Water soluble gold nanoparticles based high relaxivity MRI contrast agents

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Abstract
Magnetic resonance imaging (MRI) is one of the modern diagnostic techniques that are being used for differentiating between normal and abnormal tissues. The sensitivity of MRI can be enhanced by the use of contrast agents. In this article, the synthesis and characterisation of new derivatives of gold nanoparticles for applications as MRI contrast agents is reported. Gold nanoparticles stabilised by dimethylaminopyridine (DMAP) molecules were prepared by reduction method. These nanoparticles were characterised by UV-visible spectroscopy, transmission electron microscopy (TEM) and thermogravimetric analysis (TGA). The presence of surface plasmon band at 525–530 nm in UV-visible spectra confirmed the formation of stable gold nanoparticles. Similarly, the TEM images showed the well dispersed spherical gold nanoparticles. The average diameter of AuNPs as calculated from TEM image analysis was found 2.25 nm. The DMAP molecules were then replaced by Gd-DTPA chelates along with butanethiol molecules. The butanethiol molecules are responsible for restricted tumbling of Gd-DTPA chelates that resulted in the 38% increase in relaxivity of gold nanoparticles based MRI contrast agents.

1. Introduction

Nanoscience and nanotechnology playing significant role since last few decades in almost all fields of science i.e. electronic industry [1, 2], medical diagnosis and therapy [3, 4], catalysis [5], energy storage [6], energy conversion [7] etc. Medical diagnosis and therapy is attracting significant attention of the researchers working in the nanotechnology sector. Magnetic resonance imaging (MRI) is modern medical diagnosis technique which is in clinical practice since last many years. It has several advantages as compared to other diagnostic techniques like computed tomography (CT) scan and conventional x-rays. Although these both techniques are also non-invasive however they involved the use of x-rays that have sufficient high energy and are ionizing radiations [8, 9]. On the other hand the MRI involves the use of radio-waves that are extremely non-toxic and have significantly less energy as compared to even visible radiations. The MRI scan is carried out in the presence of strong magnetic field. It is based on nuclear magnetic resonance (NMR) spectroscopy. Widespread applications of MRI are hampered due to its inherent low sensitivity. This issue of MRI can be solved by use of paramagnetic substances known as contrast agents [10, 11]. Most commonly used MRI contrast agents is Gd-diethylenetriaminepentaacetic acid (GD-DTPA). The main reason of using Gd³⁺ based chelates is the presence of maximum number of unpaired electrons i.e. 7 in Gd³⁺. Therefore the Gd-chelates have maximum value of magnetic moment. Further, both kinetically and thermodynamically the Gd-chelates are stable. Another important feature of Gd³⁺ is the electronic relaxation time. The electronic relaxation of Gd³⁺ is much higher (∼10⁻⁹ s) as compared with other rare earth cations such as Dy³⁺, Eu³⁺ and Ho³⁺ (∼10⁻¹³ s). These special characteristics make the Gd-DTPA based compounds for applications as MRI contrast agents. The Gd-DTPA chelates are routinely used in MRI scans [12]. The efficiency of MRI contrast agents is evaluated in terms of relaxivity, which is the ability of contrast agent to increase the relaxation rate of surrounding protons. The relaxivity is expressed as mM⁻¹ s⁻¹. The relaxivity of Gd-DTPA is 4.2 mM⁻¹ s⁻¹ [13]. This relaxivity is very low;
therefore the dose of MRI contrast agent used is significantly high. This dose can be reduced by increasing the
relaxivity of contrast agents. Many strategies have been adopted by researchers to cope this issue of contrast
agents. For example, Liposomes based contrast agents have been reported in the literature [14]. They were
selected because of their extended circulation time in body. However, they could not be commercialized due to
their hampered relaxivity [15]. Micelles based MRI contrast agents were also studied, however no significant
enhancement in relaxivity was observed. Dendrimers, zeolites based and silica based MRI contrast agents were
also evaluated for clinical applications [16–18]. However they could not get much attention due to many
miscellaneous reasons. These reasons include the reduced water exchange rate between paramagnetic center and
surrounding water, toxicity, stability etc. Metal nanoparticles have also been evaluated for MRI applications as
contrast agents. Among various metals, the iron and gold are most important. Iron based contrast agents are
usually referred as T2-contrast agents and the gold nanoparticles based contrast agents are referred as T1-
contrast agents. The main reason of selection of gold nanoparticles is that at the surface of a single gold
nanoparticle, several Gd-DTPA chelates can be loaded. Thus the dose of contrast agents is expected to be
reduced significantly. First report of gold nanoparticles based MRI contrast agents was appeared in 2006 [19, 20].
This in report the dithiolated-DTPA multilayered gold nanoparticles with diameter 2–2.5 nm were reported. On
these gold nanoparticles ca. 150 gadolinium ions per nanoparticle can be loaded. These gold nanoparticles based
contrast agents showed ~30% increase in relaxivity as compared to commercially available Gd-DTPA chelates.
This increase was not as much as significant as it was hypothesized. This might be due to the relatively fast
tumbling of Gd-chelates at gold nanoparticles surface. The same authors reported their second paper on gold
nanoparticles based MRI contrast agents [20]. However, still they were not much successful. Park et al [21] also
published their paper on gold nanoparticles based MRI contrast agents that involved the use of DTPA
conjugated with glutathione. The size of gold nanoparticles was 5–7 nm. They calculated their relaxivity 17.9
mM⁻¹ s⁻¹ that was almost fivefold higher than Omniscan® (3.30 mM⁻¹ s⁻¹). They further extended their study
by using relatively large sized gold nanoparticles and on these particles almost 3000 Gd-chelates can be loaded
[22]. Based on this brief account of gold nanoparticles based MRI contrast agents, it is suggested that still there is
significant gap, which has not been explored regarding further enhancement in efficiency of gold nanoparticles
based MRI contrast agents. The efficiency of these contrast agents was also not found very much high as
compared to commercially available Gd-DTPA chelates. This might be due to the relatively fast tumbling of Gd-DTPA
chelates at gold nanoparticles surface [4, 23, 24]. The efficiency of gold nanoparticles can be enhanced by
controlling the tumbling at gold nanoparticles surface. There are various strategies to enhance the relaxivity/efficiency
gold nanoparticles based MRI contrast agents.

Here in this article, I plan to discuss the synthesis, characterization of dimethylaminopyridine (DMPA)
stabilized gold nanoparticles. The DMPA ligand molecules were then replaced by Gd-DTPA based chelates
along with insertion of butanethiol molecules to obtain the gold nanoparticles based MRI contrast agents with
enhanced relaxivity. This strategy has not been reported earlier to tailor the relaxivity of gold nanoparticles based
MRI contrast agents.

2. Experimental work

The synthesis of DMAP@AuNPs involve the following two steps. In first step the gold nanoparticles stabilized by
tetraoctylammoniumbromide ligand molecules were prepared. In second step the replacement of TOABr
molecules with DMAP molecules by ligand exchange approach was carried out [3, 25]. The synthesis of
DMAP@AuNPs is illustrated in scheme 1. Following chemicals were used for synthesis of DMAP@AuNPs as
received without further purification: HAuCl₄·xH₂O (99.99%, Sigma-Aldrich), NaBH₄ (>99%, Fluka),
4-dimethylaminopyridine (≥99% Sigma-Aldrich), tetraoctylammoniumbromide (99% Sigma-Aldrich) and
deionized water.

Step 1. TOABr@AuNPs

AuNPs stabilized by tetraoctylammonium bromide ligand molecules were synthesized by following the
modified literature protocol [26]. About 20 cm³ of 30 × 10⁻³ M aqueous solution of HAuCl₄ was taken in 50
cm³ round bottom flask. To this flask, the tetraoctylammonium bromide solution in toluene (70 cm³,
20 × 10⁻³ M) was added. The stirring on magnetic stirrer at room temperature was carried out until all the gold
ions had transferred to organic phase by tetraoctylammonium bromide. Sodium bromide freshly prepared
aqueous solution (4 × 10⁻⁴ M, 20 cm³) was added into the biphasic mixture of gold ions in aqueous-toluene in
~5 min. Upon the addition of reducing agent NaBH₄, the colour of organic phase became red. The reaction
mixture was further stirred for 2 h. The organic phase was separated from aqueous phase. The organic phase was
washed with deionized water several times to remove the soluble salts following by drying using anhydrous
sodium sulphate.

Step 2. DMAP@AuNPs
The TOABr molecules were replaced from gold nanoparticles surface by DMAP molecules by following literature procedure [25]. The above prepared TOABr@AuNPs solution was taken in 250 cm$^3$ round bottom flask. To this solution, about 100 cm$^3$ of 1 × 10$^{-4}$ M solution of 4-dimethylaminopyridine was added under constant stirring. As the DMAP solution was added, the colour of the solution became ruby red. This change in colour confirmed the replacement of TOABr with DMAP and also the phase transfer from organic to aqueous. DMAP stabilized gold nanoparticles are soluble in aqueous medium. The DMAP@AuNPs obtained were stored at 4°C for further study.

DMAP@AuNPs (AuNPs-II) (20 mg in 20 cm$^3$ deionized water) were taken in a round bottom flask. To this Gd-DTPA chelates solution was added in large excess (5 times larger than that of DMAP ligand molecules). The vigorous stirring was carried out for 4–5 h at room temperature. Analogues Gd-DTPA based chelates used in this study has been already been reported [27]. The extra ligand molecules (both DMAP, Gd-DTPA chelates) were removed by size exclusion chromatography. The insertion of butanethiol molecules (AuNPs-III) were carried out by exploiting the more affiliation of thiol containing compounds with gold surface. Suitable amount of Gd-DTPA@AuNPs (20 mg, in 30 cm$^3$ of deionized water) was taken. To this amount of gold nanoparticles suspension, the required volume of butanethiol (0.5 mM) was added. The vigorous stirring was carried out at room temperature for 4–5 h. The size exclusion chromatography was carried out to purify the butanethiol-Gd-DTPA@AuNPs. The entire process of synthesis of AuNPS-II and AuNPs-III is depicted in Scheme 2.

3. Results and discussion

3.1. UV-visible spectral analysis

The UV-visible spectra of all AuNPs i.e. AuNPs-I, AuNPs-II and AuNPs-III were carried out using dual beam Cary-60 UV-visible spectrometer at room temperature. All these spectra are shown in figure 1. The wavelength range was kept 400–800 nm. All these particles exhibit well resolved surface plasmon band in the range of 520–525 nm. The presence of surface Plasmon band (SPB) at the wave length 520–525 nm confirmed the formation of AuNPs. This band was absent in aqueous gold solution.

3.2. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was carried out in the temperature range 25 °C to 600 °C using SDT Q600 V8.2 Build 100 thermal analyzer. The TGA was done to estimate the amount of ligand present at the gold nanoparticles surface. From the amount of the ligand molecules, the relaxivity per nanoparticles could be calculated easily. The TGA curves of AuNPs-I and AuNPs-II are shown in figure 2. The TGA for AuNPs-I...
(TOABr@AuNPs) exhibited that the weight loss was observed for AuNPs-I was slightly higher as compared to that of AuNPs-II (DMAP@AuNPs). The weight loss was observed in the range of 200 °C to 400 °C. From the weight loss, and the gold nanoparticles size, the empirical formula of a gold nanoparticle can be calculated.

3.3. Transmission electron microscopic (TEM) analysis

Transmission electron microscopic (TEM) analysis was done on Jeol JEM 2100 F electron microscope. Sample preparation of gold nanoparticles was carried out using copper grids as conducting substrates. A drop of gold nanoparticles suspension was mounted on the copper grid and then was allowed to evaporate the water molecules. Typically, the TEM analysis of AuNPs-II (Gd-DTPA@AuNPs) was carried out. The main purpose of TEM analysis was to know the diameter of the gold nanoparticles and the estimation of morphological behaviour. The TEM image along with histogram is shown in figure 3. The TEM image confirmed that gold nanoparticles (Gd-DTPA@AuNPs) are spherical in morphology. All the observed gold nanoparticles are well dispersed. No aggregation was observed. From the TEM image, the diameter of almost all gold nanoparticles was determined. From the obtained data, the histogram was plotted (figure 3). The average diameter from the histogram was found 2.25 nm.
Figure 1. UV-Visible Spectra of AuNPs-I, AuNPs-II and AuNPs-III.

Figure 2. TGA curves for DMAP@AuNPs and TOABr@AuNPs.

Figure 3. TEM image of typical sample of AuNPs (AuNPs-II).

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3.4. Relaxivity measurements

The efficiency of a contrast agent is expressed in terms of relaxivity. MRI contrast agents comprise the two main parts. The first part is metal center. Highly paramagnetic metals for this purpose are selected such as Fe$^{3+}$, Mn$^{2+}$, and Gd$^{3+}$ [28–30]. Among these three metal ions, the most common used is Gd$^{3+}$. The second part of MRI contrast agents is ligand. The purpose of the ligand is to protect the metal ions to bind with other species such as hemoglobin etc. Free metal ions are extremely toxic. Initially the ethylenediaminetetracetic acid (EDTA) and its analogues were studied for the purpose of MRI contrast agents. However, the stability of Gd-EDTA and their analogues was not up to the required level. Therefore the search for the other ligands was started and finally diethylenetriaminepentaacetic acid (DTPA) was selected. The Gd-DTPA chelate has been approved for clinical purpose and is routinely used as contrast agents during MRI scans. Apart from Gd-DTPA, there are few other Gd$^{3+}$ and Fe$^{3+}$ chelates that have been approved for clinical use and are frequently employed during MRI scans [31, 32]. Based on the mode of action, the contrast agents are of two main types i.e. $T_1$ contrast agents and $T_2$ contrast agents. $T_1$ and $T_2$ are refereed to spin-lattice relaxation and spin-spin relaxation. The Gd-based contrast agents are $T_1$ contrast agents. These contrast agents affect the spin-lattice relaxation time of surrounding water protons more as compared to the spin-spin relaxation time. On the other hand the Fe-based contrast agents are $T_2$ contrast agents as their effect on spin-spin relaxation is dominant as compared to the effect on spin-lattice relaxation time [33, 34].

The spin lattice relaxation time $T_1$ for water protons signals was measured in the presence of various concentration solutions of Gd-DTPA@AuNPs (AuNPs-II) and butanethiol-Gd-DTPA@AuNPs (AuNPs-III) by inversion recovery method. The typical inversion recovery curves are shown in figure 4. Following equation was used to calculate the $T_1$

$$M_s = M_0(1 - 2 \exp(-\tau/T_1))$$

In this equation $M_0$ represents the equilibrium magnetization, $M_s$ indicates the longitudinal magnetization, and $\tau$ is the variable delay time. The magnetic field strength of 7.0 T was employed for all relaxation measurements. The value of ‘$\tau$’ was kept in the range of 0.0001–6.0 s (figure 4). Relaxivity is the ability of a contrast agent to affect the relaxation time of surrounding water protons. It is determined by using the following mathematical equation (2). According to this equation, the graph is plotted between $[\text{Gd}]$ (x-axis) $1/T_1$ (y-axis), whose slope is equal to the relaxivity ($R_1$). $R_1$ means the spin-lattice relaxivity as spin-lattice relaxation time $T_1$ is used to calculate the relaxivity. The relaxivity is usually expressed as mM$^{-1}$ s$^{-1}$ [3].

$$\frac{1}{T_1} = R_1[\text{Gd}]$$

The relaxivity curves of Gd-DTPA@AuNPs (AuNPs-II) and butanethiol-Gd-DTPA@AuNPs (AuNPs-III) are shown in figure 5. From the figure the relaxivity of Gd-DTPA@AuNPs was found 5.370 mM$^{-1}$ s$^{-1}$ while the butanethiol inserted Gd-DTPA@AuNPs exhibited 38% higher relaxivity (7.599 mM$^{-1}$ s$^{-1}$) as compared to gold nanoparticles without butanethiols. The enhanced relaxivity of AuNPs-III was due to restricted tumbling of Gd-DTPA at the surface of gold nanoparticles due to insertion of butanethiol molecules. There are several factors that control the relaxivity of MRI contrast agents. These main factors are (i) number of coordinated water...
molecules with paramagnetic center, (ii) the distance between paramagnetic center and H-atoms of water molecules and (iii) Rotational correlation time ($\tau_R$) [12, 35]. In comparison between gold nanoparticles attached with Gd-DTPA chelates at their surface with butanethiol molecules and without butanethiol molecules, it has been observed that first two factors are same in both kinds of AuNPs. However the only left factor is the rotational correlation time which is responsible for any change in relaxivity between these two types of AuNPs based MRI contrast agents. The rotational correlation time is directly influenced by tumbling rate of AuNPs as well as ligands attached onto the AuNPs. The detailed study regarding effect of tumbling of AuNPs as well as ligands on the AuNPs with relaxivity has been reported in detail by Warsi et al. My results are compatible with their findings [4].

4. Conclusion

Magnetic resonance imaging (MRI) is a non-invasive medical diagnostic technique to differentiate the normal tissues from abnormal tissues. MRI is suffered from low sensitivity. Gold nanoparticles capped by dimethylaminopyridine (DMAP) molecules were synthesized and characterised by UV-visible spectroscopy, transmission electron microscopy (TEM) and TGA. The DMAP molecules were then replaced by Gd-DTPA based chelates along with butanethiol molecules. The relaxivity for both types of gold nanoparticles i.e. without butanethiol molecules and with butanethiol molecules was measured by inversion recovery method. The values of relaxivity was found 5.370 mM$^{-1}$ s$^{-1}$ (Gd-DTPA@AuNPs) and 7.399 mM$^{-1}$ s$^{-1}$ (butanethiol inserted Gd-DTPA@AuNPs). The 38% higher relaxivity for butanethiol molecules inserted Gd-DTPA@AuNPs is highly attributed to the restricted tumbling of ligand molecules at the gold nanoparticles surface.

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