

Gadolinium-based hybrid polyionic complexes as versatile precursors for Prussian blue-like nanoparticles with enhanced MRI relaxivity

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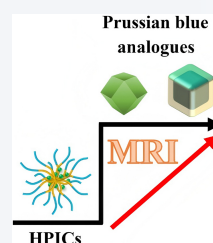
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ABSTRACT: Gd-based hybrid polyionic complexes are employed as versatile precursors to generate Prussian blue-like nanoparticles using two complementary strategies: (i) direct formation through the addition of $K_4[Fe(CN)_6]$, and (ii) post-modification of preformed Prussian blue nanoparticles. The resulting colloids are characterized in terms of size, morphology, and colloidal stability. Their magnetic resonance relaxivity is then systematically evaluated to assess their performance as magnetic resonance imaging (MRI) contrast agents. These Gd-containing Prussian blue-like nanoparticles exhibit enhanced relaxivity compared to conventional molecular Gd complexes, highlighting their strong potential as efficient and safer MRI contrast agents.

KEYWORDS: gadolinium (Gd), hybrid polyion complexes (HPCs), Prussian blue analogue (PBA), magnetic resonance imaging (MRI) contrast agent, nanoparticles



1 Introduction

Gadolinium (Gd)-based contrast agents (CAs) play a crucial role in magnetic resonance imaging (MRI), by enhancing the contrast between healthy and diseased tissues, thereby improving diagnostic accuracy. The development of novel Gd-based CAs is particularly important to minimize the retention of Gd ions in biological tissues. Two key challenges must therefore be addressed: (i) limiting the release of free Gd ions and (ii) increasing the relaxivity of Gd-based CAs in order to reduce the required injected dose [1, 2].

In this context, colloidal nanostructures have emerged as particularly promising platforms [3]. Gd-based nanostructures in the 10–100 nm size range can exhibit markedly enhanced relaxivity due to their longer rotational correlation time [4]. Although relaxivity can also be modulated by water exchange kinetics, electronic relaxation times, and particle size distribution, the Solomon–Bloembergen–Morgan theory predicts that the rotational correlation time becomes the dominating factor for nanoparticles in the 10–100 nm size range, where slowed tumbling leads to a marked increase in relaxivity [5]. One major class of colloidal systems is obtained by conjugating or associating Gd complexes

with a variety of chemical architectures, such as nanodots, tailored polymers, liposomes, and hybrid polyion complexes (HPICs) [6–8]. Furthermore, the use of inorganic nanoparticles (e.g., Gd_2O_3 , $GdPO_4$, $NaGdF_4$, and GdF_3) in place of molecular Gd complexes provides stronger confinement of Gd ions within the particle matrix, thereby minimizing in vivo ion release and, particularly at high magnetic fields, improving MRI performance [9–11]. The physicochemical properties of these nanoparticles are highly sensitive to their size, morphology, and surface coating, emphasizing the need for synthetic strategies that allow precise control over each of these parameters.

In this context, HPICs have attracted particular interest. HPICs possess coacervates structures that form spontaneously through the complexation of double hydrophilic block copolymers, comprising one neutral and one charged block, with polyvalent metal ions such as Mn(II), Cu(II), or Gd(III) [12, 13]. The resulting colloids exhibit narrow size distributions, well-defined hydrodynamic diameters, and high stability in aqueous media. These properties account for their wide use as drug carriers, MRI contrast agents [14–16], catalytic platforms [17, 18], and templates for inorganic nanomaterial synthesis [19–21].

In this context, iron based HPICs have emerged as frameworks of choice for the synthesis of Prussian blue nanoparticles, enabling precise control over nucleation kinetics and growth processes [22, 23]. Prussian blue analogs (PBAs), in which iron ions are partially substituted by other metal ions, represent a highly versatile class of materials that have been extensively investigated for applications in environmental remediation, energy storage, and

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catalysis. Their open-framework structures and tunable redox properties contribute to their broad utility [24–26]. This study explores the use of Gd-based HPICs, which hold intrinsic potential as T_1 -weighted MRI contrast agents due to the paramagnetic properties of Gd^{3+} ions, to generate Gd-based PBAs. However, the incorporation of Gd introduces unexplored challenges: Can Gd-PBA nanoparticles, synthesized via the HPIC-templated route, achieve colloidal stability under physiologically relevant conditions (e.g., in the presence of competing ions or under buffer conditions)? Do they exhibit enhanced relaxivity suitable for high-performance MRI, or does the PBA framework impose limitations on Gd^{3+} accessibility to water protons? To address these questions, two distinct synthetic strategies were employed (Scheme 1): (i) a direct formation via reaction with $K_4[Fe(CN)_6]$ and (ii) a post-modification of preformed Prussian blue nanoparticles. The resulting Gd-PBA nanoparticles were subsequently characterized to assess their size distribution, morphology, and colloidal stability under physiologically relevant conditions (e.g., ionic competition, buffered media). MRI relaxivity measurements were performed to evaluate Gd^{3+} accessibility to water protons and quantify their potential as T_1 -weighted contrast agents.

2 Experimental

2.1 Materials

Chemicals. NaH_2PO_4 , $Gd(NO_3)_3 \cdot 6H_2O$, $FeCl_3 \cdot 6H_2O$, $CaCl_2$, $K_4[Fe(CN)_6] \cdot 3H_2O$, $NaCl$, $NaOH$, HCl , and buffer solution were obtained from Sigma-Aldrich. The block copolymer PEO_{3k} - $PAA_{3.2k}$ (Polymer Source Inc.) was used as received. Deionized water (resistivity 18.2 $M\Omega \cdot cm$) was purified using a Purite filtration and ion-exchange system.

Preparation of HPIC solutions. The formation of **Gd-HPICs** was investigated by maintaining a constant concentration of PEO_{3k} - $PAA_{3.2k}$ (0.1 wt.%) while systematically varying the amount of $Gd(NO_3)_3 \cdot 6H_2O$ to achieve R values ($3[Gd^{3+}]/[AA^-]$) between 0 and 3. The pH of the resulting samples was then adjusted to different values using HCl (0.1 $mol \cdot L^{-1}$) and $NaOH$ (0.1 $mol \cdot L^{-1}$) solutions.

Preparation of Prussian blue nanoparticles (PB NPs). **PB NPs** were synthesized by reacting Fe-HPIC precursors (of different R values) with $K_4[Fe(CN)_6] \cdot 3H_2O$ in aqueous media. The detailed steps refer to previous work [12].

Preparation of Gd-Prussian blue analogues (Gd-PBA). **Gd-PBA** was synthesized using Gd-HPICs ($R = 1.0$) as the precursor. A stoichiometric amount of $[Fe(CN)_6]^{4-}$ solution was introduced, and

the mixture was stirred overnight to facilitate the formation of the product.

Synthesis of PB@Gd-PBA core-shell structure. In the first step, PB nanoparticles were prepared using the above method. The product was then subjected to centrifugation and washing, and finally redispersed in aqueous solution. In the subsequent step, Gd-HPICs and $K_4[Fe(CN)_6]$ were introduced into the PB nanoparticle dispersion, and the reaction was stopped following a 5 h stirring period.

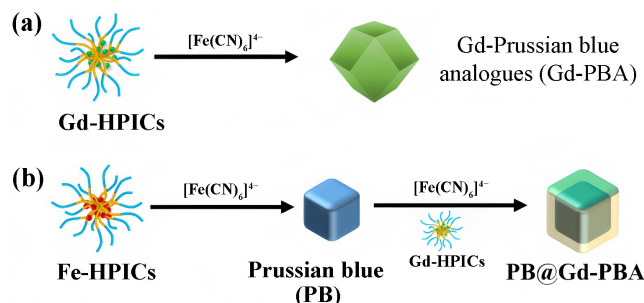
2.2 Methods

Dynamic light scattering (DLS) measurements were performed using a Zetasizer Nano-ZS (Malvern Instruments). A 4 mW He-Ne laser ($\lambda = 633$ nm) was employed, and the scattered light was detected at a 173° angle. The intensity autocorrelation function was analyzed by the cumulant method to yield the Z-average diameter and by the non-negative least squares (NNLS) algorithm to obtain the size distribution intensity plot. The hydrodynamic diameter was calculated from the diffusion coefficient using the Stokes–Einstein equation. Reported values represent the mean of three consecutive measurements. Titration by inductively coupled plasma atomic emission spectrometry (ICP-AES) was performed on an ULTIMA 2 inductively coupled plasma atomic emission spectrometer from Horiba Jobin Yvon Technology. To enable analyses, a specific nebulizer (PTFE Mira Mist Nebulizer, supplied by Horiba Jobin Yvon Technology) was used to introduce the solution into the ICP-AES. The nebulizer was inserted into a glass cyclonic chamber and operated at a maximum sample flow rate of 1 $mL \cdot min^{-1}$ and with a maximum total dissolved solute of 300 $g \cdot L^{-1}$. The optical wavelength for each element was determined to optimize the limits of quantification through calibration curves with 0–10 ppm concentrations (5 points). The sample was introduced into the ICP-AES instrument with a peristaltic pump.

For conventional transmission electron microscopy (TEM) imaging, a drop of the test solution was deposited onto a carbon-coated copper grid (Ted Pella Inc.) and dried under ambient conditions. The samples were **Gd-HPICs** ($R = 1.0$), **Gd-PBA**, and **PB@Gd-PBA**. Imaging was performed on a Hitachi HT7700 microscope operated at an accelerating voltage of 80 kV. High-resolution TEM (HRTEM) and energy-dispersive X-ray spectroscopy (EDS) analysis, including spectrum and linescan acquisition, were carried out using a JEM-2100F field-emission microscope (200 kV) in STEM mode with a HAADF detector. The particle size distribution was determined by manually measuring over 100 individual particles from TEM micrographs using Nano Measurer software.

The colloidal stability of the **Gd-PBA** nanoparticles was assessed by monitoring the evolution of their hydrodynamic diameter under various conditions. The nanoparticles were incubated in the following media: buffer alone, buffer supplemented with 0.25 mM Ca^{2+} , phosphate buffer (0.1 mM), and 0.1 M $NaCl$. Measurements over time were referenced against the nanoparticle behavior in pure aqueous solution.

Relaxivity measurements: Measurements of magnetic relaxation times in various Gd-based solutions were conducted at a constant temperature of 25 $^\circ C$, utilizing a Bruker Minispec mq20 relaxometer within a 0.47 T magnetic field. The relaxivities of “free” Gd^{3+} , **Gd-PBA**, and **PB@Gd-PBA** were calculated based on different Gd^{3+} concentrations (0.01, 0.2, 0.6, and 1.0 $mmol \cdot L^{-1}$).



Scheme 1 Schematic illustration of Gd-Prussian blue analogue formation via (a) direct addition of $K_4[Fe(CN)_6]$ to Gd-HPICs and (b) sequential addition of Gd-HPICs and $K_4[Fe(CN)_6]$ onto preformed Prussian blue nanoparticles derived from Fe-HPICs.

3 Results and discussion

3.1 Gadolinium based Prussian blue analogue (Gd-PBA) formed from Gd-HPICs

Gd-HPICs solutions (Scheme 1(a)) were first obtained by mixing a solution of the double hydrophilic block copolymer PEO_{5k}-b-PAA_{3.2k} with a solution of Gd³⁺ ions. The charge ratio between the positive charges carried by Gd³⁺ and the negative charges of the acrylic acid units was set to $R = 3[\text{Gd}^{3+}]/[\text{AA}^-] = 1$, theoretically achieving electroneutrality between the ions and the polymer. Gd-HPICs colloids exhibited a core-shell organization [12, 14], with a hydrodynamic radius of ~20 nm and an electron-dense core of 5.1 ± 0.8 nm visible by TEM (Fig. 1(a)). This architecture suggests that Gd³⁺ ions are preferentially localized within the dense polymer-rich domains, stabilized by the PAA blocks.

Gd-Prussian blue analogues formation was then initiated by adding K₄[Fe(CN)₆] to the Gd-HPICs solution. The $[\text{Gd}^{3+}]/[\text{Fe}^{2+}(\text{CN})_6]^{4-}$ molar ratio was fixed at 4/3, corresponding to the stoichiometry of a perfect PBA crystal, and the pH was adjusted to 6. Upon addition of K₄[Fe(CN)₆], the formation of larger and less regular Gd-PBA inorganic assemblies than pristine HPICs structure ($\sim 36 \pm 5$ nm, TEM, Fig. 1(b)) was observed. The leftward shift of the dynamic light scattering (DLS) correlograms and the corresponding size distributions confirm this growth process (Fig. 1(c)).

These results indicate that the Prussian blue framework nucleates within the electron-rich Gd-HPICs cores, progressively

reorganizing the polymer-metal complexes into larger hybrid structures. The irregular morphology likely reflects a balance between crystalline Gd-PBA growth and spatial confinement imposed by the polymer matrix. This mechanism highlights the role of HPICs not only as stabilizing templates but also as nanoreactors that direct the nucleation and growth of inorganic phases under mild aqueous conditions.

3.2 Core-shell Prussian blue analogue formed from Prussian blue nanoparticles

The HPICs approach was further employed to direct the growth of gadolinium Prussian blue analogue shells onto well-defined PB nanocubes resulting in core-shell architectures named PB@Gd-PBA (Scheme 1(b)). Fe-HPICs solutions, prepared by complexing the double hydrophilic block copolymer PEO_{5k}-b-PAA_{3.2k} with Fe³⁺ ions ($R = 1$), served as precursors to initiate PB formation upon addition of K₄[Fe(CN)₆]. PB nanocubes with an average size of 40 ± 5 nm were formed (Fig. 1(d)). The formation kinetics of these nanocubes, monitored by UV-visible spectroscopy, are rapid (a few minutes). The copolymer not only enables control over the size of the resulting nanoparticles but also provides good colloidal stability due to the adsorption of the polymer block on the particle surfaces.

In a second step, preformed PB nanoparticles were reacted with Gd-HPICs and K₄[Fe(CN)₆], resulting in the formation of PB@Gd-PBA core-shell nanostructures as evidenced by TEM (Figs. 1(e) and 1(g)). The shell surrounding the PB core had an average

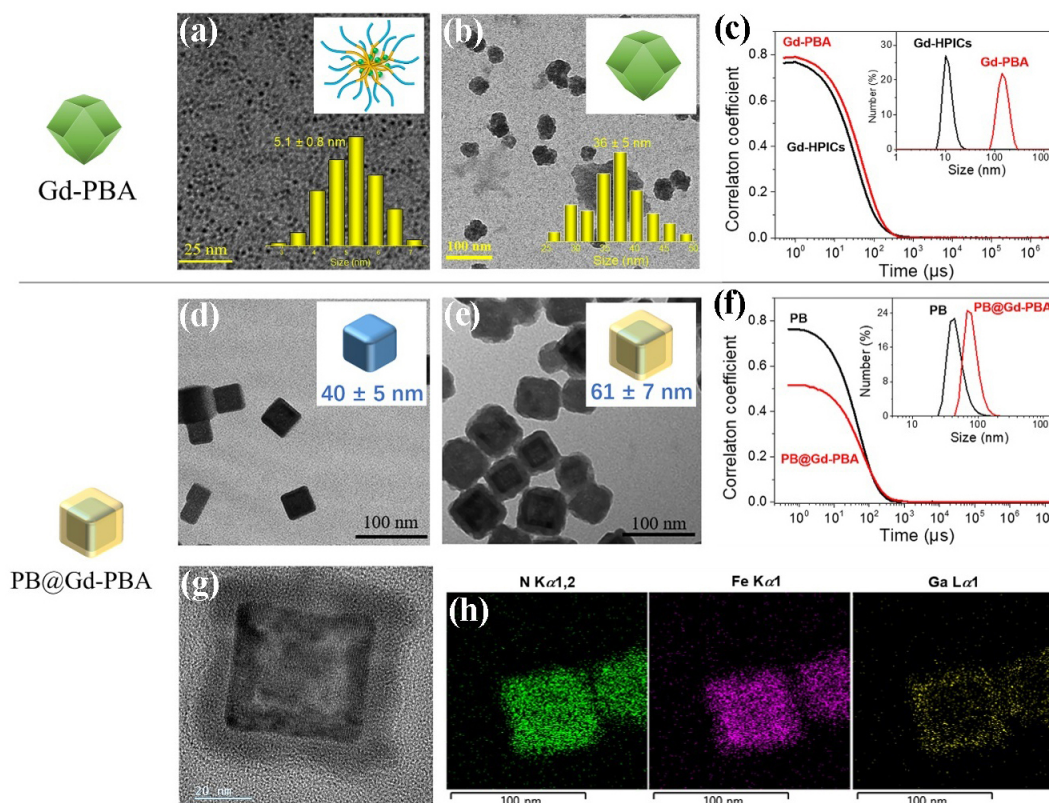


Figure 1 Synthesis and characterization of Gd-based inorganic nanoparticles. (Top) Gd-Prussian blue analogue (Gd-PBA) nanoparticles. TEM images and corresponding size distributions of (a) Gd-HPICs and (b) Gd-PBA NPs. (c) Correlograms of Gd-HPICs at $R = 1$ and Gd-PBA NPs, with an inset showing the corresponding number-averaged hydrodynamic diameter distribution (NNLS method) from DLS measurements. (Bottom) TEM images and corresponding size distributions of (d) PB nanoparticles and (e) PB@Gd-PBA. (f) Correlograms of PB and PB@Gd-PBA with an inset showing the corresponding number-averaged hydrodynamic diameter distribution (NNLS method) from DLS measurements. (g) HRTEM of PB@Gd-PBA. (h) HAADF elemental maps of N, Fe, Gd of PB@Gd-PBA. TEM images are based on 100–200 nanoparticles in different images of the same sample.

thickness of 10 ± 4 nm. DLS measurements indicated a significant increase in hydrodynamic diameter, with retained colloidal stability as evidenced by a symmetric, monomodal size distribution and a mono-exponential correlation function featuring a stable baseline (Fig. 1(f)). HRTEM revealed uniform lattice fringes characteristic of crystalline PB throughout the core, whereas the shell appeared amorphous (Fig. S1 in Electronic Supplementary Material (ESM)). Fast Fourier transform (FFT) analysis of selected core regions yielded interplanar spacings of 0.508, 0.359, 0.254, 0.226, 0.180, 0.170, 0.161, and 0.141 nm, corresponding to the (200), (220), (400), (420), (440), (600), (620), and (640) planes of PB ($\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$, JCPDS 52–1907). STEM–EDS mapping confirmed a homogeneous Fe distribution across the cubes, while Gd was predominantly localized within the shell (Fig. 1(h) and Fig. S2 in ESM).

3.3 Colloidal stability and relaxivities

To evaluate the long-term stability of our Gd-based contrast agents, we subjected Gd-PBA nanoparticles to accelerated stability testing in biologically relevant media, including buffer solutions and competitive ionic environments (NaCl , CaCl_2 , and NaH_2PO_4). As shown in Fig. 2(a) and Fig. S3 in the ESM, DLS analyses demonstrated no detectable aggregation or decomplexation over a one-week incubation period. This stability arises from steric repulsion imparted by the hydrated PEG corona, which effectively outweighs electrostatic contributions, a critical advantage for maintaining colloidal integrity in high-ionic-strength environments.

To complement these findings, we employed inductively ICP–AES to quantify Gd^{3+} leaching following nanoparticle separation via centrifugation. The absence of measurable Gd^{3+} release confirms the chemical robustness of the Gd-chelate framework. These results are consistent with established literature: prior studies have demonstrated that unaltered particle size distributions (DLS) correlate with negligible metal ion dissolution [27], while direct Gd^{3+} quantification (ICP–MS) provides definitive evidence of chelate stability [28]. Collectively, these data highlight the dual stability, colloidal and chemical, of our PEGylated Gd-PBA nanoparticles, a key prerequisite for their translation into in vivo applications, where minimal ion leaching and sustained colloidal integrity are essential for safety and efficacy.

The relaxivity of Gd-PBA, PB@Gd-PBA, and “free” Gd ions was further investigated in aqueous medium (Fig. 2(b)). Whereas “free” Gd ions exhibit a low r_1 relaxivity of $9.9 \pm 0.2 \text{ mM}^{-1}\text{s}^{-1}$, Gd-PBA and PB@Gd-PBA show significantly higher r_1 values of 52.5 ± 0.5 and $49.7 \pm 0.4 \text{ mM}^{-1}\text{s}^{-1}$, respectively (25°C , 0.47 T).

Correspondingly, the r_2 values for “free” Gd ions, Gd-PBA, and PB@Gd-PBA were 10.0 ± 0.1 , 58.3 ± 0.8 , and $55.6 \pm 0.3 \text{ mM}^{-1}\text{s}^{-1}$, respectively (25°C , 0.47 T). As expected, the incorporation of Gd into the Prussian blue structure induced a fivefold increase of the measured relaxivity. This relaxivity is lower than that of Gd/Zr@HPICs ($65 \pm 1 \text{ mM}^{-1}\text{s}^{-1}$), which may be attributed to more efficient water diffusion within the polymer matrix in this system [29]. The observed r_1 values also exceed those reported for gadolinium-based inorganic nanoparticles such as GdPO_4 and NaGdF_6 , for which relaxivities typically range between 1 and $30 \text{ mM}^{-1}\text{s}^{-1}$ depending on particle size and the nature of the stabilizing agent [3]. Furthermore, these values are substantially higher than those of commercial small-molecule Gd complexes reported under comparable measurement conditions (Table 1) or in human whole blood at 37°C and 1.5 T (Gd-DTPA, $r_1 = 4.3 \pm 0.4 \text{ mM}^{-1}\text{s}^{-1}$; Gd-DOTA, $r_1 = 3.9 \pm 0.2 \text{ mM}^{-1}\text{s}^{-1}$ at 1.5 T) [30, 31].

Colloidal stability of Gd-PBA or PB@Gd-PBA was not affected by the presence of various ions (Fig. 2(c)). However, relaxivity was reduced after several days, but only in the presence of NaH_2PO_4 . This decrease is likely due to strong interactions between phosphate ions and Gd, which may partially digest the nanoparticles, as previously observed for certain oxides, thereby altering their relaxation properties [37].

4 Conclusions

In summary, Gd-based hybrid polyion complexes have been successfully employed to synthesize Prussian blue analogue nanoparticles through two complementary strategies: i) direct formation from Gd-HPICs leading to Gd-PBA, and ii) core-shell growth onto preformed PB nanocubes leading to PB@Gd-PBA. In both approaches, the HPICs acted as stabilizing templates and nanoreactors, controlling nucleation and growth under mild conditions. TEM, HRTEM, and STEM–EDS analyses confirmed the formation of well-defined hybrid nanostructures, with Gd preferentially localized in the electron-dense cores or shells, depending on the strategy. The resulting nanoparticles exhibited excellent colloidal and chemical stability, which was maintained even in the presence of various competitive ions, highlighting the protective role of the polymer corona.

Magnetic resonance relaxivity measurements revealed that incorporation of Gd into the Prussian blue framework significantly enhanced r_1 values, which reached up to five times those of free Gd^{3+} ions in solution and surpassed typical values reported for Gd-based inorganic nanoparticles and commercial molecular

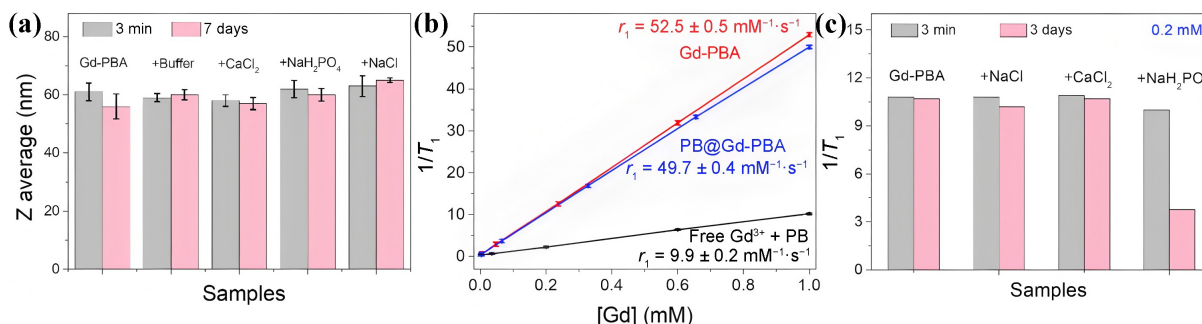


Figure 2 (a) Evolution of Z-average values over time for Gd-PBA in the presence of PBS buffer or various competitive ions (CaCl_2 : 0.25 mM, NaH_2PO_4 : 0.1 mM, NaCl : 0.1 M). (b) Relaxation rates ($1/T_1$) of three different systems, “free” Gd in a Prussian blue (PB) nanoparticle solution, Gd-PBA, and PB@Gd-PBA, measured at various Gd^{3+} concentrations, along with the corresponding r_1 relaxivities at $B_0 = 0.47 \text{ T}$ and $T = 25^\circ\text{C}$. All solutions were dialyzed prior to measurement. (c) Evolution of relaxation rate of Gd-PBA measured at 3 min and 3 days in the presence of different ions.

Table 1 Comparison of the relaxation properties of Gd-based nanomaterials under different conditions

No	Materials	Solvent	Temperature	Magnetic field strength	r_1 (mM ⁻¹ ·s ⁻¹)	Refs.
1	Gd-DTPA	Water	35 °C	0.47 T	4.2	[32]
2	Gd-DTPA	Water	—	—	4.18	[33]
3	Gd-DTPA	Human whole blood	37 °C	1.5 T	4.3	[31]
4	Gd-DTPA	Human whole blood	37 °C	7 T	3.1	[31]
5	Gd-DOPA	Physiological saline	37 °C	0.47 T	3.4	[34]
6	Gd-DOPA	Water	25 °C	0.47 T	3.6	[35]
7	Gd-DOPA	Water	37 °C	1.41 T	2.8	[35]
8	Gd-DOTA	Water	37 °C	1.4 T	3.5	[36]
9	Gd-PBA	Water	25 °C	0.47 T	52.5	This work
10	PB@Gd-PBA	Water	25 °C	0.47 T	49.7	This work

complexes under comparable conditions. These findings demonstrate that the Gd-HPIC approach provides an efficient means to produce stable, high-relaxivity contrast agents, thereby combining precise structural control with superior performance. Overall, this work establishes HPICs as versatile platforms for the rational design of advanced MRI contrast agents based on Prussian blue analogues.

Electronic Supplementary Material: Supplementary material (TEM measurements and colloidal stability studies in presence of competitive ions) is available in the online version of this article at <https://doi.org/10.26599/NR.2026.94909018>.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and the Electronic Supplementary Material. Additional data related to this paper may be requested from the corresponding author upon request.

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Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

L. M. P.: Data curation, experimental design, investigation, formal analysis, validation, writing – manuscript, writing – review & editing. F. B.-M.: Project administration, conceptualization, validation, formal analysis. J.-D. M.: Conceptualization, project administration, formal analysis, resources, funding acquisition, writing manuscript, writing – review & editing.

Use of AI statement

None.

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