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Catechin tuned magnetism of Gd-doped orthovanadate through morphology as T_1 - T_2 MRI contrast agents

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Tetragonal (*t*)- LaVO_4 has turned out to be a potential host for luminescent materials. Synthesis of *t*- LaVO_4 till date has been based on chelating effect of EDTA making it not ideal for bioimaging applications. An alternative was proposed by us through the use of catechin. In recent times there is interest for new MRI contrast agents that can through appropriate doping function both as MRI contrast and optical/upconversion materials. It is generally believed that under appropriate doping, *t*- LaVO_4 would be a better upconversion material than monoclinic (*m*)- LaVO_4 . Based on these postulations, this work explores the use of gadolinium doped *t*- LaVO_4 as an MRI contrast agent. From literature, gadolinium oxide is a good T_1 contrast agent. Through this work, using catechin as a template for the synthesis of Gd doped *t*- LaVO_4 , we demonstrate the possible use as a T_1 contrast agent. Interestingly, as the catechin concentration changes, morphology changes from nanorods to square nanoplates and spheres. In this process, a switch from T_1 to T_2 contrast agent was also observed. Under optimal concentration of catechin, with a rod shaped Gd doped *t*- LaVO_4 , an r_2/r_1 value of 21.30 was observed. Similarly, with a spherical shape had an r_2/r_1 value of 1.48 was observed.

In recent years, efforts to couple imaging modalities such as optical and magnetic resonance imaging have met with success. Such coupling brings to the fore the advantages of both the methods, say, with respect to imaging resolution and penetration depth^{1,2}. Magnetic resonance imaging (MRI) is a non-invasive method to diagnose diseases owing to its high spatial resolution and good soft-tissue contrast. It works either by shortening the longitudinal (T_1) or the transverse (T_2) relaxation time of water protons. MRI contrast agents (CAs) can be classified as either positive (T_1) CAs or negative (T_2) CAs. Typically, MRI signal obtained by T_2 CAs is easily confused with other artifact signals, like calcification, bleeding, and metal deposits, etc. Generally positive T_1 CAs is widely used as extracellular, hepatobiliary, and blood pool agents in medical imaging. Positive T_1 CAs gained its advantage for a bright MR image, high longitudinal relaxation rate, low cytotoxicity, and low intake dose. Currently, Gadolinium chelates like Gd-DOTA and Gd-DTPA are used as T_1 CAs but release a certain amount of free Gd ions, which inhibit calcium channels which leads to cardiovascular and neurologic toxicity. Also, Gd-based inorganic nanoparticles, such as carbonate ($\text{Gd}_2(\text{CO}_3)_3$), fluoride (GdF_3 , NaGdF_4), oxide (Gd_2O_3), and vanadate (GdEuVO_4) were investigated³. The advantage of doping Gd ions into the host crystal structure lies in a very low leaching of free Gd ions and even more stable than Gd based MRI contrast agents⁴. In Gd doped host lattices, surface Gd^{3+} ions offer all seven of its unpaired electron for water hydration by inner sphere contribution, which cooperatively induce the longitudinal relaxation of water proton. Gd^{3+} chelates can only offer one hydrate position since their other six unpaired electrons are coordinated by chelates. This synergistic effect enhances relaxivity value of Gd doped host lattices than Gd chelates³. Nanostructures based on Gd^{3+} doped NaYF_4 , codoped with $\text{Yb}^{3+}/\text{Er}^{3+}$ has been reported for upconversion imaging coupled with MRI⁵. Unfortunately, fluorides tend to be hygroscopic and have less favorable chemical and photophysical stabilities⁶.

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Lanthanide orthovanadates are potential hosts for luminescent materials, when in appropriate matrices. LaVO_4 exists in two phases, viz., the monoclinic, monazite structure and tetragonal zircon structure. La^{3+} generally prefers the monazite structure as the thermodynamically stable state. While $m\text{-LaVO}_4$ is not a suitable host for luminescent activators, $t\text{-LaVO}_4$ is a promising phosphor. This variability in the properties of the polymorphs, had created an extensive interest in selective synthesis and phase change processes⁷. Through the years, hydrothermal method based on EDTA has emerged as an effective way to synthesize the metastable $t\text{-LaVO}_4$ ⁸.

Though $t\text{-LaVO}_4$ has emerged as a potential luminescent material, the success of the same as an upconversion phosphor has been limited. It is only recently that Singh *et al.*⁹ and Zheng *et al.*¹⁰ reported the upconversion properties of $\text{Yb}^{3+}/\text{Er}^{3+}$ doped $t\text{-LaVO}_4$. No such reports were found in the literature for Gd-doped $t\text{-LaVO}_4$. One of the challenges for the bioimaging applications of the orthovanadate is in the use of EDTA for the selective synthesis of $t\text{-LaVO}_4$. EDTA is known to bring about cytotoxicity¹¹.

Encouraged by the need to overcome the drawbacks, we for the first time report catechin assisted $t\text{-Gd}$ -doped lanthanum vanadate (GL) nanoparticles with varying morphologies as T_1 contrast agents. Catechin possesses a large number of phenolic hydroxyl groups susceptible for metal chelation, and its biocompatibility led to the choice compared to that of other existing additive systems like EDTA, and citric acid. As structure of catechin is pH dependent, it is stable in highly acidic solution and unstable in neutral or alkaline solution. In general, Catechin is absorbed from the human intestinal tract, largely metabolized and distributed as conjugated derivatives in blood, and that these forms are excreted in urine¹². Catechin is known for its superior hydrophilic antioxidant property because of its higher number of hydroxyl groups and retards lipid oxidation. It can scavenge hydroxyl, peroxy, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. The thermal stability of catechin in the presence of oxygen is 227 °C and weight loss from 50 to 110 °C is due to water evaporation¹³. Catechin interacts with plasma proteins through different covalent and noncovalent bonds (i.e., hydrogen bonding, π -bonding, hydrophobic, and ionic interactions), and brings about significant changes in structure, physicochemical properties, and the activity of proteins¹⁴. It has a strong affinity with lipid bilayers, which facilitates their entry into cancer cells¹⁵. Since catechin is known for its beneficial effects like antioxidative, anticancer, anti-inflammatory and antithrombogenic activities^{7,11,16} it is expected that catechin modulated hydrothermal synthesis could offer a 3-fold advantage, viz., phase, morphology, and magnetization directed synthesis.

Results and Discussion

The role of catechin hydrate (*cat*) in polymorph selection for a doped system can be seen from Fig. 1. The product obtained from the hydrothermal treatment of $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$, $\text{Gd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ and Na_3VO_4 in the absence of catechin, was well indexed to $m\text{-LaVO}_4$ (JCPDS No. 500367) with a space group (p21/n), cell parameters $a = 7.043 \text{ \AA}$; $b = 7.279 \text{ \AA}$; $c = 6.721 \text{ \AA}$ and cell volume = 333.071 \AA^3 (Fig. 1A(a)). Incorporation of *cat* as ligand accelerates the formation of tetragonal phase with cell parameters $a = b = 7.4578 \text{ \AA}$; $c = 6.5417 \text{ \AA}$ and cell volume = 363.841 \AA^3 [JCPDS no. 10-705226; space group I41/amd (141)] as shown in Fig. 1A(b). It can thus be seen that at an appropriate concentration of *cat*, the formation of pure $t\text{-LaVO}_4$ without the presence of impurity phases such as $m\text{-LaVO}_4$ is possible, similar to our earlier observations (Fig. 1B). Catechin act as the capping as well as stabilizing agent by the interaction of Ln^{3+} ($\text{Ln} = \text{La}, \text{Gd}$) with phenolic OH groups at 5, 7, 3', 4' positions (Fig. 2)¹⁷. Well-resolved peaks, as can be seen in Fig. 1B, indicates a highly crystalline nature, alongside lower defects, the added advantage being the use of low hydrothermal treatment temperature (180 °C). Sharp peaks with even peak profiles coupled with highly crystalline nature is an indication of smaller crystallite sizes. This can be further confirmed from the crystallite size calculated by Debye-Scherrer formula. Cell parameters thus obtained are provided in Table 1. Lattice strain calculated by Williamson-Hall (W-H) method employing the plot in Fig. 1C, further demonstrates the formation of the metastable state. Crystal structure of five GL nanoparticles was established from Rietveld structural refinement of slow scan powder XRD data (Fig. 3).

An indication of the morphological features of the nanoparticles was obtained from transmission electron microscopic images (TEM). Gd doped $m\text{-LaVO}_4$ (marked as *MGL* for better representation) nanoparticles were spherical with an average size of around 40 nm (Fig. 4a). In the presence of *cat*, $t\text{-LaVO}_4$, with a rod-like morphology (mean length of 30 nm, mean diameter of 9 nm, the aspect ratio of 3) was obtained (Fig. 4b, marked as *TGL* for better representation). Morphological changes with varying *cat* concentration are depicted in Fig. 4c–h, where at 0.01 mM *cat* (marked as *01GL*), nanorods with the length of 20–30 nm and diameter of 7 nm, the aspect ratio of 3 was observed. That the LaVO_4 existed in the tetragonal form was confirmed by comparing the lattice fringes ($d = 2.2388 \text{ \AA}$), with the (301) plane of standard $t\text{-LaVO}_4$. At 0.05 mM *cat*, the nanoparticles (marked as *5GL*) existed as irregular rectangular NPs with the length of 14–25 nm and diameter of 12–22 nm respectively. Corresponding high-resolution images and SAED pattern (inset of Fig. 4e) showed the single crystalline character that could easily be correlated to standard $t\text{-LaVO}_4$. As the concentration of *cat* is increased (0.1 mM, marked as *1GL*), a thermodynamically stable spherical morphology is obtained, with a diameter in the range of 12 nm. HRTEM image of *1GL*, indicated well-defined 2D lattice planes with d spacing of 1.9231 Å indexed to (312) plane [JCPDS-10705226]. SAED (Fig. 4g inset) of *1GL* shows a single crystalline diffraction pattern, indexed to (200), (211) and (103) planes of $t\text{-LaVO}_4$.

Gd doped LaVO_4 nanoparticles obtained by employing *cat* as a chelating agent was analysed by TGA and FTIR. The spectra presented in Fig. 5 provide an indication of 8–14% organic matter being still present in the residue. TGA profile of nanoparticles showed dehydration of water around 100 °C¹⁸, followed by further weight loss between 200–450 °C, corresponding to catechin, as reported elsewhere¹¹. From the FTIR spectrum, it can be seen that the hydroxyl groups in phenolic and water molecules appear as broad absorption band around 3400 cm^{-1} , the doublet bands observed at 1634 and 1410 cm^{-1} are related to the localized vibration of VO_4 groups and C=C stretching frequencies from the aromatic rings. A band around 800 cm^{-1} , corresponds to the characteristic peak of V-O from VO_4 groups¹⁹ and C-O-C group in catechin molecules^{7,16}.

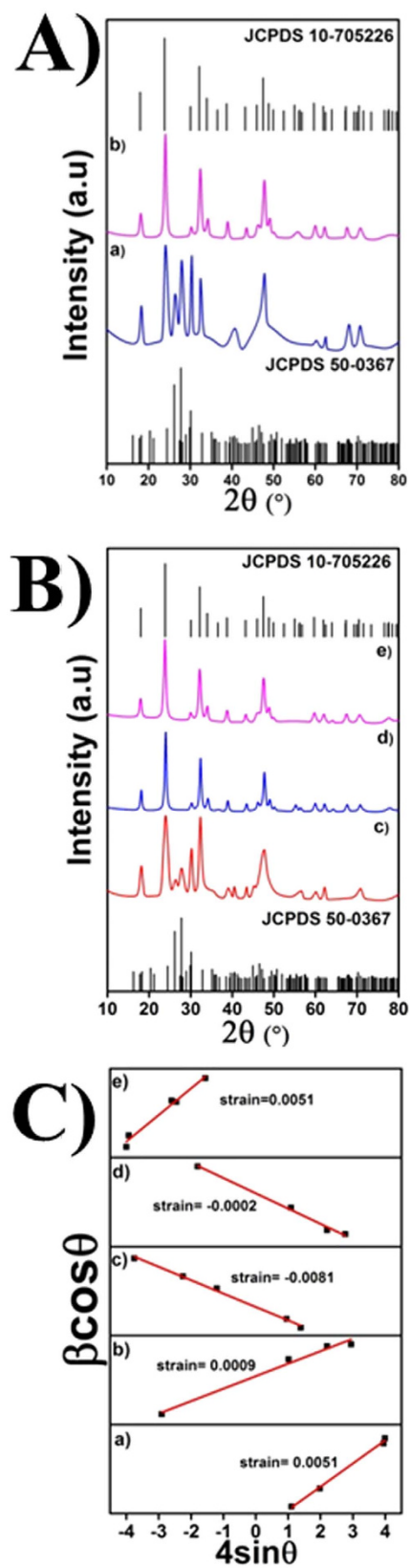


Figure 1. XRD pattern of GL nanoparticles (A) without *cat* (a) and *cat* (b, [cat⁴⁺]/[La³⁺] = 1:0.05) (Experimental conditions: T = 210 °C, t = 4 h, pH = 7), (B) [cat⁴⁺]/[La³⁺] = 1:0.01 (c), [cat⁴⁺]/[La³⁺] = 1:0.05 (d) and [cat⁴⁺]/[La³⁺] = 1:1 (e) (Experimental conditions: T = 180 °C, t = 24 h) and (C) Corresponding W-H plot.

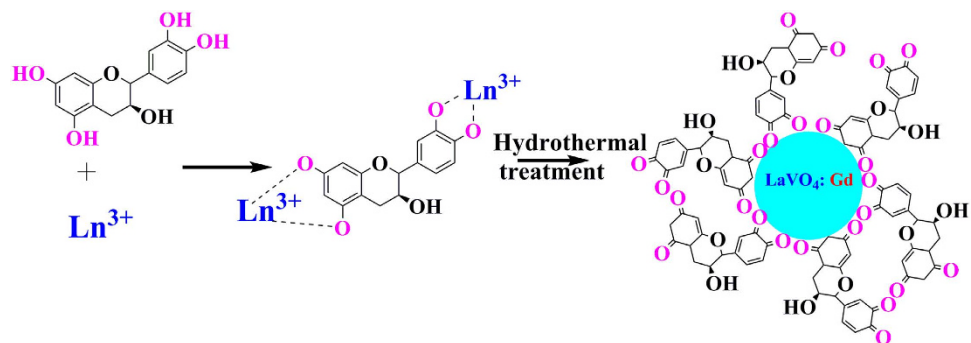


Figure 2. Depicts the formation of GL nanoparticles using catechin hydrate.

Sample	Catechin molar ratio	Temperature (°C)	Duration (h)	Lattice parameters (Å)	Cell volume (Å ³)	Crystallite size (nm)	Number mean diameter d (nm)	PDI
MGL	0	210	4	a = 7.0168 Å; b = 7.2518 Å; c = 6.6957 Å	329.31	8.82	798	0.59
TGL	0.05	210	4	a = b = 7.4306 Å; c = 6.5236 Å	360.19	13.46	31.03	0.24
01GL	0.01	180	24	a = b = 7.4066 Å; c = 6.5088 Å	357.06	6.84	68.99	0.33
5GL	0.05	180	24	a = b = 7.4464 Å; c = 6.5247 Å	361.79	16.4	65.92	0.27
1GL	0.1	180	24	a = b = 7.4465 Å; c = 6.5321 Å	362.21	13.32	32.57	0.27

Table 1. Summary of the experimental conditions, crystal lattice parameters and the corresponding size of the GL nanoparticles.

Dynamic Light Scattering (DLS) in back scattering geometry was performed to determine the hydrodynamic size of the Gadolinium doped LaVO_4 nanoparticles. Figure 6a presents the hydrodynamic diameters of the nanoparticles dispersed in double distilled water (1 mg/5 mL). Assuming a spherical geometry, DLS measurement has been carried out. The nanoparticles demonstrated polydisperse behavior (PDI = 0.590) with a number average diameter of 798 nm, attributable to the nonuniform size and nanoparticle aggregation. Number average diameter of nanoparticles in the presence of catechin was low, suggesting that strong capping effect had rendered uniform size. Polydispersity index (PDI) of 0.24, 0.33, 0.27, and 0.27 respectively indicate a near monodisperse distribution.

Zeta potential values provide information on the stability of the nanoparticles in a given environment^{20–22}. The pH at which charge of the nanoparticle and its immediate surroundings (double layer) becomes zero (point of zero charge (PZC)) was monitored (Fig. 7A) and it was found that PZC changes from 6.91 to 3.25 and then increases to 7.93. This shift in PZC to a higher pH value could be attributed to the presence of catechin molecules on the nanoparticle surface. In the absence of *cat* the Gd doped LaVO_4 synthesized had a positive charge (28.7 ± 0.5 mV) at pH 8, which shifted to a negative value of -17.1 mV on treatment with *cat*, indicating that the surface of the nanoparticles was covered with organic moiety⁷. At *cat* concentration of 0.05 to 0.1 mM, the zeta potential values of the doped vanadates were more or less constant at around -16 ± 1 mV. A high negative zeta potential, as observed in this study is an indication of the stability of the Gd doped *t*- LaVO_4 making it viable for potential biological applications. A zeta potential value of 1.56 mV observed for the nanoparticles at a *cat* concentration of 0.01 mM could be attributed to the fact that cationic Ln^{3+} ions were coordinated to phenolic -OH groups in catechin, resulting in the neutralization of the negative surface charge. The presence of Gd, V, La, O and C was confirmed from the EDAX spectra (Fig. 7B). The atomic ratio for La^{3+} and Gd^{3+} was determined as 0.92 and 0.06 respectively, approaching the theoretical value. Gadolinium concentration in MGL, TGL, 01GL, 5GL, 1GL was found to be 2.83, 0.574, 7.712, 10.32, 1.89 mg/kg from ICP-OES measurements.

Luminescence properties of Gd doped *t*- LaVO_4 nanoparticles is shown in Fig. 8. The strong absorption band around 267 nm corresponds to charge transfer from the oxygen ligands to central vanadium metal in VO_4^{3-} groups²³. Gd doped *t*- LaVO_4 exhibit emission peak at 334 nm corresponds to ${}^6\text{P}_{8/2} \rightarrow {}^8\text{S}_{7/2}$ transition of Gd^{3+} ²⁴ whereas emission group lines between 360 and 520 nm, corresponds to VO_4^{3-} transitions²⁵. MTT assay²⁶ was performed in order to understand the effect of Gd- doped tetragonal LaVO_4 on cell viability and toxicity. The results of MTT assays are given in Supporting Figure S1. The results showed that treatment of HaCaT cells with Gd- doped tetragonal LaVO_4 did not affect the viability of the cells. The cells did not show significant toxicity at Gd- doped tetragonal LaVO_4 concentration as high as 100 μg . The results are consistent with the microphotographs which revealed that the cell structure and morphology were not affected at a concentration as high as 100 μg (Figure S1).

Magnetization curves measured in the applied magnetic field sweeping from -15 to 15 kG at 300 K, in the presence and absence of *cat* is presented in Fig. 9. The samples were found to be paramagnetic (P) with a high

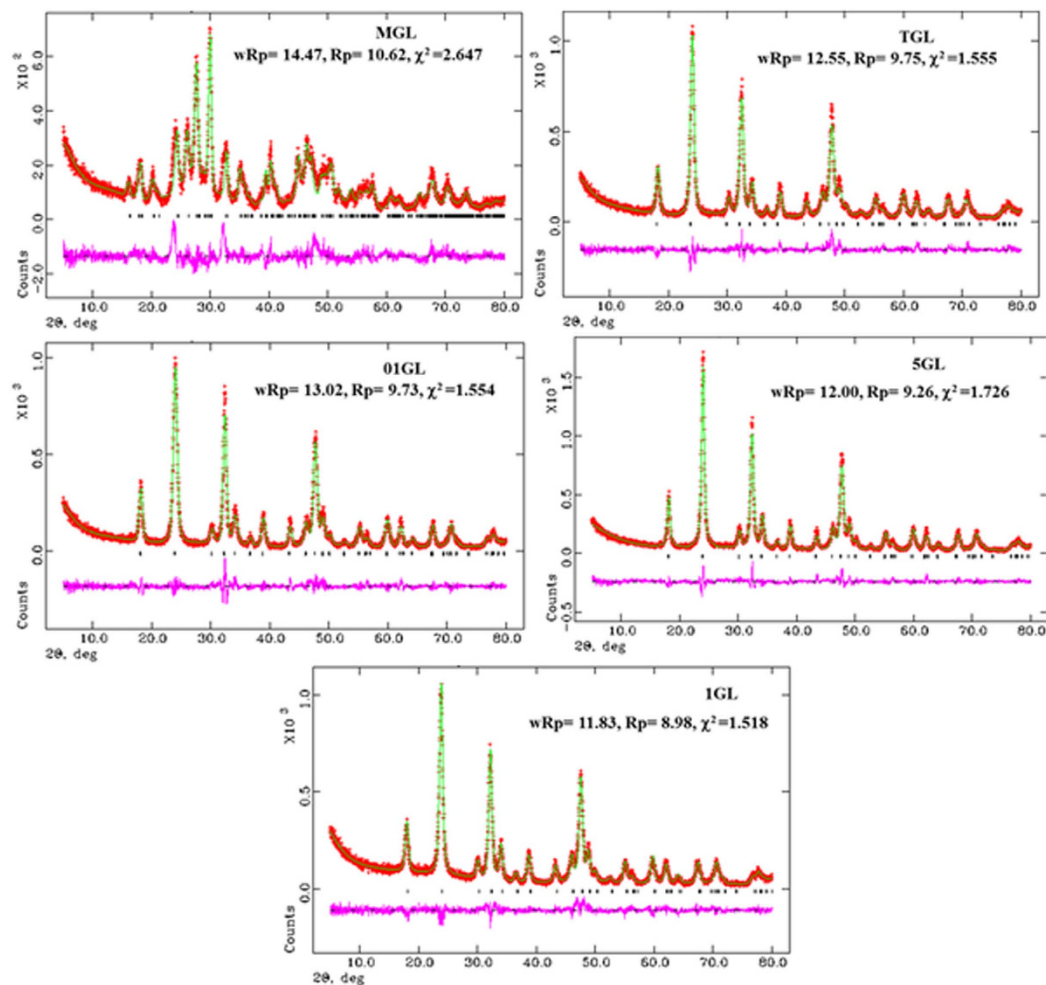


Figure 3. Final Rietveld XRD data plot of GL nanoparticles with the values of agreement factors and χ^2 (red, observed; green, calculated; black, vertical bars – positions of the Bragg reflections; pink, difference between observed and calculated intensities).

paramagnetic moment, attributable to a higher number of unpaired electrons in the half-filled $4f^7$ outermost orbital of the Gd^{3+} ion²⁷ with M_s value of 42.4, 18.32, 56.19 and 58.87 emu/g respectively. It is known that saturation magnetization of nanoparticles can be affected by structural defects; crystallite size, shape and amount of catechin present on the $LaVO_4$ nanoparticle, i.e. surface state^{28–33}. At higher *cat*, nanoparticles become superparamagnetic (SP), with a low M_s value of 0.0288 emu/g^{34,35}. This shift in M_s may be due to strong co-ordination ability of the catechin molecules³⁶. Comparatively, saturation magnetization on a per-gram basis is lower may be due to the lack of full spin alignment in the particles i.e. spin canting effect induced by the high mass of the nonmagnetic catechin coating on the nanoparticle surface^{37,38}. This clearly establishes that catechin molecules play a key role on magnetic properties of nanoparticles. Table 2 records the coercivity (H_c), saturation magnetization (M_s), remnant magnetization (M_r) and squareness ratio values for the nanoparticles. The ratio of M_r to M_s is almost found to be constant for all paramagnetic material.

We examined the possibility of developing P-Gd and SP-Gd as MRI bimodal contrast agents. To evaluate the MRI imaging properties, series of gadolinium doped $LaVO_4$ nanoparticles in aqueous solutions containing different concentrations (3.6, 1.8, 0.9, 0.45, 0.23 and 0 mM) were prepared for MRI phantom and relaxivity studies. The longitudinal relaxivity (r_1) and transverse relaxivity (r_2) of the Gd doped *t*- $LaVO_4$ (with *cat*) were determined and compared with that of Gd doped *m*- $LaVO_4$ nanoparticles (without *cat*) (Fig. 10). It is clear from the Fig. 10 that tetragonal phase had better positive contrast enhancement than that of monoclinic phase. Gd doped *t*- $LaVO_4$ nanoparticles had an r_1 of $0.142 \text{ mM}^{-1}\text{s}^{-1}$, which was more than five times that of Gd doped *m*- $LaVO_4$ nanoparticles ($0.030 \text{ mM}^{-1}\text{s}^{-1}$). The ratio between transverse and longitudinal relaxivity (r_2/r_1) was found to be low for Gd doped *t*- $LaVO_4$ nanoparticles (2.55), compared to that of Gd doped *m*- $LaVO_4$ nanoparticles (5.2). This increase in the r_1 value coupled with a reduction in r_2/r_1 provides for the Gd doped *t*- $LaVO_4$ nanoparticles being ideal for use as T_1 contrast agent^{39,40}.

In order to understand the role of anisotropic morphology, lanthanum chloride was employed as a precursor at 180°C for 24 h. The results presented in Fig. 11 and Table 3 indicates a variation in the r_2/r_1 values. Interestingly

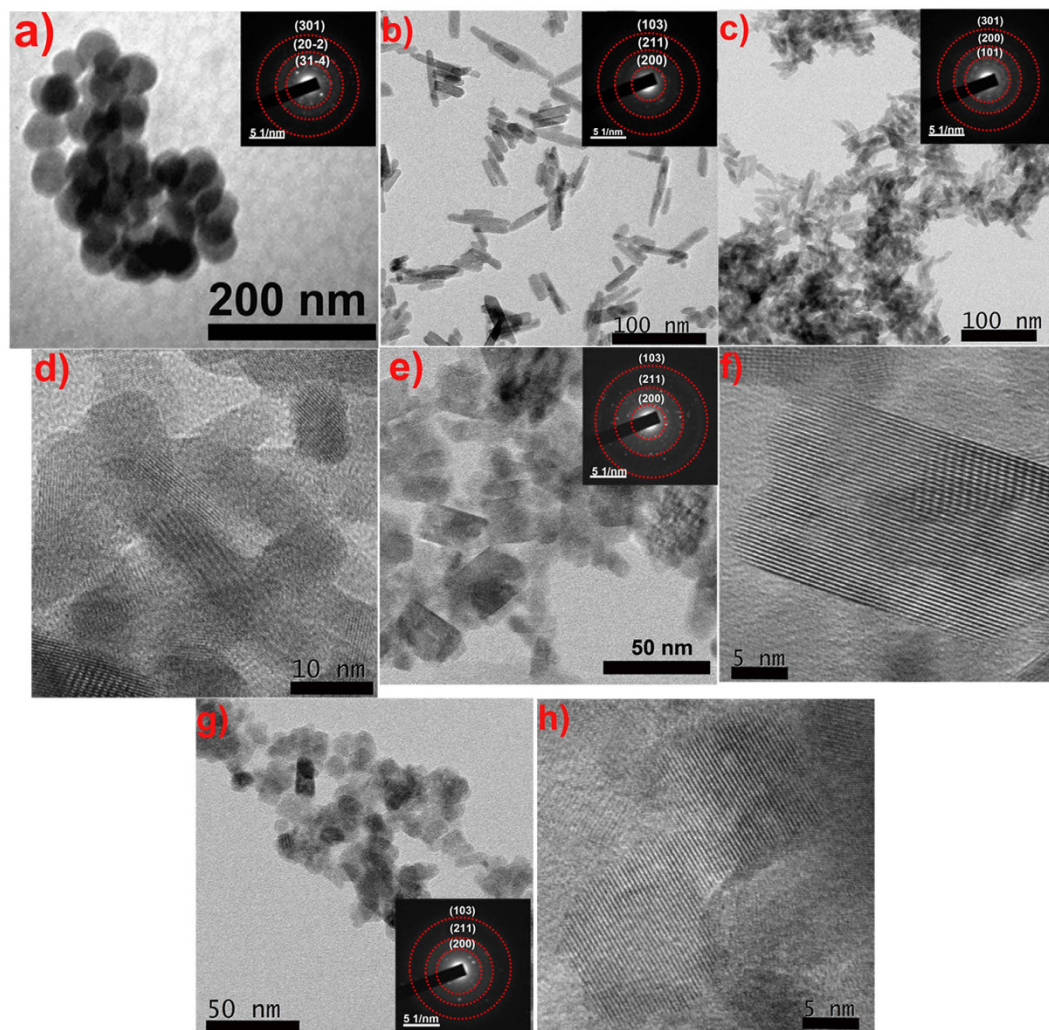


Figure 4. TEM Image for MGL (a), TGL (b), 01GL (c), 5GL (e) and 1GL (g) and HRTEM images of 01GL (d), 5GL (f) and 1GL (h) nanoparticles [Inset represents the corresponding SAED pattern].

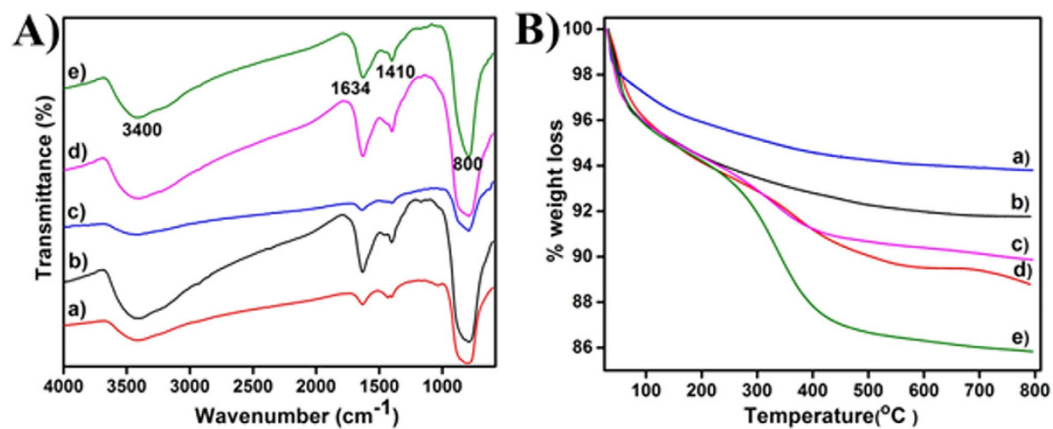


Figure 5. FTIR spectrum (A) and TGA (B) for (a) MGL, (b) TGL, (c) 01GL, (d) 5GL and (e) 1GL nanoparticles.

at low *cat* concentration (0.01 mM), nanoparticles exhibited properties ideal for a T_2 contrast agents with high r_2 value ($3.749 \text{ mM}^{-1}\text{s}^{-1}$) and r_2/r_1 of 21.30^{39,41}. At 0.05 mM of catechin, nanoparticles lose their ability as T_2 instead

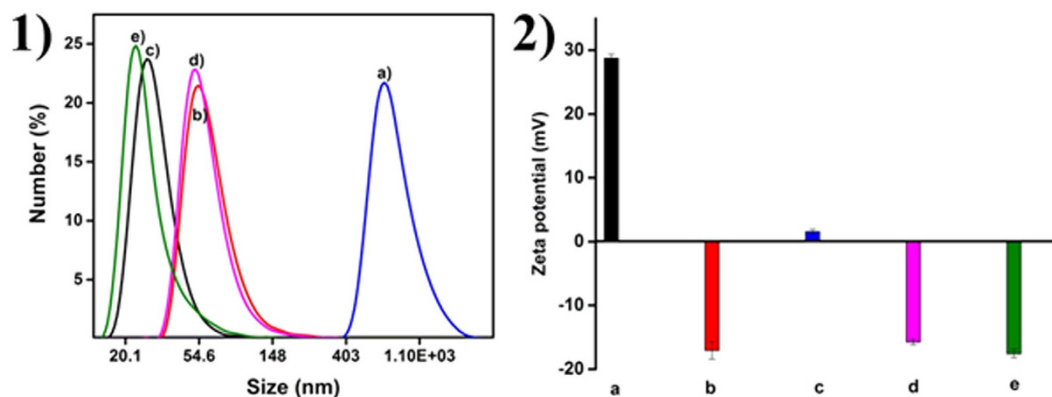


Figure 6. DLS (1) and Zeta potential (2) for (a) MGL, (b) TGL, (c) 01GL, (d) 5GL, and (e) 1GL nanoparticles.

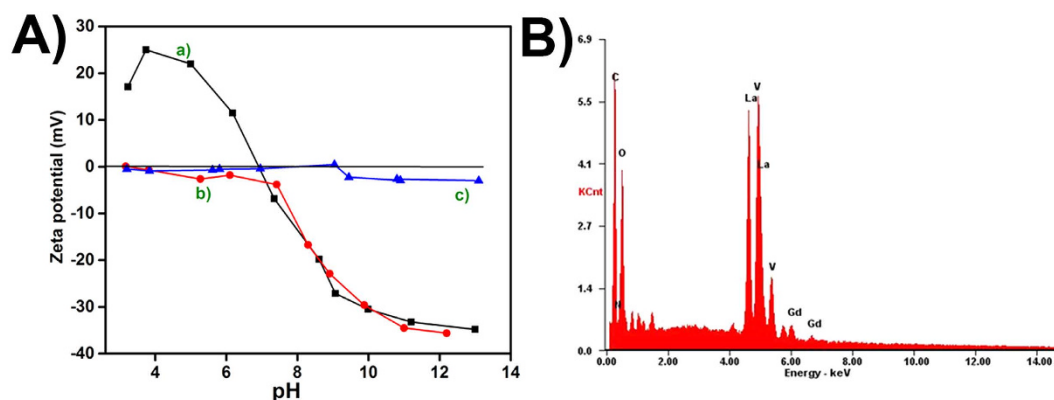


Figure 7. Zeta potential at various pH values for (A) 01GL (a), 5GL (b) and 1GL (c) and EDAX spectrum (B) nanoparticles.

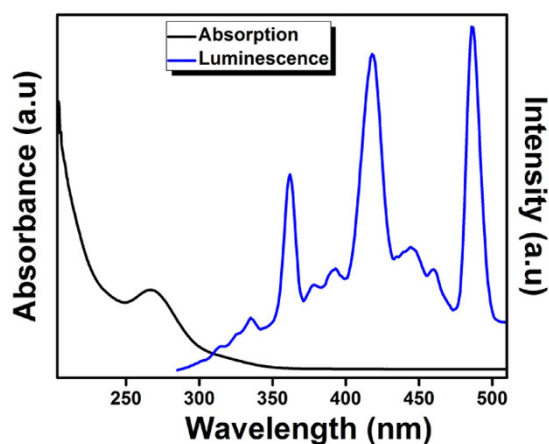


Figure 8. Absorption (Black line) and luminescence spectra (Blue line) for Gd doped *t*-LaVO₄ nanoparticles.

to T₁ contrast agent with a decrease in the r_2/r_1 ratio (6.46) and r_1 and r_2 values are greatly reduced^{42,43}. At a higher cat concentration, SP nanoparticles with almost identical r_1 ($0.046 \text{ mM}^{-1}\text{s}^{-1}$) and r_2 ($0.068 \text{ mM}^{-1}\text{s}^{-1}$) values and moderate r_2/r_1 (1.48) ratio, with potential to serve as an excellent candidate for T₁-T₂ dual-mode contrast were obtained. This observation is further supported by phantom imaging studies (Fig. 11)^{39,44}. To conclude, based on the r_2/r_1 ratio, r_1 , and r_2 values, it has been found that the Gd-doped LaVO₄ nanoparticles developed in this

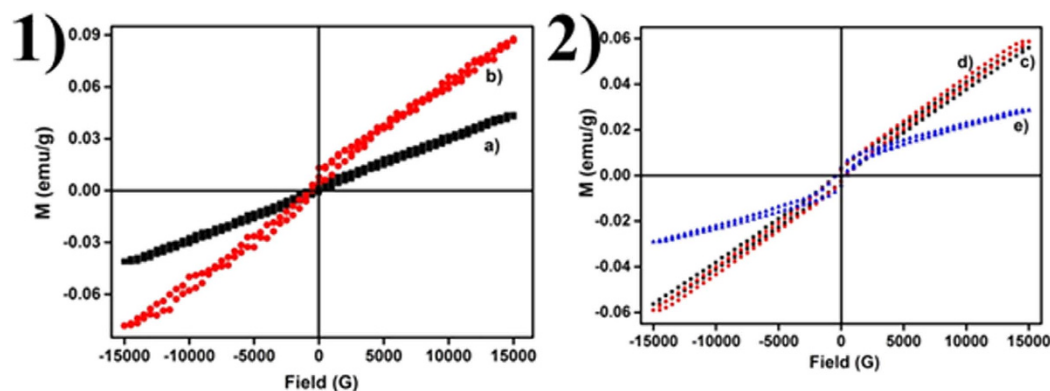


Figure 9. Magnetization curves of GL nanoparticles at 300 K **1)** without *cat* **(a)** and *cat* **(b)**, $[\text{cat}4^-]/[\text{La}3^+] = 1:0.05$ (Experimental conditions: $T = 210^\circ\text{C}$, $t = 4$ h, $\text{pH} = 7$), **2)** $[\text{cat}4^-]/[\text{La}3^+] = 1:0.01$ **(c)**, $[\text{cat}4^-]/[\text{La}3^+] = 1:0.05$ **(d)** and $[\text{cat}4^-]/[\text{La}3^+] = 1:1$ **(e)** (Experimental conditions: $T = 180^\circ\text{C}$, $t = 24$ h).

Sample	M_s (emu/g)	$M_r \cdot 10^{-3}$ (emu/g)	H_c (G)	$S = M_r/M_s$
MGL	42.4	2.03	525.71	$5 \cdot 10^{-5}$
TGL	18.32	0.36	137.30	$2 \cdot 10^{-5}$
01GL	56.19	2.55	441.46	$5 \cdot 10^{-5}$
5GL	58.87	2.67	441.82	$5 \cdot 10^{-5}$
1GL	0.0288	3.94	474.08	$13.68 \cdot 10^{-2}$

Table 2. Magnetic characteristics of the GL nanoparticles.

study can be tailored to function as T_1 , T_2 and T_1 - T_2 contrast agents through tuning of *cat* concentration. Such multi-contrast MRI labeling provides unique opportunities for non-invasive multicellular tracking.

Conclusion

In this paper, we have synthesized Gd-doped LaVO_4 nanoparticles with different crystal structure and varying morphology, viz., sphere, rods, and irregular rectangular nanocrystals by a catechin directed hydrothermal method. With catechin concentration, the saturation magnetization values of rod shaped Gd-doped LaVO_4 was greater than that with spherical shape. During this process, the magnetic properties shifted to superparamagnetism from paramagnetism, owing to catechin strong coordination. The direct result of catechin concentration to magnetic property had a remarkable role in MRI applications. MRI studies established that superparamagnetic Gd-doped LaVO_4 could be employed as both T_1 and T_2 contrast agent, as against the common perspective of the same as a T_1 contrast agent alone.

Methods

Synthesis of Gd contrasts with different crystal structure. Gd doped LaVO_4 (GL) nanoparticles were prepared by co-precipitation method followed by ligand assisted hydrothermal method, carried out according to previously published methods⁷. For tetragonal LaVO_4 synthesis, we used an efficient ligand- catechin hydrate as a phase transfer agent. 0.06 mmol of catechin hydrate (molar ratio of catechin is 0.05 with respective to La^{3+} ions) was dissolved in 10 mL of double distilled water, to which molar ratio (1:0.05) of $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ and $\text{Gd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ aqueous solutions were added in drops and kept stirring for 30 min. To that, 1.2 mmol of the Na_3VO_4 solution was added in drops resulted in the brown color precipitate. The pH of the brown color precipitate was adjusted to 7. The reaction mixture was autoclaved at 210°C for 4 h, and the resultant product was washed thrice with water and ethanol twice by centrifugation (1500 rpm for 15 min). It was then air-dried to get the desired product. For monoclinic phase, the same procedure was adopted without catechin hydrate⁷.

Synthesis of Gd contrasts with varying concentration of catechin hydrate. Different concentrations of catechin hydrate (0.01, 0.05, 0.1 mmol) in 10 mL of distilled water, 1 mmol of $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ and $\text{Gd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (molar ratio = 1:0.05) was added in drops and left stirring for 30 min. Then, 1.05 mmol of Na_3VO_4 solution added in drops and stirred for 10 mins to get a brown color precipitate. The resulting solution undergoes hydrothermal treatment at 180°C for 24 h followed by centrifugation (1500 rpm for 15 min) with double distilled water thrice and twice with ethanol. The final product was obtained by air drying.

The slow-scan powder XRD data for five Gd doped LaVO_4 nanoparticles, were collected with a step size of 0.01° in the 2θ range of 10 – 80° . The GSAS-EXPGUI58 program was used for the Rietveld structure refinement from the powder XRD data. The refined parameters were scale factor, background as Chebyshev polynomial, unit

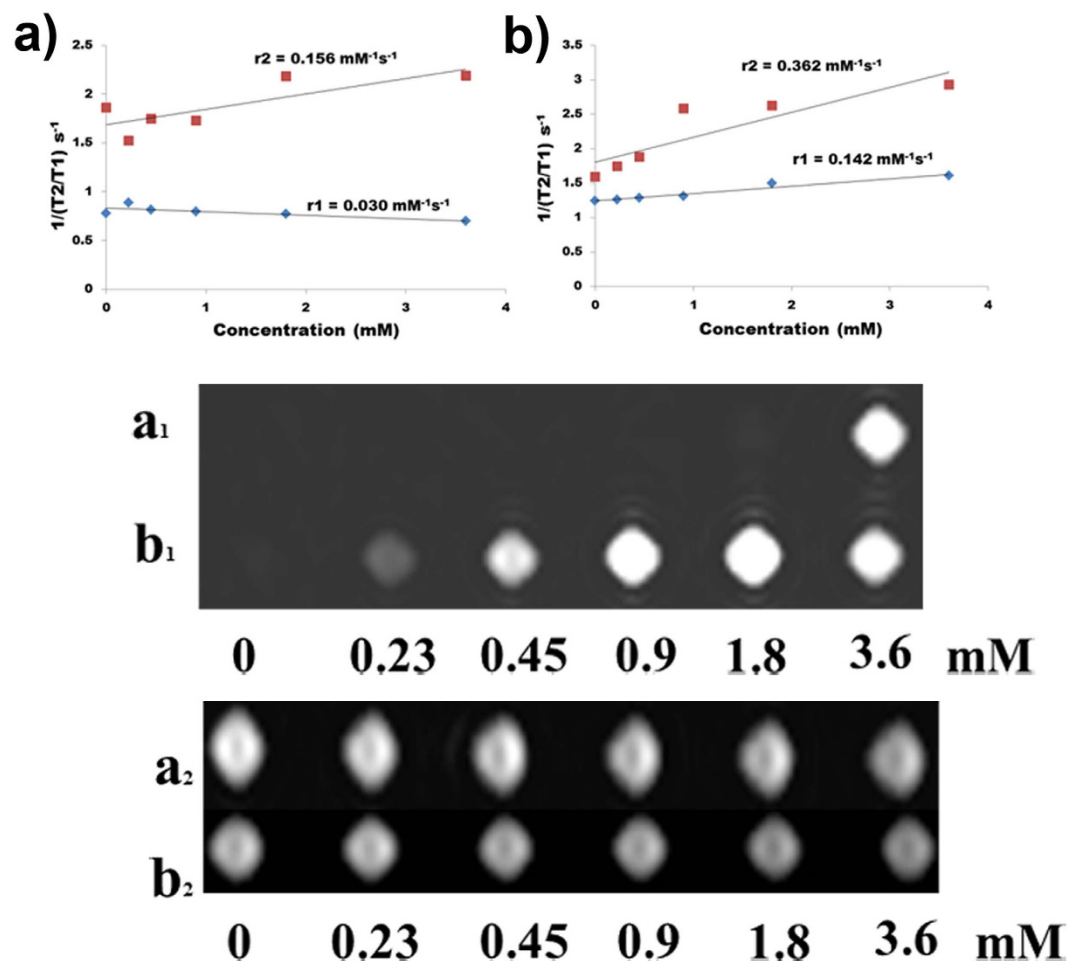


Figure 10. Linear fit plot employed for the calculation of r_1 and r_2 ; T_1 - and T_2 -weighted phantom images of GL nanoparticles with different concentrations where (a) MGL and (b) TGL. Subscript 1 and 2 represents T_1 and T_2 relaxivity.

Sample	magnetism	$r_2(\text{mM}^{-1}\text{s}^{-1})$	$r_1(\text{mM}^{-1}\text{s}^{-1})$	r_2/r_1
MGL	P	0.156	0.03	5.2
TGL	P	0.362	0.142	2.55
01GL	P	3.749	0.176	21.30
5GL	P	0.181	0.028	6.46
1GL	SP	0.068	0.046	1.48

Table 3. Summary of r_1 , r_2 , and r_2/r_1 ratios of the GL nanoparticles.

cell parameters, profile function (Gaussian and Lorentzian parameters, sample displacement) and atomic positions. The initial structural models for five Gd doped LaVO_4 , were based on their single crystal X-ray structures. The single crystal X-ray structure of Monoclinic LaVO_4 was used as a structure model for MGL. The single crystal X-ray structure of Tetragonal LaVO_4 was used as a structure model for TGL, 01GL, 5GL, and 1GL. The structural models turned out to be the correct ones in all cases. For all atoms, the isotropic thermal parameters from the single crystal X-ray structure were used and not refined. Positional parameters and profile functions were refined in alternate cycles until no substantial changes were observed in the positional parameters. The structure refinement proceeded smoothly to yield acceptable agreement factors.

Lattice strain was calculated by Williamson-Hall (W-H) method⁴⁵. A positive slope denotes tensile strain, and a negative slope of the W-H plot denotes compressive strain. A very low lattice strain observed owing to the effective ionic radii mismatch between La^{3+} and Gd^{3+} ions.

Measurement of magnetic resonance relaxivities. MR relaxivities of GL nanoparticles were measured using a clinical 1.5 T MR scanner (MAGNETOM Avento Tim System, M/s. Siemens, Germany) equipped

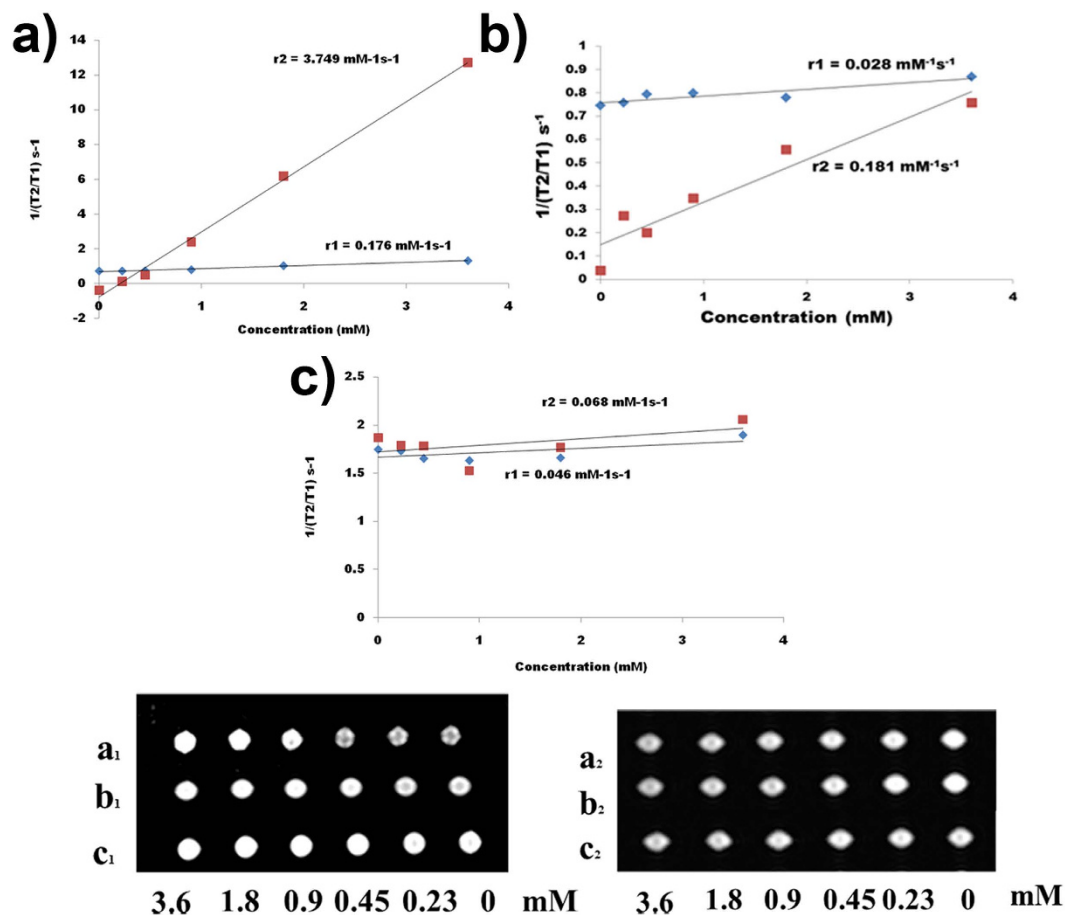


Figure 11. Linear fit plot employed for the calculation of r_1 and r_2 ; T_1 - and T_2 -weighted phantom images of GL nanoparticles with different concentrations where (a) 01GL, (b) 5GL and (c) 1GL. Subscript 1 and 2 represents T_1 and T_2 relaxivity.

with a head coil. For this, phantoms of different concentration of GL (0–3.6 mM) were prepared in deionized water and used. For T_2 relaxometry calculations, a modified T_2 relaxometry spin echo sequence with TE varying from 15–120 ms with Repetition Time (TR) of 2000 ms were run at three different planes of the phantoms and the pixel intensity with respect to concentration extracted. From the pixel intensity output, the transverse relaxation for each concentration was calculated by employing a linear fit program. For T_1 measurements, an inversion-recovery sequence was used with 7 non-equidistant time delays of 50, 100, 300, 700, 1200, 2000 and 3000 ms between inversion and the first 90° excitation pulse. Time of Echo (TE) and Time of Repetition (TR) are chosen as 15 and 4000 ms respectively. From the MR images corresponding to these inversion times, signal intensities for all the T_1 were obtained. The T_1 relaxation time of each sample was calculated applying these data to the intensity function of the MR signal.

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Author Contributions

S.K.J. wrote the main manuscript text. T.V. and A.S. carried out the experiments. J.S.R. and N.B.U. mented the work. All authors reviewed the manuscript.

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