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One-pot hydrothermal synthesize and characterization of Au/Gd bimetallic nanostructure as potential contrast agents in CT and MR imaging

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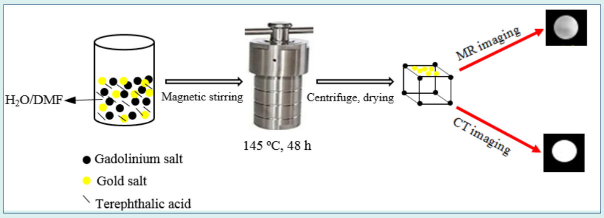
Abstract

Introduction: Multimodal contrast agents play an important role in early diagnosis of diseases and monitoring the treatment outcomes by increasing the accuracy and clarity of images.



Methods: Herein, a one-step simple hydrothermal route is utilized to prepare the gadolinium-1,4 H_2BDC- metal-organic framework (Gd-BDC-MOF) nanoparticles decorated with gold nanoclusters. The physicochemical properties of bimetal nanostructures were evaluated, their safety and ability to enhance contrast in both CT and MR imaging were also examined.

Results: The spherical nano-sized Au decorated Gd bimetal nanostructures have an average diameter of 64 nm. The presence of both Au and Gd metals in the prepared nanostructure was confirmed using EDAX. The XRD pattern shows that, in the hydrothermal synthesis of two metals using a terephthalic acid linker, gold nanoclusters are decorated onto the gadolinium metal organic framework. The FTIR analysis confirmed the attachment of Gd to the carboxylate group of the organic linker. The bimetal nanostructure sample with a concentration of 40 mM showed similar X-ray attenuation to that of iodine at a concentration of 128 mM. At a magnetic field strength of 1.5 T, the longitudinal relaxivity value of the bimetal nanostructure was determined to be 13.635 $mM^{-1} s^{-1}$. The MTT assay demonstrated the cytocompatibility and safety of the contrast agent synthesized for biomedical applications.

Conclusion: The fabricated bimetal nanostructure exhibits dose-dependent positive contrast enhancement in both MR and CT imaging techniques, making it a promising candidate for use as a contrast agent in medical applications.

Introduction

From the economic and practical point of view, it is necessary to develop new contrast agents that maximize the diagnostic potential of current imaging tools. Multifunctional contrast-enhanced nanomaterials overcome the limitations of single contrast agents and enable multimodal imaging for biological, molecular, diagnostic and therapeutic applications.[1] Multifunctional nanomaterials have shown considerable applications in various fields of biomedicine, including drug/gene delivery, disease diagnosis, and treatment monitoring.[1-4] In this case, gold nanoparticles (AuNPs) of specific shapes and sizes can be utilized for both imaging and photothermal therapy purposes. Researchers have explored the potential of utilizing exogenous nanostructures, including metals such as Au, Ag, and Pt,[5,6] as well as quantum dots,[7,8] iron and lanthanide oxides[9-12] for various bioimaging applications. Current imaging modalities, including optical imaging, ultrasound (US), computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), and single photon emission computed tomography (SPECT), each possess distinct

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advantages and disadvantages.[13] Given the inherent constraints of each imaging technique, it is improbable to provide a complete diagnostic assessment using a single approach. Therefore, multimodal imaging technologies have been developed to integrate the advantages of different imaging techniques into a single system. Combined methods include PET/CT, MRI/PET, CT/SPECT, and MRI/optical imaging.[14-18] CT is a clinically available and cost-effective imaging technology that provides 3D tomographic information with high spatial resolution. However, it suffers from limited soft-tissue resolution due to restricted density differences.[19] MRI, on the other hand, is a non-invasive and powerful imaging technology that offers high-resolution visualization of soft tissues with no ionizing radiation and unlimited tissue penetration depth.[20-23] However, one drawback of this technique is its low sensitivity.[24] The simultaneous use of CT and MRI techniques can alleviate the limitations of each individual modality and facilitate precise diagnosis through improving image sensitivity and contrast.[25] To achieve this goal, the development of a single multimodal nanostructure through the integration of various contrast agents can enable effective resolution simultaneously in both CT and MRI techniques.[26] Furthermore, utilizing a single contrast agent for multiple imaging modalities not only reduces treatment costs but also enhances patient comfort and health. Gadolinium (Gd) chelates are extensively used in clinical MR imaging as they effectively shorten the longitudinal relaxation time (T1) of water protons.[27] Gold nanostructures have garnered significant attention as potential contrast agents for CT due to their good biocompatibility, high atomic number, tunable morphology, and high X-ray attenuation coefficient.[28] Although some studies [29-32] have reported the combination of Au nanoclusters with Gd chelates for multimodal MR/CT imaging, their synthesis faces challenges in terms of further functionalization of small-sized Gd chelates. Additionally, the process requires two different steps and involves a complicated chemical conjugation process. Therefore, it is necessary to develop alternative synthetic methodologies for bimetal nanostructure preparation that can provide effective contrast in both CT and MRI methodologies. To the best of our knowledge, the hydrothermal synthesis of a bimetal nanostructure containing Gd and Au metals in a one-pot simple route using terephthalic acid as an organic linker has not been performed. The potential of the prepared bimetal nanostructure was examined for both X-ray attenuation in CT and as a positive contrast agent in MRI.

Material and Methods

Chemical reagents

Gadolinium (III) nitrate hexahydrate, chloroauric acid, terephthalic acid (98%), and N,N-dimethylformamide (DMF) were purchased from Sigma-Aldrich. Iodixanol (VISODIX 320 mg/ml, 50 ml) was purchased from Daroupakhsh Distribution Co, Iran. Also, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT reagent), phosphate-buffered saline (PBS), fetal bovine serum (FBS), and Dulbecco's modified eagle medium/nutrient mixture F-12 (DMEM/F-12) medium, were obtained from Sigma-Aldrich. The fibroblast cell line was obtained from the Pasteur Institute of Iran (IPI).

Synthesize of bimetal Au decorated Gd MOF nanostructure

The synthesis of nanoparticles is based on the studies that prepared the Gd MOF NPs using hydrothermal route,[33,34] which has been modified by adding gold. In this regard, a mixture of $Gd(NO_3)_3{,}6H_2O$ (25 mg, 0.055 mmol), $H(AuCl_4)\ 3H_2O$ (10 mg, 0.025 mmol), terephthalic acid (12.5 mg, 0.075 mmol), 80 ml DMF and distilled water (1:1) was poured into a Teflon-lined stainless-steel autoclave and heated at 145 ^{o}C for 2 days. After cooling the autoclave to ambient temperature, the resulting solution was centrifuged, washed with distilled water, and air-dried to obtain crystalline powder of NPs.

Characterization

The zeta potential, hydrodynamic diameter, and polydispersity index (PDI) data for Au-decorated Gd MOF nanostructures were determined using Zetasizer apparatus (Malvern Instruments Ltd., UK). Transmission electron microscopy (TEM) and scanning electron microscopy images were obtained using a TEM Philips EM 208S and SEM VEGA3, respectively. Xray diffraction (XRD) analysis was conducted using Inel Equaniox 3000 instrument (France) operating at 30 kV and 20 mA, with Cu Kα radiation. The FTIR spectra of the bimetal MOF was acquired using a Shimadzu-IR2000 spectrometer. The Iodine and metal contents (Au and Gd) of iodixanol and the bimetal MOF were determined using inductively coupled plasma atomic emission spectrometry (ICP 5300 DV, Perkin-Elmer).

MRI imaging

The MR images were acquired using a 1.5 T MRI scanner (GE Signa HD, USA). The longitudinal relaxation time (T1)-weighted images were recorded using echo sequence scanning with the following imaging parameters: field-of-view (FOV) of 34, slice thickness of 4 mm, TE of 15 ms, and the repetition time (TR) values of 150, 230, 520, 1000, 1800, and 3000 ms. The bandwidth was set to 31.25 kHz. Various concentrations of nanoparticles were prepared, and 300 µL of each concentration was poured into a 96-well plate for ELISA. All images were analyzed using ImageJ software with the MRI analysis plugin. The signal intensity of each MR image was recorded by selecting the region of interest, and the changes in signal intensities at various repetition times were applied for the nonlinear fitting of the curves.

CT imaging

For CT imaging, the prepared bimetal nanostructures were dispersed in water at different Au concentrations, and 300 µl of suspensions were placed into a 96-well plate. The CT contrast ability of Au-decorated Gd MOF was studied using a Siemens CT scan machine at a low magnification of 80 kVp, current of 30 mAs and slice thickness of 0.6 mm. For each sample, X-ray attenuation values were averaged over a region of interest and reported based on Hounsfield units.

In vitro cytotoxicity assay

The cytotoxicity of the nanoparticles was studied through the MTT assay on fibroblast cells (NCBI code: C 192, HSF-PI 16). The cells were divided into two groups without and with different concentrations of nanoparticles (0-40 mM). Afterward, the control and experimental media were collected and washed with sterile PBS to remove any components of the test composite. Then, 50 µL of MTT color solution (5 mg/mL PBS) was added to each well and incubated for 4 h at 37 °C in a humidified atmosphere of 95% air and 5% CO_2. Subsequently, the colored formazan formed in each well was dissolved in 200µl of DMSO. The absorbance was measured at 570 nm utilizing a plate reader spectrophotometer (Lonza BioTek ELx808 Absorbance Plate Read). The cell viability chance was calculated using the following formula:

$$\text{Cell viability } (\%) = \frac{A570(sample)}{A570(control)} \times 100$$

Results and Discussion

Characteristics of the Au decorated Gd MOF nanostructure

The average hydrodynamic diameters of Au-decorated Gd MOF nanostructure was measured to be 64 nm. The particles had a positive charge and a zeta potential of 32.1 mV. They were well-dispersed in water and had a low polydispersion index (PDI) of 0.347, as determined by DLS analysis. Fig. 1 illustrates the microscopic morphology, structure, and chemical composition of the nano-sized Au-decorated Gd bimetal structures, which were investigated using SEM, TEM, and EDAX analysis. It is evident from the SEM image that the majority of the nanoparticles exhibit a relatively spherical shape, and they are uniformly distributed and loosely agglomerated. The TEM images displayed the presence of polyhedral crystals with dimensions of about 50 nm. The energy dispersive X-ray spectra confirmed the bimetallic composition of the synthesized NPs.

The XRD pattern of the as-synthesized nano-sized Au decorated Gd MOF bimetal structure presented in Fig. 2. A series of characteristics diffraction peaks corresponding to both Gd and Au metals indicated the polycrystalline lattice structure of the nanoparticles. The observed diffraction peaks related to Gd were consistent with the reference pattern of Gd-BDC-MOF reported previously.[35] Additionally, the slight displacements of the diffraction peak positions from their expected angles were attributed to the interaction between the bimetal centers in the formed nanostructure. The absence of additional peaks in the pattern confirmed the phase purity of the formed

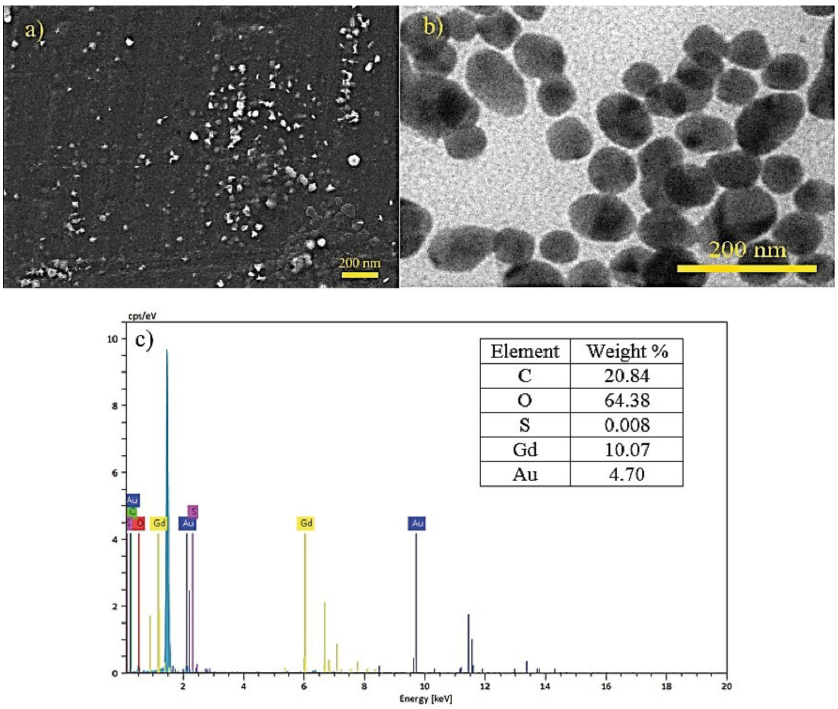

Fig. 1. a) SEM, b) TEM and c) EDAX analysis of the as-synthesized bimetal nanostructure.

crystal.

The FTIR spectrum of Au-decorated Gd MOF bimetal nanostructure is illustrated in Fig. 3. The broad band at 3400 cm^{-1} is attributed to the OH stretching of water molecules. The band at 1647 cm^{-1} corresponds to the C=O stretch of carbonyl group. A band related to the stretching mode of -CH is observed at 2930 cm^{-1}. A band at 1390 cm^{-1} corresponds to the C-C symmetric vibration.[36] The C–O stretch appears at 1255 cm^{-1}. Moreover, the two bands at 478 and 663 cm^{-1} are related to the Gd-O stretching vibrations that confirm the binding of Gd to the carboxylate group of the organic linker.[37-39]

In vitro X-ray attenuation measurements

To examine the effectiveness of the Au-decorated Gd MOF nanostructures as a CT contrast agent, different concentration of the bimetal nanostructure in water were prepared, and their contrast values were compared with Iodixanol. The in vitro CT imaging is illustrated in Fig. 4. As illustrated, the bimetal nanostructure exhibited CT contrast capability at all examined concentrations. Increasing the concentration of the bimetal nanostructures and iodine resulted in an increased contrast in the images. According to the similar brightness observed in the image, it can be concluded that a concentration of 40 mM of bimetal nanostructures provides the same contrast as 128 mM of iodine. The values of attenuated CT numbers for bimetal nanostructures and iodine were measured as 608.2 HU and 612.5 HU, respectively. Compared to iodine, gold has a higher atomic number and electron density, resulting in higher X-ray attenuation. It should also be mentioned that the concentration of bimetal nanostructures, containing both gold and gadolinium elements, is taken into account in CT imaging, because Gd is an element with a high atomic number that can cause a large attenuation coefficient in CT imaging.[40,41] Finally, the comparable X-ray attenuation of the synthesized nanoparticles to that of clinically used contrast agents confirms the feasibility of the Au-decorated Gd MOF bimetal nanostructure for CT imaging.

In vitro MR imaging

The relaxivity values of the Au-decorated Gd MOF nanostructures were studied at a 1.5 T magnetic field. The MR images of samples with different concentrations of gadolinium ions and the dependence of T1 relaxation time on metal concentration are presented in the Fig. 5. An enhancement in brightness was observed with increasing Gd concentration. A clear linear relationship between the inverse relaxation time and metal concentration was evident. From the slope of 1/T1 values versus concentration, the r1 value of the Au-decorated Gd bimetal nanostructure turned out to be 13.635 mM^{-1} s^{-1}. These mixed metal nanostructures exhibited higher longitudinal relaxivity compared to

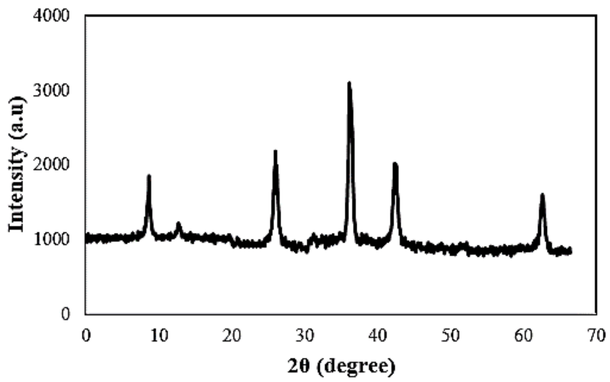

Fig. 2. XRD pattern of the as-synthesized bimetal nanostructure

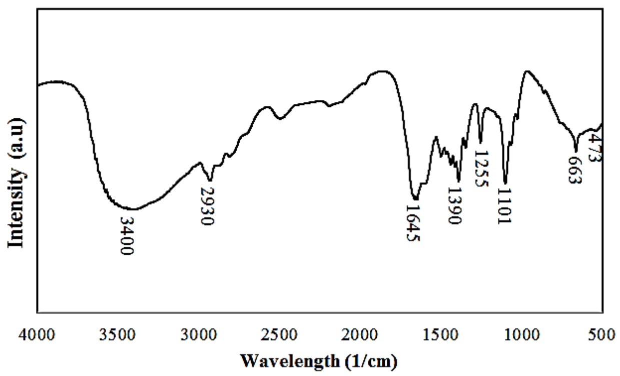

Fig. 3. FTIR spectra of the as-synthesized bimetal nanostructure

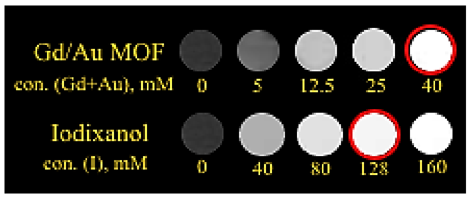

Fig. 4. CT images of different concentrations of the as-synthesized bimetal nanostructure and iodixanol

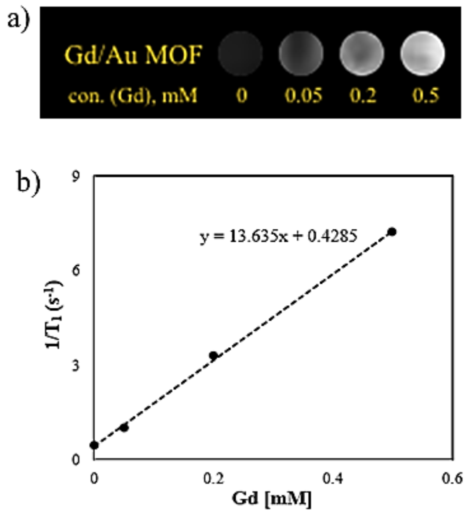

Fig. 5. a) T1 weighted MR images of the as-synthesized bimetal nanostructure, and b) relaxation rate versus different concentration of Gd

the clinically used contrast agent Magnevist complex (3.58 $mM^{-1}s^{-1}$).[42] The integrated bimetal contrast agent of Gd MOF with decorated Au nanoclusters, instead of combining modified Gd chelates with gold nanoparticles, has a larger size and a high payload of magnetic centers (Gd^{3+}), resulting in an enhanced retention time and relaxation rates.[43] The positive MRI signal enhancement showed by these bimetal nanostructures, compared to water, demonstrated their ability as an efficient MRI contrast agent.

In vitro cytotoxicity

MTT assay was used to investigate the cytotoxicity of nano-sized Au-decorated Gd MOF bimetal structure at different concentrations on fibroblast cell lines (Fig. 6). When compared with the control group, the nanostructure did not significantly decrease cell viability percentages in fibroblast cells after 24 and 48 h. This indicates the cytocompatibility and safety of the nanostructure for biomedical applications.

Most of the developed nanoparticles for dual-modal CT/MR biomedical imaging have focused on adding Au NPs to Gd chelates. The disadvantages of these NPs is the low Gd^{3+} magnetic payload per particle and some limitations related to further surface functionalization. The Gd metal organic frameworks can overcome such challenges of those contrast agents prepared using Gd chelates due to their tunable size and high metal loading as well as multivalency.[26] Furthermore, the good structural integrity of MOFs leading to reduced free Gd ions concentration in the environment which results in low toxicity related side effects.[44] Previous studies synthesized Gd MOF NPs using surfactant-assisted microemulsion method and exhibited enhanced T1 relaxation properties.[45,46] The drawback of such emulsion based method is using the large quantity of harmful organic solvents.[44] In another work by Tian et al,[26] nanoparticles of Gd MOF were prepared by solvothermal method. The MOFs were then connected AuNPs using poly acrylic acid as a bridge. These hybrid NPs showed CT and MRI contrast enhancement. A range of longitudinal relaxivity values were obtained in the vast majority of works previously conducted on multimodal contrast materials containing both Gd and Au metals. These variations are attributed to the particle morphology and the magnetic field strength which affect the MRI relaxivities.[47] However, the concentration of Au NPs is an influential parameter for CT contrast than their size and shape.[48] Similarly, the synthesized bimetal NPs in the present study are also able to increase the contrast of the images in both CT and MRI methods. The advantage of this study is the one-step synthesis of Au/Gd complex with a simple, low-cost and environmentally friendly route, in which the least amount of hazardous chemicals is utilized.

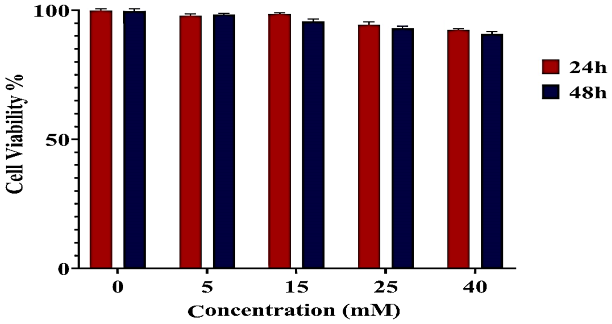

Fig. 6. In-vitro cytotoxicity of the bimetal nanostructure on fibroblast cells compared to control (concentration = 0).

Conclusion

The one-pot hydrothermal synthesis route is a useful method for the successful preparation of a bimetal Au-decorated Gd MOF nanostructure, which can be used as a positive contrast agent in both CT and MRI modalities. The structure of the Au-decorated Gd-BDC-MOF was established through XRD analysis. The 40 mM bimetal contrast agent has an attenuation of 608 HU in the CT experiment. The Gd-BDC-MOF nanostructure, which is larger in size and has a higher paramagnetic Gd payload, exhibited a higher longitudinal relaxivity compared to that of the clinically used contrast agent Magnevist complex. The signal enhancement by the proposed bimetal nanostructure compared to water in both CT and MRI techniques highlights its potential as an efficient bimodal contrast agent.

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Supervision: Negin Farhadian, Sajad Moradi, Mohsen Shahlaei.
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Writing–original draft: Negin Farhadian, Rashed Ahmadyani, Hamed Ahmadyani, Saleh Salehi Zahabi, Faranak Aghaz, Kave Moloudi.
Writing–review & editing: Sajad Moradi, Mohsen Shahlaei, Milad Moradi.

Competing Interests

All authors have no conflict of interest to declare.

Research Highlights

- Recently, multimodal contrast agents developed for biomedical imaging can provide comprehensive diagnostic information, reduce costs and improve patient care.
- This work introduces a new complex of Au-decorated Gd MOF nanostructure synthesized in a simple and one-pot hydrothermal route for MRI/CT.

Ethical Statement

Ethics Committee of Kermanshah University of Medical Sciences was confirmed this study (IR.KUMS.REC.1399.228).

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