Miguel Toro-González, Ashley N. Dame, Saed Mirzadeh and Jessika V. Rojas*

Encapsulation and retention of ^{225}Ac , ^{223}Ra , ^{227}Th , and decay daughters in zircon-type gadolinium vanadate nanoparticles

<https://doi.org/10.1515/ract-2019-3206>

Received September 3, 2019; accepted August 6, 2020;

published online September 16, 2020

Keywords: actinium-225; gadolinium vanadate; radium-223; targeted alpha therapy; thorium-227.

Abstract: Unwanted targeting of healthy organs caused by the relocation of radionuclides from the target site has been one of the limiting factors in the widespread application of targeted alpha therapy in patient regimens. GdVO_4 nanoparticles (NPs) were developed as platforms to encapsulate α -emitting radionuclides ^{223}Ra , ^{225}Ac , and ^{227}Th , and retain their decay daughters at the target site. Polycrystalline GdVO_4 NPs with different morphologies and a zircon-type tetragonal crystal structure were obtained by precipitation of GdCl_3 and Na_3VO_4 in aqueous media at room temperature. The ability of GdVO_4 crystals to host multivalent ions was initially assessed using La, Cs, Bi, Ba, and Pb as surrogates of the radionuclides under investigation. A decrease in Ba encapsulation was obtained after increasing the concentration of surrogate ions, whereas the encapsulation of La cations in GdVO_4 NPs was quantitative (~100%). Retention of radionuclides was assessed *in vitro* by dialyzing the radioactive GdVO_4 NPs against deionized water. While ^{227}Th was quantitatively encapsulated (100%), a partial encapsulation of ^{223}Ra (~75%) and ^{225}Ac (>60%) was observed in GdVO_4 NPs. The maximum leakage of ^{221}Fr (1st decay daughter of ^{225}Ac) was $55.4 \pm 3.6\%$, whereas for ^{223}Ra (1st decay daughter of ^{227}Th) the maximum leakage was $73.0 \pm 4.0\%$. These results show the potential of GdVO_4 NPs as platforms of α -emitting radionuclides for their application in targeted alpha therapy.

1 Introduction

The clinical efficacy of Xofigo® ($^{223}\text{RaCl}_2$) for treatment of patients with castration-resistant prostate cancer has encouraged the development of new radiopharmaceuticals based on α -emitting radionuclides for cancer treatment [1–3]. Alpha particles have shown greater cytotoxicity compared to β -particles and γ -rays for the treatment of different cancers [4]. The higher toxicity of α -particles, associated to their high linear energy transfer and relative biological effectiveness, can lead to a large fraction of DNA double-strand breaks which are less likely to be repaired by the cell [5–7]. Despite these characteristics, the use of α -emitting radionuclides in clinical settings has been limited by the availability of radionuclides with proper physical and chemical characteristics, the production of radionuclides in clinical quantities, and the relocation of radionuclides from the target site [3, 8]. The latter represents a significant challenge in biological settings since free radionuclides can deliver substantial dose to healthy tissue [1]. To address this challenge, radioimmunoconjugates [9–12], inorganic nanoparticles (NPs) [13–23], liposomes [24–28], Pd-based polyoxometalates [29], and polymersomes [30–33] have been proposed as platforms to deliver α -emitting radionuclides and minimize the relocation of decay daughters from the target site.

Most clinical trials using α -emitting radionuclides have been conducted with radioimmunoconjugates where a radionuclide is attached to a monoclonal antibody or peptide using a chelating agent [5, 34–36]. It is well-known that chelating agents cannot sustain the recoil energy of decay daughters (100–200 keV), which results in chemical bond breaking and hence the relocation of radionuclides from the target site [5, 37, 38]. Furthermore, the lack of stable chelating agents for radium isotopes has restricted the use of radium-based radioimmunoconjugates for cancer treatment [39]. Liposomes and polymersomes have shown high encapsulation of radium and actinium radionuclides in

*Corresponding author: Jessika V. Rojas, Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA, USA, E-mail: jvrojas@vcu.edu. <https://orcid.org/0000-0002-2268-4613>

Miguel Toro-González, Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA, USA; Isotope and Fuel Cycle Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA, E-mail: torogonzalezm@vcu.edu. <https://orcid.org/0000-0003-3320-423X>

Ashley N. Dame and Saed Mirzadeh, Isotope and Fuel Cycle Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA, E-mail: damean@ornl.gov (A.N. Dame), mirzadehs@ornl.gov (S. Mirzadeh). <https://orcid.org/0000-0002-9577-5006> (A.N. Dame). <https://orcid.org/0000-0002-1774-7958> (S. Mirzadeh)

biological media [24–28]. Nonetheless, there are some difficulties associated with the synthesis and preparation of liposomes and polymersomes as well as the fact that the retention of decay daughters is dependent on their size [20, 26]. Inorganic particles made of lanthanide phosphate, zeolites, magnetite, hydroxyapatite, barium sulfate, and calcium carbonate have shown high encapsulation of radium radioisotopes, while decay daughters have been partially retained [13, 18, 19, 22, 23, 40, 41]. Additionally, quantitative encapsulation of ^{225}Ac and partial retention of decay daughters have been obtained in titanium dioxide and lanthanide phosphate core-shell NPs [14–17, 20]. All in all, inorganic NPs and polymer vesicles have displayed high encapsulation of α -emitting radionuclides, partial retention of decay daughters, diagnostic and therapeutic functionalities, and the ability to potentially deliver large activities.

The widespread application of inorganic NPs in targeted alpha therapy requires further assessment and enhancement of radionuclide retention and the development of simple and quick synthetic routes. In this work, a simple, quick procedure based on the precipitation of Gd^{3+} and $[\text{VO}_4]^{3-}$ ions at room temperature was used for the synthesis of gadolinium vanadate (GdVO_4) NPs as platforms for encapsulation and delivery of α -emitting radionuclides. To evaluate the influence of hydrogen ion concentration on the GdVO_4 NPs crystal structure and morphology, the synthesis of GdVO_4 NPs was conducted at pH ranging from 4 to 12. The ability of the GdVO_4 structure to host multivalent ions was assessed by using La, Ba, Bi, Cs, and Pb as surrogates of ^{225}Ac , ^{223}Ra , ^{213}Bi , ^{221}Fr , and ^{211}Pb , respectively. The precipitation and encapsulation of surrogate cations within GdVO_4 NPs was evaluated by characterizing the crystal structure and elemental concentration of surrogate-doped GdVO_4 NPs. Radioactive GdVO_4 NPs suspensions were dialyzed against deionized (DI) water to assess the encapsulation of α -emitting radionuclides (^{227}Th , ^{225}Ac , and ^{223}Ra) and the *in vitro* retention of decay daughters (^{221}Fr , ^{213}Bi , ^{223}Ra , and ^{211}Pb). The partial encapsulation and retention of radionuclides in GdVO_4 NPs, combined with the optical and magnetic functionalities of lanthanide-doped nanomaterials [42, 43] are promising for the development of radioactive GdVO_4 NPs as platforms for theranostic applications.

2 Experimental procedure

2.1 Reagents and radionuclides

The following reagents were used without further purification: gadolinium(III) chloride hexahydrate ($\text{GdCl}_3 \cdot 6\text{H}_2\text{O}$, 99%, Sigma Aldrich),

lanthanum(III) chloride heptahydrate ($\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, 99.9%, Sigma Aldrich), cesium chloride (CsCl , 99.99%, Acros Organics), barium chloride dihydrate ($\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$, 99+%, Alfa Aesar), bismuth(III) chloride anhydrous (BiCl_3 , 99.99%, Alfa Aesar), lead(II) chloride (PbCl_2 , 99%, Alfa Aesar), and sodium orthovanadate (Na_3VO_4 , 99%, Acros Organics). The pH of Na_3VO_4 was adjusted to 12.5 using NaOH (1 M). A MilliQ® water purification system was used to obtain DI water (18 M Ω). Biotech regenerated cellulose membrane with an 8–10 kDa molecular weight cut-off was purchased from Spectra®. A four-step chemical process consisting of both anion and cation exchange chromatography was used to obtain carrier-free ^{225}Ac ($T_{1/2} = 9.9$ days) from a thorium stock consisting of ^{228}Th , ^{229}Th , and ^{232}Th [44]. Briefly, the bulk separation of Ra and Ac from Th was accomplished by using an anion exchange resin (BIO-RAD MP1 250 $\pm$ 50 mesh) in 8 M HNO_3 . A similar but much smaller column was used to remove the last traces of Th. Next, a small anion exchange column (MP1 resin) in 10 M HCl was used to remove traces of U(VI) and Fe(III). The solution containing Ac, Ra, Pb, and Bi was passed through a column containing a low cross-linking cation exchange resin (BIO-RAD AG50 $\times$ 4 200–400 mesh) in 1.2 M HNO_3 to separate Ac from Ra, Pb, and Bi. Ac was eluted from this column with 8 M HNO_3 and evaporated to near dryness. A final Ac purification is performed by repeating previous step using a 0.4 mL AG50 $\times$ 4 cation exchange column. Thorium-227 ($T_{1/2} = 18.7$ days) and ^{223}Ra ($T_{1/2} = 11.4$ days) were obtained from ^{227}Ac ($T_{1/2} = 21.7$ years) generated via thermal neutron irradiation of a ^{226}Ra target. Recovery of carrier-free ^{223}Ra and ^{227}Th was achieved using an anion exchange resin (BIO-RAD AG® MP1-M 100–200 mesh). First, the mixture of ^{227}Th and ^{223}Ra in 0.1 M HNO_3 was loaded on a 0.3 mL column of MP1-M resin prepared in a Pasteur pipette (~5 mm in diameter). Carrier-free ^{223}Ra was eluted from the column after washing with eight column volumes of 8 M HNO_3 , while eight column volumes of 0.1 M HNO_3 were used to obtain carrier-free ^{227}Th after recovering ^{223}Ra . Radiochemical preparations and purifications of ^{223}Ra , ^{225}Ac , and ^{227}Th were performed at ORNL.

2.2 Synthesis of GdVO_4 NPs

GdVO_4 NPs were prepared in aqueous media by precipitation of Gd^{3+} and $[\text{VO}_4]^{3-}$ ions at room temperature [45]. To evaluate the influence of hydrogen ion concentration, $\text{GdCl}_3 \cdot 6\text{H}_2\text{O}$ (1 mmol, 0.1 M) was added dropwise to an aqueous solution of Na_3VO_4 (1 mmol, 0.1 M, pH = 12.5) under constant stirring. The pH of the mixture was monitored continuously using a pH meter and kept at either 8, 10, 11, or 12 during the addition of GdCl_3 by using NaOH (1 M). After adding the GdCl_3 solution, the turbid suspension was left under constant stirring for 30 min. For surrogate-doped GdVO_4 NPs, aqueous solutions of $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, CsCl , and BiCl_3 were mixed to obtain La, Cs, and Bi cations at concentrations of either one atom% or 10 atom% with respect to Gd. This mixture was evaporated to dryness at 80 °C, and then it was mixed with a GdCl_3 solution (1 mmol, 0.1 M) using a vortex mixer and an ultrasonic bath. The Na_3VO_4 solution (1 mmol, 0.1 M, pH = 12.5) was added dropwise to the aqueous solution containing Gd, La, Cs, and Bi cations under constant stirring. The pH of the mixture was adjusted to ~11 using NaOH (1 M) followed by stirring for 30 min. The turbid suspension was transferred into a dialysis membrane and dialyzed against DI water to assess the concentration of cations in the dialysate and in the dialyzed suspension. Similarly, a mixture containing $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ and PbCl_2 at concentrations of either one atom% or 10 atom% of Ba and Pb cations with respect to Gd, were evaporated to dryness and mixed with GdCl_3 . Afterwards, the same steps described above for the synthesis and dialysis of GdVO_4 NPs

were followed. Pure GdVO_4 NPs suspensions were also prepared by adding Na_3VO_4 into an aqueous solution of GdCl_3 and the pH of the final mixture was adjusted to either four or 12, followed by 30 min of stirring.

For radiochemical synthesis, a 0.1 M HNO_3 solution containing either 4.8 μCi of ^{223}Ra , 7.4 μCi of ^{225}Ac , or 14.9 μCi of ^{227}Th was evaporated to dryness in a conical vial using an infrared heat lamp and a hot plate. A GdCl_3 solution was added to the conical vial, stirred for 10 min, and then the Na_3VO_4 solution was added drop-by-drop. A sample of GdVO_4 NPs containing 25.6 μCi of ^{223}Ra was synthesized by mixing Na_3VO_4 with the radionuclides, followed by dropwise addition of the GdCl_3 solution. The adjustment of the pH, stirring, and dialysis of the radioactive GdVO_4 NPs suspensions were performed as described for the surrogate-doped NPs.

2.3 Characterization of GdVO_4 NPs

Characterization of the crystal structure, morphology, and chemical yield was performed using nonradioactive GdVO_4 NPs. For X-ray diffraction, surrogate-doped and pure GdVO_4 NPs suspensions were precipitated by centrifugation and dried overnight in a muffle furnace at 70 °C. The fine powder required for characterization was obtained by grinding the dried material on a mortar and pestle. The diffraction patterns were collected using a PANanalytical X'Pert Pro X-ray diffractometer with a Cu anode (Cu K_α , $\lambda = 1.504 \text{ \AA}$) operated at 45 kV and 40 mA. Morphology of GdVO_4 NPs was characterized by transmission electron microscopy using a Zeiss Libra® 120 with a LaB₆ filament operated at 120 kV. Each sample was prepared by dispersing GdVO_4 NPs in acetone using a vortex mixer and an ultrasonic bath followed by drop-casting the NPs suspension onto a formvar/carbon copper grid (Mesh 300). The concentration of metal cations in both dialysate and dialyzed surrogate-doped GdVO_4 NPs suspensions was assessed by inductively coupled plasma-optical emission spectroscopy (ICP-OES) using an Agilent 5110. Surrogate-doped GdVO_4 NPs suspensions were dialyzed against DI water for 20 h after synthesis. Volumetric flasks previously cleaned with 10% v/v nitric acid were used for the preparation of samples and standards. Inductively coupled plasma standards containing 1000 ppm of either Gd, La, Ba, Cs, Bi, or Pb were purchased from Inorganic Ventures™. Each standard was serially diluted from 150 to 0.075 ppm to build a calibration curve for each element.

Radioactive GdVO_4 NPs were dialyzed against DI water to assess the encapsulation and radiochemical yield of α -emitting radionuclides (^{227}Th , ^{225}Ac , and ^{223}Ra) and the leakage of decay daughters (^{221}Fr , ^{213}Bi , ^{223}Ra , and ^{211}Pb). The radiochemical yield was measured based on the initial activity used for the synthesis of radioactive GdVO_4 NPs and the activity lost during synthesis (e.g., vial, pipette tip) and dialysis (Eq. 1). The leakage of radionuclides from GdVO_4 NPs was assessed over time by taking aliquots from the dialysate and comparing them with the activity inside the dialysis membrane (Eq. 2).

$$\text{Radiochemical Yield (\%)} = \frac{A_0 - (A_{\text{dial}} + A_{\text{vial}} + A_{\text{tip}})}{A_0} \times 100 \quad (1)$$

$$\text{Leakage (\%)} = \frac{A_{\text{dial}}}{A_{\text{mem}}} \times 100 \quad (2)$$

where A_0 , A_{dial} , A_{vial} , A_{tip} , and A_{mem} correspond to the activities measured from the radioactive sample before synthesis, the dialysate aliquot, the vial used for synthesis, the tip used to transfer the radioactive suspension, and the radioactive suspension inside the membrane, respectively. The activity of ^{223}Ra , ^{225}Ac , ^{227}Th , and their

decay daughters was determined by γ -ray spectroscopy using a high-purity germanium (HPGe) detector (Ortec, Oak Ridge, TN) with a crystal active volume $\sim 100 \text{ cm}^3$ and a Be window that was coupled to a PC-based multichannel analyzer (Canberra Industries, Meriden, CT). Energy and efficiency calibrations were determined by γ -ray sources traceable to the National Institute of Standards and Technology. The γ -energy and intensities used to determine the activity of each radionuclide were ^{227}Th (235.9 keV, 12.9%), ^{225}Ac (150.1 keV, 0.6%), ^{223}Ra (269.5 keV, 13.9%), ^{221}Fr (218.1 keV, 11.4%), ^{213}Bi (440.4 keV, 25.94%), and ^{211}Pb (404.8 keV, 3.8%) [46].

3 Results

3.1 Crystal structure of GdVO_4 NPs

The diffraction patterns of pure GdVO_4 NPs synthesized at different pH levels and synthetic conditions are shown in Figure 1. A zircon-type structure having a tetragonal system and a space group of $I4_1/amd$ (pdf: 00-017-0260) was obtained for pure GdVO_4 NPs. The crystallite size was calculated using the Scherrer equation ($D = K\lambda/\beta \cos\theta$), where D is the crystallite size, λ is the wavelength of the Cu- K_α radiation, β is the full-width at half maximum of the selected reflection, θ is the Bragg angle, and K is a shape factor set as 0.9 [47]. As expected from the broadening of the Bragg reflections, a decrease in the crystallite size was observed by changing the pH from 12 to 8 (Table 1). For GdVO_4 NPs synthesized by adding Na_3VO_4 into GdCl_3 , the crystallite size increased from 5.7 to 7.0 nm at pH 4 and 12, respectively.

The diffraction patterns of surrogate-doped GdVO_4 NPs are shown in Figure 2. GdVO_4 NPs doped with one atom% and 10 atom% of Ba and Pb cations have a zircon-type structure with a tetragonal system corresponding to GdVO_4 (pdf: 00-017-0260). GdVO_4 NPs doped with one atom% and 10 atom% of La, Cs, and Bi cations are characterized by two phases: GdVO_4 (pdf: 00-017-0260) and BiOCl (pdf: 01-085-0861). The presence of the BiOCl phase with tetragonal system and space group $P_{4/129}$, which Bragg reflections of are highlighted with *, is clearly observed for 10 atom%, while only the Bragg reflection $\sim 25.8^\circ$ can be seen for one atom% (Figure 2). The crystallite size of the surrogate-doped GdVO_4 NPs was not significantly affected by the composition and concentration of surrogate ions since the values are between 6.9 and 7.9 nm (Table 2).

3.2 Morphology and particle size distribution of GdVO_4 NPs

Transmission electron micrographs and particle size distributions of GdVO_4 NPs prepared at different pH are shown in

Figure 3. The particle size distribution of each sample is represented by two characteristic dimensions, width and length, with mean sizes and standard deviations reported in Table 3. GdVO_4 NPs synthesized at a pH of eight are characterized by anisotropic particles of various sizes (Figure 3a,b). Keeping the pH ~ 10 during NP synthesis resulted in the formation of GdVO_4 NPs with ellipsoidal shape (Figure 3d,e), whereas a pH ~ 11 led to the formation of NPs with ellipsoidal and trapezoidal shapes (Figure 3g,h). Large ellipsoidal and trapezoidal NPs, as well as aggregates of small crystallites, were observed in the micrographs of GdVO_4 NPs synthesized at pH ~ 12 (Figure 3j,k).

3.3 Chemical yield of GdVO_4 NPs

The chemical yield of Gd, La, and Ba cations was calculated by comparing the concentration measured by ICP-OES in the dialysate and dialyzed NPs suspension with respect to the initial concentration of each cation. The average chemical yield and standard deviation for each metal cation are summarized in Table 4. For Gd, independently of the concentration of surrogate cations, a chemical yield of $\sim 100\%$ was obtained for all samples. The chemical yields of La in GdVO_4 NPs doped with one atom% and 10 atom% of La, Cs, and Bi were $\sim 100\%$. An increase of Ba and Pb concentration from one atom% to 10 atom% resulted in a decrease of the chemical yield from $79.9 \pm 15.5\%$ to $58.2 \pm 24.3\%$, respectively.

3.4 Radiochemical yield and retention of ^{227}Th , ^{225}Ac , ^{223}Ra , and decay daughters in GdVO_4 NPs

The fraction of radioactivity found in the dialysate (hereafter referred to as leakage, Eq. 2) of ^{223}Ra , ^{225}Ac , ^{227}Th , and decay daughters originating from GdVO_4 NPs is presented in Figure 4. The error bars reported correspond to propagation of errors incorporating the uncertainties associated with pipetting, detector efficiency, and activity measurement. A partial encapsulation of ^{225}Ac in GdVO_4 NPs was observed after an increase in dialysate activity from 17.4 ± 1.2 to $36.7 \pm 2.2\%$ after 7 days in dialysis (Figure 4a). The leakage of ^{221}Fr (1st decay daughter of ^{225}Ac) and ^{213}Bi (3rd decay daughter of ^{225}Ac) reached a maximum of 55.4 ± 3.6 and $25.6 \pm 1.5\%$ after 5 days in dialysis, and then it decreased to 41.1 ± 2.5 and $19.8 \pm 1.16\%$ after 11 days, respectively (Figure 4a). $\text{Gd}(^{227}\text{Th})\text{VO}_4$ NPs displayed quantitative encapsulation of ^{227}Th (100%), while the leakage of ^{223}Ra (1st decay daughter) reached a maximum of $73.0 \pm 4.0\%$ after

Figure 1: Diffraction patterns of GdVO_4 NPs synthesized at different pH levels and synthetic conditions. Samples highlighted with * correspond to GdVO_4 prepared by adding a Na_3VO_4 solution into a GdCl_3 solution under constant stirring.

Table 1: Crystallite size of GdVO_4 NPs synthesized at different pH levels and synthetic conditions.

pH	Crystallite size (nm)
12 ^a	7.0
12	23.2
11	17.2
10	13.0
8	8.4
4 ^a	5.7

^a GdVO_4 prepared by adding a Na_3VO_4 solution into a GdCl_3 solution under constant stirring.

4 days, and then decreased to $30.0 \pm 1.7\%$ at 33 days (Figure 4b). The leakage of ^{211}Pb was comparable to that of ^{223}Ra , however, the fraction radioactivity found in the dialysate increased from 11.1 ± 1.0 to $44.8 \pm 3.1\%$ after 35 days in dialysis. $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs, in which Na_3VO_4 was added into the ^{223}Ra - GdCl_3 mixture, had a partial encapsulation of ^{223}Ra since $\sim 25\%$ of the initial activity was found in the dialysate over time (Figure 4c). On the other hand, a continuous increase in ^{223}Ra dialysate activity was observed for $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs, in which the GdCl_3 solution was added into the ^{223}Ra - Na_3VO_4 mixture, to a maximum of $43.6 \pm 2.4\%$ (Figure 4d). The leakage of ^{211}Pb from both $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs followed a similar trend to that of ^{223}Ra . The radiochemical yield or fraction of activity that was encapsulated within GdVO_4 NPs was calculated using Eq. (1) based on the initial activity used for each α -emitting radionuclide and the activity lost during synthesis and dialysis. A ^{223}Ra

Figure 2: Diffraction patterns of surrogate-doped and pure GdVO_4 NPs synthesized prepared under identical conditions.

Table 2: Crystallite size of surrogate-doped GdVO_4 NPs.

Surrogate cations	Surrogate concentration (atom%)	Crystallite size (nm)
Ba, Pb	1	7.8
	10	6.9
La, Cs, Bi	1	7.9
	10	7.6

radiochemical yield of $34.1 \pm 2.9\%$ was obtained for $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs in which the GdCl_3 solution was added into the $^{223}\text{Ra}\text{-Na}_3\text{VO}_4$ mixture. The radiochemical yield for $\text{Gd}(^{225}\text{Ac})\text{VO}_4$, $\text{Gd}(^{227}\text{Th})\text{VO}_4$, and $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs suspensions was 67.9 ± 2.4 , 66.8 ± 7.2 , and $72.3 \pm 3.0\%$, respectively.

4 Discussion

The focus of this work was to evaluate the encapsulation of ^{225}Ac , ^{223}Ra , ^{227}Th , and the *in vitro* retention of their decay daughters in GdVO_4 NPs for their application in targeted alpha therapy. GdVO_4 NPs could be a promising alternative for the encapsulation and retention of α -emitting radionuclides based on the radiation resistance shown by $^{241}\text{AmVO}_4$ and $^{237}\text{NpA}^{2+}(\text{VO}_4)_2$ oxides, which preserved their zircon-type structure after self-irradiation at doses as high as 14×10^{18} α -decay events g^{-1} [48]. We have demonstrated that $\text{Gd}_{0.8}\text{Eu}_{0.2}\text{VO}_4$ and GdVO_4 core and core +2 shells NPs,

synthesized following a multi-step synthetic approach, partially encapsulated α -emitting radionuclides (^{225}Ac and ^{227}Th) and retained decay daughters (^{221}Fr , ^{213}B , ^{223}Ra , and ^{211}Pb) [49, 50]. The proposed GdVO_4 NPs were synthesized by a simple and quick procedure based on the precipitation of Gd^{3+} and $[\text{VO}_4]^{3-}$ ions in aqueous media using GdCl_3 and Na_3VO_4 as precursors, respectively [45]. Dextran-coated GdVO_4 NPs, prepared using this synthetic method, have displayed fluorescence and magnetic resonance imaging functionalities and a low toxicity (25% cell death) based on a cell mortality MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide – test [42]. It is expected that surface modification of GdVO_4 NPs with functional groups, targeting vectors, or coating layers may enhance their biocompatibility and minimize their cytotoxicity [43, 51].

To assess the influence of hydrogen ion concentration on the crystal structure and morphology of pure GdVO_4 NPs, the pH was continuously monitored during the addition of GdCl_3 into Na_3VO_4 and adjusted to either 8, 10, 11, or 12 using NaOH (1 M). It is important to highlight that the pH of the Gd-VO_4 mixture must not be >13 or <8 to prevent the precipitation of $\text{Gd}(\text{OH})_3$ and formation of polyvanadate species, respectively [45]. The diffraction patterns of pure GdVO_4 NPs suggest that neither $\text{Gd}(\text{OH})_3$ or polyvanadate species were precipitated since GdVO_4 was the only phase observed (Figure 1). A decrease in the pH resulted in the broadening of the Bragg reflections and hence a reduction of the crystallite size (Table 1). It is assumed that the decrease in crystallite size is related to a slower formation and precipitation of GdVO_4 NPs as a result of the simultaneous and competing process where orthovanadate groups change into polyvanadate species given the low pH of the mixture. The micrographs of GdVO_4 NPs synthesized at pH levels of 8, 10, and 11 displayed particles with a discontinuous contrast (Figure 3b,e,h), which could be associated to the formation of particles through aggregation of small crystallites given the difference between the crystallite (Table 1) and mean particle sizes (Table 2) [52, 53]. On the other hand, increasing the pH to 12 led to the precipitation of a small fraction of large particles with homogeneous contrast (Figure 3j). The large size of the GdVO_4 NPs is consistent with their large crystallite size (23.2 nm), while the homogenous contrast may suggest the precipitation of single crystals or a reduction of defects and/or porosity. The formation of aggregates of small crystallites could be caused by the rapid precipitation of $\text{Gd}(\text{OH})_3$ at the high pH used during synthesis (Figure 3k). The slow interaction between gadolinium hydroxide and vanadate species may result in the formation of a significant number of small crystallites and few

Figure 3: Transmission electron micrographs and particle size distribution of GdVO_4 NPs synthesized at pH of 8 (a–c), 10 (d–f), 11 (g–i), and 12 (j–l).

crystalline GdVO_4 NPs having a large size. This hypothesis is supported by the lower intensity of the Bragg reflections of GdVO_4 NPs synthesized at pH 12 with respect to those prepared at pH 10 and 11 (Figure 1).

The surrogate-doped and radioactive GdVO_4 NPs were synthesized by dropwise addition of Na_3VO_4 into GdCl_3 . This modification was made to ensure complete dissolution and homogeneous distribution of surrogate cations or

Table 3: Mean particle size and standard deviation of GdVO_4 NPs synthesized at various pH levels.

pH	Length (nm)	Width (nm)
12	48.2 ± 12.7	32.7 ± 5.7
11	42.4 ± 12.9	26.8 ± 6.7
10	46.4 ± 14.2	28.7 ± 8.7
8	23.2 ± 11.2	16.1 ± 7.2

Table 4: Mean chemical yield and standard deviation of Gd, La, and Ba in surrogate-doped GdVO_4 NPs.

Sample	Chemical yield (%)		
	Gd	La	Ba
1 atom% Ba, Pb	99.5 ± 0.5		79.9 ± 15.5
10 atom% Ba, Pb	100.0 ± 1.2		58.2 ± 24.3
1 atom% La, Cs, Bi	99.9 ± 0.1	98.4 ± 1.5	
10 atom% La, Cs, Bi	100.0 ± 4.4	100.0 ± 3.5	

radionuclides within the GdCl_3 solution. Altering the way both reagents are mixed may promote the formation of polyvanadate species due to the acidic nature of the GdCl_3 solution (pH 4.16). The diffraction patterns of pure GdVO_4 NPs, prepared by the addition of GdCl_3 into Na_3VO_4 , revealed a zircon-type structure (Figure 1). Although the suspensions were stirred for 30 min after adjusting the pH to either four or 12, the change in crystallite size was not as significant as observed for GdVO_4 NPs synthesized via the addition of GdCl_3 into Na_3VO_4 (Table 1). These results suggest that the nucleation of GdVO_4 NPs occurs immediately after both solutions are mixed given the high concentration of species and that the influence of the pH in the crystallite size is noteworthy only when it is controlled during the addition and mixing of GdCl_3 and Na_3VO_4 solutions. In surrogate-doped GdVO_4 NPs, the absence of secondary phases in the diffraction patterns suggests that both Ba and Pb cations were incorporated within the GdVO_4 crystal lattice (Figure 2). This observation indicates

Figure 4: Radionuclide leakage from (a) $\text{Gd}(^{225}\text{Ac})\text{VO}_4$, (b) $\text{Gd}(^{227}\text{Th})\text{VO}_4$, (c) $\text{Gd}(^{223}\text{Ra})\text{VO}_4$, and (d) $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ (prepared by adding GdCl_3 into Na_3VO_4).

that radionuclides such as ^{223}Ra and ^{211}Pb may be encapsulated in GdVO_4 NPs for the development of platforms for targeted alpha therapy. For GdVO_4 NPs doped with La, Bi, and Cs, the presence of BiOCl is related to the tendency of BiCl_3 to hydrolyze to oxychloro species in aqueous media at $\text{pH} \geq 4$. The precipitation of BiOCl as a secondary phase implies that Bi cations may not be incorporated within the GdVO_4 crystal lattice, whereas successful incorporation of La and Cs cations is assumed because no additional phases were observed (Figure 2). The morphology of surrogate-doped GdVO_4 NPs is expected to be characterized by polycrystalline particles with anisotropic morphology given the low pH values maintained during synthesis.

Radioactive GdVO_4 NPs were synthesized following the same steps described for surrogate-doped samples, however, it is expected that their crystal structure and morphology will be similar to those of pure GdVO_4 NPs given the low concentration of radionuclide cations. The similar chemical properties, effective ionic radii of La (103.2 pm) and Ac (112 pm) cations for a coordination number (CN) of 6, and chemical yield results suggest that Ac cations may be quantitatively retained in GdVO_4 NPs [54]. It is assumed that the presence of ^{225}Ac in the dialysate (Figure 4a) is related to the preference of tetragonal structures to encapsulate tetravalent actinides [55] and to differences in effective ionic radii between Gd (93.8 pm, CN = 6) and Ac [54]. These assumptions are supported by the quantitative encapsulation of ^{227}Th in $\text{Gd}(^{227}\text{Th})\text{VO}_4$ NPs (Figure 4b), where ^{227}Th is a tetravalent cation and both Th and Gd cations have similar effective ionic radii (~94 pm, CN = 6) [54]. The radiochemical yield ($72.3 \pm 3.0\%$) and encapsulation (~75%) of ^{223}Ra in $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs are consistent with the $79.9 \pm 15.5\%$ chemical yield of Ba cations obtained from the surrogate-doped GdVO_4 NPs (Figure 4c). The difference in effective ionic radii of both Ra (148 pm, CN = 8) and Ba (135 pm, CN = 6) cations compared to that of Gd may decrease the encapsulation of ^{223}Ra in GdVO_4 NPs because of limitations associated with a quantitative isomorphous substitution of Gd^{3+} for $\text{Ra}^{2+}/\text{Ba}^{2+}$ ions without changing the basic crystal structure [56]. The high activity fraction of ^{223}Ra observed in the dialysate from $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs, where GdCl_3 was added into the $^{223}\text{Ra}\text{-Na}_3\text{VO}_4$ mixture, may be related to the precipitation of radium hydroxides [$^{223}\text{Ra}(\text{OH})_2$] given the high pH of the Na_3VO_4 solution (12.5). This assumption is supported by the continuous increase of ^{223}Ra dialysate activity over time (Figure 4d), because as a free radionuclide the activity of ^{223}Ra is expected to stabilize in the dialysate after 24–48 h of dialysis based on surrogate-doped experiments. Overall, both $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs suspensions had lower encapsulation of ^{223}Ra compared to that of LaPO_4 core +2 shells NPs (>99.9%) [13], nanozeolites

(>99.5%) [18, 19], Fe_3O_4 NPs (>95%) [21], hydroxyapatite (85–95%) [22, 40], and CaCO_3 (>95%) [41].

The leakage of ^{221}Fr and ^{213}Bi (decay daughters of ^{225}Ac), ^{223}Ra and ^{211}Pb (decay daughters of ^{227}Th), and ^{211}Pb (3rd decay daughter of ^{223}Ra) from GdVO_4 NPs is attributed to their 100–200 keV recoil energy [14]. The 105.5 keV recoil energy of ^{221}Fr (calculated from classical conservation of momentum) was responsible for more than 50% leakage of ^{221}Fr from $\text{Gd}(^{225}\text{Ac})\text{VO}_4$ NPs (Figure 4a). The leakage obtained is comparable to the retention of ~40% and $60.2 \pm 3.0\%$ observed in $\text{La}(^{225}\text{Ac})\text{PO}_4$ and $\text{La}_{0.5}\text{Gd}_{0.5}(^{225}\text{Ac})\text{PO}_4$ core NPs [14, 16]. The higher retention of ^{221}Fr displayed by $\text{Gd}(^{225}\text{Ac})\text{VO}_4$ NPs with respect to $\text{Gd}_{0.8}\text{Eu}_{0.2}(^{225}\text{Ac})\text{VO}_4$ core NPs, prepared via citrate route, could be attributed to their larger size and tendency to aggregate [50]. Although the retention of ^{221}Fr was similar to that obtained in 100 nm polymersomes containing InPO_4 [30], the facile preparation of GdVO_4 NPs may be advantageous for their production as radiopharmaceuticals. Additionally, the small size of GdVO_4 NPs (<100 nm) could contribute to a longer circulation time and hence higher accumulation in tumor tissue with respect to polymersomes having a mean diameter >100 nm [57]. The leakage of ^{213}Bi was lower to that of ^{221}Fr even though ^{213}Bi is the third decay daughter of ^{225}Ac and its range in GdVO_4 with a crystal density of 5.47 g/cm^3 is 30.5 nm (Figure 4a). The range of ^{213}Bi was calculated using the Stopping and Range of Ions in Matter program for an ion energy of 130 keV [58]. The higher retention of ^{213}Bi could be attributed to a slower transport through the GdVO_4 lattice and the dialysis membrane [14] as well as its implantation into adjacent GdVO_4 NPs [37] facilitated by its chemical characteristics in comparison with the alkali metal ion of ^{221}Fr .

The $67.9 \pm 2.4\%$ radiochemical yield of ^{225}Ac from $\text{Gd}(^{225}\text{Ac})\text{VO}_4$ NPs is comparable to that reported for $\text{La}(^{225}\text{Ac})\text{PO}_4$ ($66 \pm 4\%$) [14], $\text{Ln}(^{225}\text{Ac})\text{PO}_4$ (57.5%) [16], and polymersomes (>64%) NPs [33]. Although the $66.8 \pm 7.2\%$ radiochemical yield of ^{227}Th in $\text{Gd}(^{227}\text{Th})\text{VO}_4$ NPs is lower than that of radioimmunoconjugates (>95%) [2, 59, 60], $\text{Gd}(^{227}\text{Th})\text{VO}_4$ NPs may decrease the expected demetallation of ^{227}Th from radioimmunoconjugates since the radionuclide is bound to an inorganic crystal structure. The difference in ^{223}Ra radiochemical yield between both $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs suspensions, 72.3 ± 3.0 and $34.1 \pm 2.9\%$, is attributed to the precipitation of $^{223}\text{Ra}(\text{OH})_2$ during synthesis. The radium hydroxide species seem to have slow transport and clearance from the dialysis membrane based on the continuous increase in dialysate activity observed over time. Overall, the ^{223}Ra radiochemical yield of both $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs suspensions was lower than that of nanozeolites (>99.9%) and Fe_3O_4 NPs (85–99%) [19, 21].

Increasing the radiochemical yield and retention of ^{223}Ra in GdVO_4 NPs would be a promising contribution towards the development of radium platforms for targeted alpha therapy since LnVO_4 NPs can also be used for multimodal molecular imaging [49, 50]. The retention of decay daughters in GdVO_4 NPs may be enhanced by designing core-shell structures with a composition similar to that of the core or different (e.g., gold or silica) [13, 16].

5 Conclusions

GdVO_4 NPs were successfully doped with ^{223}Ra , ^{225}Ac , and ^{227}Th to assess the encapsulation of α -emitting radionuclides and the *in vitro* retention of their decay daughters. GdVO_4 NPs crystallized in a tetragonal structure within a broad pH range of 4–12. The morphology of GdVO_4 NPs was influenced by the pH at which the suspension was kept during synthesis, resulting in the formation of polycrystalline particles with anisotropic or ellipsoidal/trapezoidal shape when the pH was low (~8) or high (~11). Doping GdVO_4 NPs with surrogate cations provided a tool to assess and compare the encapsulation and radiochemical yield of radionuclides in GdVO_4 NPs with respect to their chemical yield. Based on the results obtained for $\text{Gd}(^{223}\text{Ra})\text{VO}_4$ NPs, the order in which GdCl_3 and Na_3VO_4 were mixed during the synthesis influenced the encapsulation of ^{223}Ra and the *in vitro* retention of ^{211}Pb . The encapsulation and *in vitro* retention of radionuclides in GdVO_4 NPs were determined by the chemical characteristics of α -emitting radionuclides and the recoil energy of decay daughters. Quantitative encapsulation of ^{227}Th (~100%) suggests the potential use of GdVO_4 NPs as platforms for targeted alpha therapy with the ability to incorporate molecular imaging functionalities. The *in vitro* retention of decay daughters (^{221}Fr , ^{213}Bi , ^{223}Ra , and ^{211}Pb) within GdVO_4 NPs may be enhanced by modifying the particle surface with functional groups and/or an inorganic shell.

Acknowledgments: This research was supported by Virginia Commonwealth University with the support of the Mechanical and Nuclear Engineering Department and the NRC-HQ-84-14-FOA-002, Faculty Development Program in Radiation Detection and Health Physics at Virginia Commonwealth University, an appointment to the Oak Ridge National Laboratory Nuclear Engineering Science Laboratory Synthesis program, sponsored by the U.S. Department of Energy and administered by the Oak Ridge Institute for Science and Education, and the U.S. Department of Energy Isotope Program, managed by the Office of

Science for Nuclear Physics. The authors would like to thank the assistance received from the staff of the Nuclear and Radiochemistry Group at Oak Ridge National Laboratory, the Nanomaterials Core Characterization Facility from the School of Engineering, and the Instrumentation Laboratory from the Department of Chemistry at Virginia Commonwealth University.

Author contribution: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: This research was supported by the Virginia Commonwealth University, Oak Ridge National Laboratory, U.S. Department of Energy.

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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