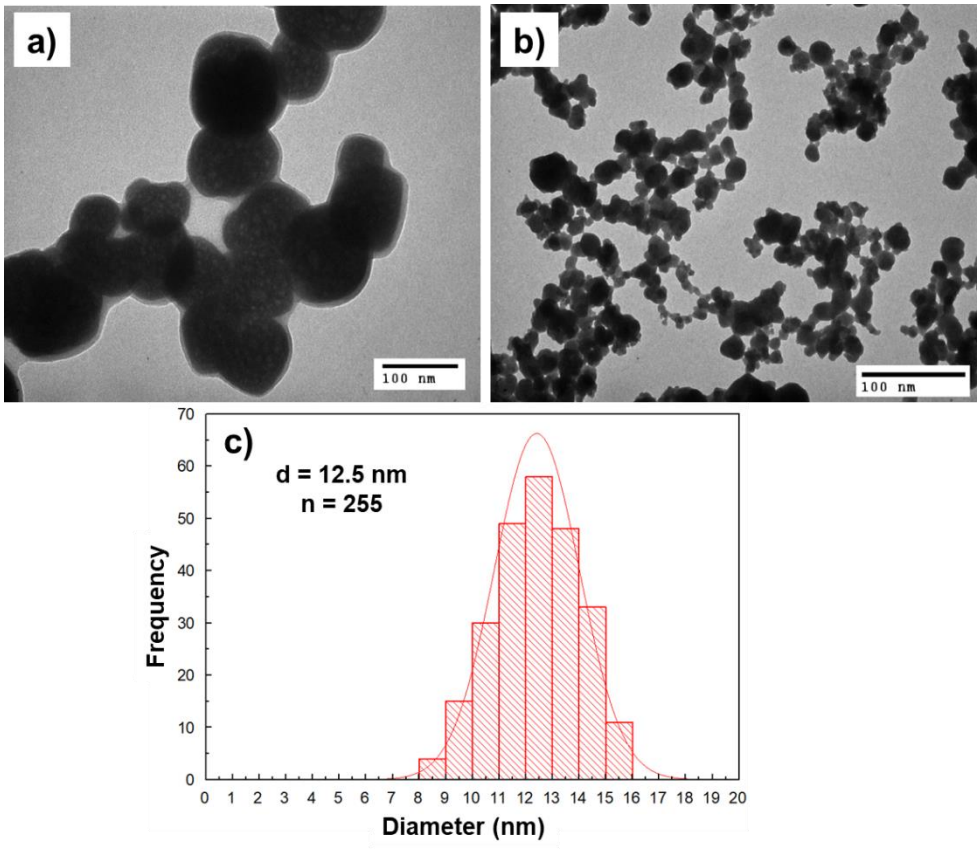


*Figure 3.* TEM images of samples $Gd_2O_3$ (a), $Gd_2O_3$@PVP (b) and size distribution histogram of $Gd_2O_3$@PVP at 200 $^oC$ for 6 hours.

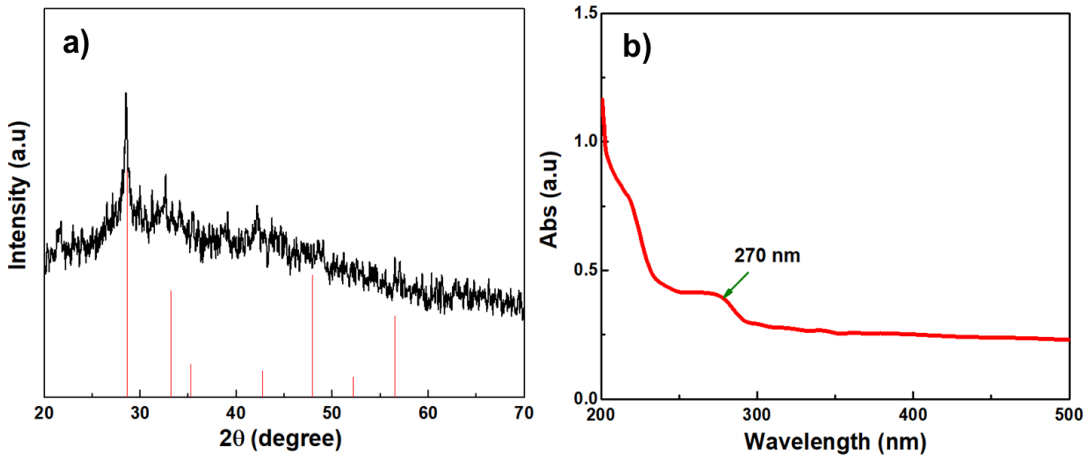


*Figure 4*. X-ray diffraction pattern (a) and UV-Vis spectrum (b) of $Gd_2O_3$ nanoparticles synthesized at 200 $^oC$ for 6 hours.

Figure 4a shows the X-ray diffraction pattern of the synthesized $Gd_2O_3$ particles. The obtained results show peaks at diffraction angles of 28.5; 32.6; 35.3; 46.2; and 56.5, corresponding to the lattice planes of (222), (400), (411), (440), and (622), respectively, in the

cubic structure of $Gd_2O_3$. In addition, Figure 4b shows the absorption spectrum of $Gd_2O_3$ nanoparticles at wavelengths between 200 and 500 nm. The absorption edge can be observed in the UV region at 270 nm, which is the characteristic absorption wavelength of microscopic $Gd_2O_3$ nanoparticles. Besides, in the sample, there is also an impressive small peak in the absorption spectrum at position 230 nm, which is an insignificant peak of the remaining solvent.

To determine the binding capacity between solvent molecules and PVP on the nanoparticle surface, we carried out an FT-IR analysis of the $Gd_2O_3$@PVP sample. The results are shown in Figure 5a. The peaks at 2922 $cm^{-1}$ and 2854 $cm^{-1}$ are the absorption site of the symmetric bond and the asymmetric bond of C-H. The peak position at 3457 $cm^{-1}$ of O-H shows the water-absorbed surface of the particles. At 1568 $cm^{-1}$ and 1402 $cm^{-1}$ on the FT-IR spectra, there is asymmetric and symmetric contraction. The peak corresponding to the contraction of functional group (COO-) locates at 1078 $cm^{-1}$. It shows the presence of C-O bonds on the grain surface. More specifically, the infrared spectrum of PVP-coated particles has an absorption peak at position 1648 $cm^{-1}$ corresponding to the amide group of PVP formed by C=O and C-N bonds. This combination leads to the absorption peak in shift relating to the absorption peak of C=O (1750 $cm^{-1}$ – 1700 $cm^{-1}$). Furthermore, there is a strong absorption band at the peak position of 613 $cm^{-1}$. This peak indicates the presence of Gd-O oscillation of $Gd_2O_3$. The above analysis results are consistent with previous studies other authors on using PVP coating agents [13] on nanoparticle systems. From the position of the characteristic absorption peaks of the bonds (C-H), (C-O), (N-C=O), functional groups (COO-) appearing on the corresponding coated sample, it proves that the $Gd_2O_3$ nanoparticle surface was successfully functionalized by PVP coating.

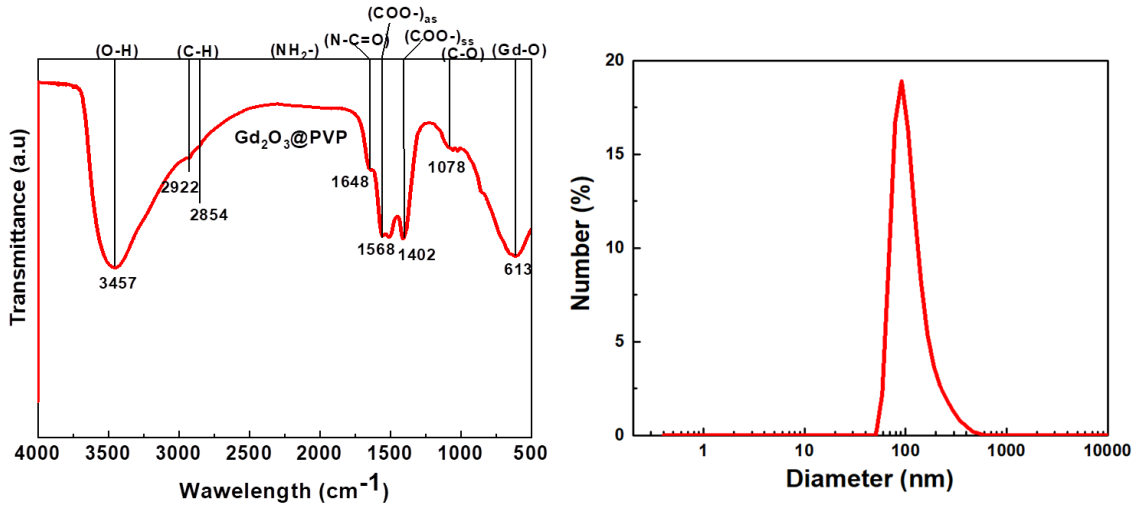


*Figure 5*. FT-IR spectra (a) and DLS spectrum (b) of $Gd_2O_3$@PVP nanoparticles formed at a temperature of 200 $^oC$ and reaction time of 6 hours.

Dynamic light scattering is used to analyze and evaluate the hydrodynamic size of $Gd_2O_3$@PVP nanoparticles dispersed in water, as shown in Figure 5b. The water-dispersed $Gd_2O_3$@PVP nanoparticle has an average diameter of 91.2 nm with a sharp peak and high concentration. Besides, the Zeta potential value of the $Gd_2O_3$@PVP sample is +19.5 mV with 100 % area, indicating good dispersion and stability in their aqueous environment.

### 3.2. Imaging applications

### *3.2.1. Application of $Gd_2O_3$@PVP for magnetic resonance imaging*

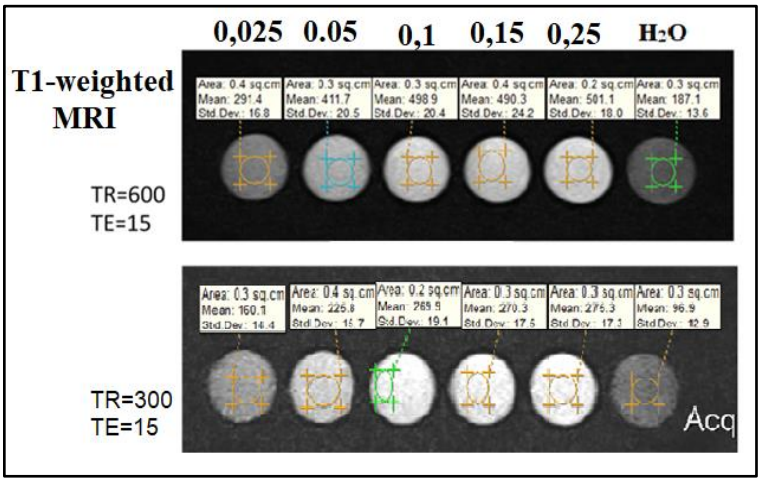


*Figure 6.* MRI images using different concentrations in TE = 15 TR = 300 and TE = 15 TR = 600 imaging modes.

Figure 6 shows the results of the contrast agent for the MRI technique test applying the $Gd_2O_3$@PVP nanoparticle sample. The sample with a concentration of 0.025 mM affects the contrast signal. There is an excellent contrast even at a concentration of 0.1 mM when TR = 300 ms and at 0.05 mM when TR = 600 ms. The increased concentrations change almost negligibly because the contrast of the sample is maximum. Thus, it can be said that the $Gd_2O_3$@PVP nanoparticle used in the MRI technique could make an increase in the potential $R_1$ recovery. Moreover, nanoparticles from $Gd_2O_3$ coated with PVP biocompatible substance are introduced into the body in a smaller amount, so it is safer.

### *3.2.2. Application of $Gd_2O_3$@PVP for computed tomography scan*

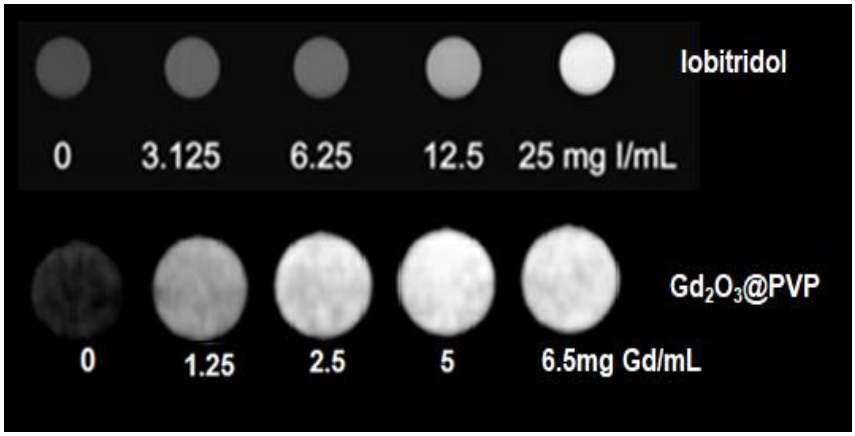


*Figure 7.* CT scan using commercial Iobitridol and synthetic $Gd_2O_3$@PVP at 200 ºC for 6 hours.

Figure 7 shows the CT images of a commercial Iobitridol sample and a $Gd_2O_3$@PVP sample. The obtained result indicates that the $Gd_2O_3$@PVP sample has better potential CT

scanning applications than the commercial sample. Specifically, a concentration of 1.25 mg/mL gives a good CT signal with an intensity equal to the signal of a commercial Iobitridol sample at a concentration of 12.5 mg/mL. The signal of 5 mg/mL - $Gd_2O_3$@PVP sample is as good as that of 25 mg/mL - commercial sample. It can be seen that the small-sized spherical $Gd_2O_3$@PVP nanoparticle is superior with good X-ray dispersion and absorption. Thus, the liquid sample from $Gd_2O_3$@PVP provides a potential good contrast for CT techniques.

## 4. CONCLUSIONS

$Gd_2O_3$ nanoparticles are successfully synthesized by the polyol method in the presence of EG. The obtained $Gd_2O_3$ nanoparticles with a size of 12 nm are introduced into the aqueous medium by the ligand exchange method using PVP phase transition agent. Thanks to their small $Gd_2O_3$ core size and hydrophilic PVP coating, the $Gd_2O_3$@PVP nanoparticles show a significant improvement in increasing the contrast in MRI and CT scans. The results of MRI and CT scans show excellent image quality, much better than the commercial complexes in use even at high concentrations. This result has implications for reducing the dose of contrast agent in vivo in both MRI and CT imaging modalities. This is also a prerequisite result for the study of dual contrast agents for multimodal imaging applications (combining MRI and CT at the same time).

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***CRediT authorship contribution statement.*** Nguyen Thi Thuy Khue: Methodology, Investigation, Funding acquisition. Le Thi Thanh Tam: Experiment, writing the manuscript. Ngo Thanh Dung: Formal analysis. Nguyen Thi Ngoc Linh: Experiment. Nguyen Tuan Dung: Formal analysis. Le The Tam: MRI and CT. Le Trong Lu: writing-review and editing, supervision.

***Declaration of competing interest.*** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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