Chapter 2

2.1 Literature Review

Gadolinium oxide nanoparticles (Gd_2O_3 NPs) play a critical role in biomedical applications, mainly in multimodal imaging. As multimodal imaging agents, they offer enhanced contrast and sensitivity in magnetic resonance imaging (MRI) and computed tomography (CT) scans, enabling precise visualization and characterization of tissues and organs. [196,197] Furthermore, their high payload capacity and functional ability make them promising candidates for drug delivery systems, facilitating targeted therapy and efficient drug release. [198] These versatile nanoparticles hold great potential in advancing diagnostic accuracy, early disease detection, and personalized medicine, making them valuable assets in the field of nanomedicine. [199] Despite their significant advantages, gadolinium oxide nanoparticles also have some limitations and challenges. One major concern is the potential toxicity associated with gadolinium-based contrast agents, as gadolinium can accumulate in the body, particularly in patients with impaired kidney function. This phenomenon, known as nephrogenic systemic fibrosis (NSF), [200] has raised safety concerns and led to restrictions on the use of some gadolinium-based agents. Researchers are actively investigating safer coatings and surface modifications to reduce toxicity risks. Additionally, the long-term biocompatibility and potential biodistribution of these nanoparticles require further investigation to ensure their safe and effective use in clinical settings. [201] Striking a balance between enhancing imaging capabilities and addressing potential health risks remains a crucial aspect of harnessing gadolinium oxide nanoparticles' full potential in biomedical applications. In addition, the development of simpler synthetic approaches via the utilization of non-hazardous reactants and solvents is also desirable in order to enhance their commercialization on a large scale.[202]

2.2 Development of Gd_2O_3 nanomaterial

A large number of reports have been published on gadolinium-based NPs synthesis, such as oxides, [203] carbonates, and oxysulfide. [204] Despite having significant interest in the application of Gd_2O_3 NPs, currently available synthesis methods are complex, require high reacting temperatures (180 °C), utilize hazardous organic solvent medium, and are time-consuming. The size of these particles varies greatly in the range between 1–200 nm, depending on the synthesis methodologies applied. Among the synthesis protocols, the polyol method is the most common and particularly useful for preparing ultrasmall Gd_2O_3 NPs (1–3 nm). [205] However, for large-size particle synthesis, this procedure is time-taking due to the slow nucleation rate and the need for repetition of seed growth, and poor reproducibility, as there is no control over the yield and uniformity of the resultant NPs. Concerns have also been raised concerning the polyol method's potential to impede neutrophil oxidative bursts due to the presence of diethylene glycol on the surface of particles generated in such a solvent. [206] Furthermore, the solvothermal method is dominating in the synthesis of gadolinium oxide NPs with highly controlled size and homogeneous uniformity. The resulting NPs have capitative applicability in optical imaging, but their applicability with respect to MRI is limited. [207] Moreover, Hydrothermal and microwave-assisted methodologies required high-temperature synthesis, take longer reaction time and having poor size control leading to uneven nanoparticle synthesis. Another limitation is the potential formation of unwanted by-products or impurities during the synthesis process due to using a non-aqueous reaction medium. [208] Currently, the miniemulsion technique, widely utilized in polymer chemistry, is however uncommon for the preparation of inorganic NPs. [207]

In a different approach, Ningqi Luo and a coworker synthesized spherical Gd_2O_3 nanoparticles using a laser ablation method performed by focusing the laser beam onto a Gd target has been resulting using a microsecond Nd: YAG laser with a wavelength of 1064 nm, 6 ms pulse duration, a repetition of 100 Hz, and power of 70 mJ per pulse, was focused onto the Gd target surface. The ablation process lasted for 15 min. [209] J. G. Assouline et.al have been reported Eu-doped Gd_2O_3 nanoparticles with 5–200 nm size range by chemical vapor synthesis at high temperature for multimodal/sequential CAs application prepared. [207] In regards, Luc Faucher et al. reported the synthesis of polyethylene glycol encapsulated ultrasmall. gadolinium nanoparticles using the polyol-like method; in this particular approach, they utilized poly (ethylene glycol) bis-(carboxymethyl) ether 600 as a solvent and particle surfactant and heat the solution at a high temperature (180 ºC) in order to acquire ultrasmall (5 nm) particle for cell labeling and MRI tracking application. [210] Ja Young Park et al. investigated the synthesis of Gd_2O_3 nanoparticles using three different kinds of gadolinium ion salts and by refluxing each of the salts in tri propylene solvent under oxygen flow. They utilized glucuronic acid as a surface coating agent and 260 ºC reaction temperature. These particles were applied as an MR imaging contrast agent. [211] Lu Han et al. developed albumin-stabilized gadolinium oxide-gold nanocluster hybrid via an albumin-based biomineralization process for multimodal imaging and drug delivery purpose. The developed particles exhibit photoluminescent activity in the NIR region and are capable of producing singlet oxygen species under NIR laser irradiation for photodynamic therapy. [212] In a different approach, Le HUU Trinh et al. synthesized Gd_2O_3 nanoparticles by modified polyol method with microwave assistance by using a triethylene glycol solvent. He noticed that after thermal treatment at 700 ºC, Gd_2O_3 NPs showed a uniform spherical shape with unchanged particle size compared with the Gd_2O_3@TEG precursor. [213] Leena Vinolia Thaninki et.al

developed zinc doped Gd_2O_3 nanoparticles using wet chemical synthetic approach and investigated their photocatalytic activity for dye degradation under UV light. The noted that adsorption of dye molecules increases the rate of photodegradation. [214] Parisa Vahdatkhah co-worker demonstrated rapid microwave assisted synthesis of PVP coated ultrasmall gadoliunm oxide nanoparticles for MR imaging purpose. NPs were synthesized in less than five minutes. Gd $(NO_3)_3$ 6 H_2O was dissolved in diethylene glycol (DEG) and heated overnight at 100 ºC. Afterwards, NaOH was added and reaction mixture was then microwave irradiated under an O_2 environment, there were two steps in the reaction mechanism: (1) metal ion complexation and (2) hydrolysis/condensation. In the first stage, alcohol groups from ethylene glycol (EG) were oxidized to aldehyde and then to diglycolic acid in the presence of nitrate ions. NaOH was utilized as a hydrolysis agent in the second step. Gadolinium hydroxide (Gd $(OH)_3$) was produced through the substitution of hydroxyl groups in nitrate ions. Microwave irradiation of Gd $(OH)_3$ resulted in the formation of Gd_2O_3. Following that, the surface of Gd_2O_3 was modified with PVP, yielding spherical-shape-coated NPs with a size of 2.5 - 5 nm. [215] The sol-gel method is a wet-chemical approach that consists of the following steps: (1) hydrolysis and polycondensation, (2) gelation, (3) ageing drying, (4) densification, and (5) crystallization. Niftaliev et al. described the sol-gel synthesis of gadolinium oxide NPs using Gd $(NO_3)_3$ as the salt precursor and agar-agar as a stabilizer. A white gel with 10 nm particle size was produced. To remove the water from Gd $(OH)_3$ gel, the gel was frozen in a freezing camera at 20 ºC (this temperature was proven to be best after various tests) and dried at 100 ºC. The annealing of the gel at 700 ºC produced the Gd_2O_3 particles, which were mostly rounded and had an average size of 8-16 nm. [216]

Chaudhary S. et al. reported the hydrothermal synthesis and characterization of Gd_2O_3 NPs functionalized with ethylene glycol (EG) starting from $GdCl_3$ and EG. The concentration

of $GdCl_3$ was varied from 5 mM to 25 mM to investigate the impacts of synthetic parameters on optical, photoluminescence, and band-gap variation. The nanoparticles exhibited crystallites with an uneven pseudo-spherical form with a size distribution ranging from 7 to 15 nm. Using neutral pH cyclic voltametric and amperometry techniques, the nanoparticles were tested as an effective electrocatalytic material for detecting hydrazine and p-nitrophenol. The created sensor had a linear range of 1 to 10 M with a low detection limit of 1.527 and 0.704 M for p-nitrophenol and hydrazine, respectively. Gd_2O_3 NPs are a promising nanomaterial for detecting contaminants due to their sensitivity, selectivity, repeatability, recyclability, wide linear range, and detection limit. [217]

Wu et al. used a one-pot hydrothermal technique to create hyaluronic acid-functionalized Gd_2O_3 NPs (HA Gd_2O_3 NPs). The prepared NPs had an average diameter of 105 nm, homogeneous dispersion, and a quasi-spherical shape. The addition of HA improves the water dispersibility, cytotoxicity, and biocompatibility of Gd_2O_3. Bifunctional HA- Gd_2O_3 NPs showed promise for tumor diagnostics and treatment. [218]

NPs	Synthesis Method	Temp, Solvent	Capping agent	Size	Shape	Application	Reference
Gd_2O_3	Hydrothermal	180 °C, 300 °C (calcination)	Ethylene glycol	7-15 nm	Pseudo spherical	Detection of hydrazine and p-nitrophenol	[217]
Gd_2O_3	Wet-chemical route	75 °C, DI water	Poly (ethylene glycol)	40 nm	Nanorod	Drug delivery and imaging	[219]
Gd_2O_3	Microwave-assisted	60 C°, 300 C° (Calcinated)	Peel extract of Moleifera	26 ± 2 nm	Rod shape	Antimicrobial	[220]
Gd_2O_3	Hydrothermal	120 °C (Oven),700 °C (Furnace)	..	13.7 nm	Rod shape	Photocatalytic	[221]
Gd_2O_3	Co-precipitation	~ 90 °C	Folic acid and D-gluconic acid	20 nm (FA), 425 nm (GA)	Nanorods, Nanocuboids	MR imaging	[222]
Gd_2O_3	Hydrothermal	90 °C, 180°C, Water	Dextrose, Fe_3O_4	30-40 nm	Core-shell	Not reported	[223]
Gd_2O_3	Precipitation	65 °C, Ethanol	L-ascorbic acid	6.1 ± 0.7 nm	Spherical	Antibacterial	[224]
Gd_2O_3–AuNCs	Biomineralization approach	37°C, water	BSA	5.4 nm	Crystals	MR imaging	[225]
Gd_2O_3	Sonochemically precipitation	---	--	1.5 nm to 200 nm	Spherical shape	---	[226]
Gd_2O_3	Wet chemical method	773–1273 K	...	23 ±1.0 nm	Spherical	MR contrast agent	[227]
Gd_2O_3	Wet chemical	100 °C	Poly (acrylic acid)	1.9 nm	Spherical	MR imaging	[228]
Gd_2O_3	Polyol synthesis	80 °C, Triethylene glycol	Fluorescein	3.92 nm	Spherical	Multimodal imaging	[229]
$GdPO_4$	Hydrothermal		Dextron	6-15 nm	Nanorod	MR angiography	[230]
Gd_2O_3	Polyol	200 °C	Inner-cy5, outer-carboxylic acid	~ 2nm	Core-shell	Multimodal imaging, Theragnostic	[231]

Gd_2O_3	Gamma irradiation reduction	140 °C, 800 °C (Annealing)	Chitosan	30-45 nm	Spherical	MR imaging	[232]
Gd_2O_3	Thermal decomposition	873.15 K, Glycine	..	10 nm	....	Antibacterial	[233]
Gd_2O_3	Polyol synthesis	60 °C, EG	Citric acid	1-3 nm	Spherical	Emission, Excitation	[202]
Gd_2O_3	Polyol synthesis	90-100 °C	Diethylene glycol (DEG)	3-4 nm	.....	MR imaging	[206]
Gd_2O_3	Polyol synthesis	180 °C, EG	Ethylene glycol (EG)	12 nm	Globular	MR Imaging	[234]
Gd_2O_3	Polyol synthesis	180 °C, PEG	PEG	17 nm	Globular	MR imaging	[235]
Gd_2O_3S	Ligand exchange method	160 °C, Ethanol	PVP	6 nm	Nanoplates	Multimodal imaging	[236]
Gd_2O_3	Wet chemical	100-175 °C	DEG	10 nm	Spherical	MR Imaging	[237]
Gd_2O_3	Wet chemical	100-175 °C	PVP	5 nm	Spherical	MR Imaging	[237]
Gd_2O_2S :Eu3	Precipitation followed by sulfuration	750 °C, Ethanol	Amino-silica	107 ±9 nm	Spherical	Bioimaging	[238]
Eu doped Gd_2O_3	Hydrothermal method	180 °C	PEG	10-20 nm	Nanorod	Anticancer drug delivery, MR imaging	[239]

Table 2.1: Synthesis route and application of previously reported gadolinium oxide nanomaterial with their representative images (refer to appendix C (Section - C1-C4))

2.3 Texture, Shape, and Size Effect on Gadolinium Oxide Nanoparticle on Properties

Size and morphology control plays an essential role in the application of NPs. For example, it has been demonstrated that non-spherical shapes translate into cytotoxicity due to a higher chance of damaging the cell membranes. [223] Furthermore, the cellular, as well as tissue and organ distribution of NPs, is highly dependent on the particle size. Particles less than 100 nm in diameter can easily pass through the vasculature, and the smallest ones can even spread into organs. In the case of the application of NPs as contrast agents (CAs) for magnetic resonance imaging (MRI), the size becomes particularly essential as it determines their usefulness for either T1- or T2-weighted imaging. Since the efficacy of positive (T1) nanoparticulate CAs depends on the interaction of water molecules with paramagnetic ions at the surface of NPs, a high surface-to-volume ratio is required and thus NPs with a diameter smaller than 10 nm are preferred. On the other hand, negative (T2) contrast depends on magnetic susceptibility and the magnitude of magnetic moment, which are in direct relation with the number of paramagnetic ions per particle and hence the size of the applied NPs.

2.3.1 Porous Sheet-like Particles

Porous nanomaterials have demonstrated an excellent capacity for efficient drug delivery and release owing to a range of advantageous characteristics, including their large surface area, surface functions, and tunable composition. Recently, Meng Luo demonstrated the synthesis of porous gadolinium oxide nanosheet using a two-step colloidal synthesis pathway. In the first step, they synthesized Gd_2O_3 nanosheets using the thermal decomposition method with a surfactant; in the second step, they performed etching of Gd_2O_3 nanosheet with tri-octyl phosphine oxide (TOPO) in order to obtain porous Gd_2O_3 nanosheets. Their synthesized particle exhibits a larger surface area which aids in promising

pH-responsive drug release properties and consecutively kills cancerous cells. Moreover, they utilized their particles as efficient contrast agents. [198]

2.3.2 Nanodisks

Singh et al. reported the synthesis of Gd_2O_3 nanodisks using the thermal decomposition of oleate-based precursors. He suggested that the intermolecular interaction between metal and ligands is foremost to control the shape of NPs. He developed different sized gadolinium oxide nanodisks through the thermal decomposition of Gd- oleate precursor by mixing it with oleic acid (OA) and heated at 320°C under inert atmosphere. Synthesized OA capped Gd_2O_3 NPs having a disk size with a 11.2 nm diameter and 3 nm thickness, respectively. In his study he also demonstrated that the diameter of nanodisk is greatly affected by concentration of OA. Higher concentration of OA produced nanodisk with a larger diameter. Authors also remarked that particles with size less than 5 nm are suitable for MRI contrast agents. [240]

2.3.3 Spherical NPs

Wuyuan Zhang et.al presented a microemulsion technique to prepare a lanthanide containing nanoparticles in the range between 5 to 40 nm. Authors demonstrated that formation of nanodroplets under emulsion condition is the key step in the size control of NPs. [241] Vahdatkjah et al. synthesised spherical shaped PVP coated nanoparticles with the size of 2.5 nm. They have used diethylene glycol (DEG) as a solvent to dissolve gadolinium salt and poly vinyl pyrrolidone (PVP) as stabilizing agents to synthesis ultrafine gadolinium oxide NPs using microwave assisted method at 100°C temperature. [242]

2.3.4 Rod Shaped

Surendra et al. ecological synthesized of gadolinium oxide nanoparticles (Gd_2O_3 NPs) using the methanolic extract of the Moringa oleifera peel. The paper also investigates the

characterization of the synthesized Gd_2O_3 NPs using a variety of techniques, UV Vis, XPS, XRD SEM and TEM. The paper also assesses the antifungal and antibacterial activity and toxicity of the synthesized Gd_2O_3NPs on human erythrocytes. The paper concludes that green-synthesized Gd_2O_3 nanoparticles are effective antifungal agents, are benign, and can be used as photocatalysts. Additionally, the paper discusses the RSM optimization of the Gd_2O_3 NPs synthesis using the BBD model. [243] Mohd Javed Akhtar et al. examine the road shape gadolinium-based nanoparticles (NPs) with their toxicity processes (membrane damage) towards the MCF-7 cell line. The authors used oxidative stress measures for nonlethal and lethal quantities of gadolinium Oxide NPs and G ions in a time-dependent investigation to investigate bio reactions to NPs and ions. The study demonstrated time- and concentration-dependent toxicity and oxidative damage from gadolinium oxide NPs and G ions. The study demonstrated that NP- and ion-mediated cytotoxicity relies on cellular antioxidants. [244]

2.3.5 Nanofiber

R.Thangappan et al. focused on the production of Gd_2O_3 nanofibers by the use of the electrospinning method followed by calcination employing PVA as a template for structural guidance with the average diameter of 80 nm. The nanofibers demonstrate advantageous optical characteristics and possess potential utility in sophisticated optical apparatus. The thermal characteristics of the PVA/$Gd_2(NO_3)_2$ hybrid fibers and the electrospinning technique are also examined in the research. [245]

Yuting Wei et al. synthesized the biofunctionalized GdOF: Er^{3+} with average size of 88 nm. The combination of electrospinning and fluoro-oxidation calcination yields upconversion luminescent-magnetic bifunctional GdOF: Er^{3+} nanofibers. The research presents a new method for making rare-earth oxyfluoride upconversion luminescent-magnetic nanostructures with different shapes. The study shows GdOF: Er^{3+} sample

morphology using XRD and SEM image analysis. The research also analyses how Er^{3+} molar concentration affects upconversion luminous intensity and product emission colors. [246]

2.4 Thermogravimetric study of Gd_2O_3

The investigation of thermal activity in nanomaterials has significant interest in understanding their composition and the presence of contaminants. Thermogravimetric analysis (TGA) was utilized to determine the thermodynamic characteristics of all the samples. [247] The determination of kinetic parameters, such as thermal activation energy (Ea), change in enthalpy (ΔH), change in entropy (ΔS), and change in Gibbs free energy (ΔG), has been performed using statistical analysis of thermogravimetric analysis (TGA) data. [248] The thermal stability of the nanoparticles was examined by thermogravimetric analysis (TGA), which involved conducting heat trials. Several constructed technologies have been created to compute the nucleation rate and interfacial energies of ultra-small clusters within a low temperature range of 0-100 °C. These technologies aim to enhance our understanding of the formation process of such clusters. The aforementioned methodology was dependent on the computation of nucleation rate utilizing the principles of Classical Nucleation Theory (CNT). [249] As widely acknowledged, as per the research conducted by CNT, nucleation initiates either at a specific level of supersaturation or due to the impact of elevated temperatures on amorphous particles in a solid state. Homogeneous nucleation encompasses the fundamental phenomena of growth, crystallization, aggregation, and phase transition. [250] The interfacial surface plays a crucial role in the nucleation process, facilitating various interfacial-based synthesis processes including CO_2 sequestration, biomineralization, battery operations, and scaling control procedures. [251]

2.4.1 Non iso-conversional method to compute activation energy

The investigation of the dynamic behavior of inorganic materials has been a prominent area of research for many centuries, particularly in relation to the transition from solid to liquid and gaseous states. [252] Numerous mathematical models have been devised thus far to ascertain the activation energy prerequisites when investigating the thermal degradation characteristics of diverse inorganic substances. [253] The TGA machine provides data on mass loss as a function of temperature and time in an experimental procedure. This data may be utilized to calculate the apparent activation energy of dissociation of nanomaterial using the iso-conversational approach. [254] Various model-free approaches have been employed by the scientific community to estimate the apparent activation energy, including the KAS, [255] Tang, [256] Starink, [257] Friedman, [257] FWO, [258] Vyazovkin, [259] and Vyazovkin AIC models. [259] Among the several models considered, it is believed that the estimation of apparent activation energy by the use of the Friedman technique is associated with a lower degree of systematic error. However, due to the presence of experimental noise, this technique exhibits modest fluctuations, leading to a certain level of instability. In contrast, the Vyazovkin technique yields averaged activation energy values ranging from 0 to α. The Vyazovkin AIC technique eliminates approximations and does not rely on a single average activation energy value. As a result, the comprehensive approach utilized in the Vyazovkin AIC procedure is devoid of any systematic inaccuracy. [260]

Krishna Kattel et.al developed D-glucuronic acid- coated ultrasmall Gd_2O_3 nanoparticles. He recorded the maximum amount of surface coating with D-glucuronic acid using TGA curve of Gd_2O_3 powder at room temperature to 700 ºC under oxygen flow. [261] Mohammad Yaseen Ahmad et.al reported also estimated the amount (P) of surface-coated PMVEMA in wt.%. He estimated weight loss to be 50.5% from the TGA curve of

PMVEMA-coated NPs after considering water and air desorption (12.2%) between room temperature and ~105 ºC. The remaining mass was attributable to the Gd_2O_3 NPs (37.3%). [262] Nitya Ramesh Chawda et.al analyzed for average weight loss to evaluate changes in phase transition and changes in the amount of capping agent for the experimental condition used for the samples. [222]

2.4.2 Thermodynamics parameter calculation

It is imperative to collect thermodynamic and kinetic data pertaining to the interactions between proteins and nanoparticles in order to establish a comprehensive framework that enables the prediction of biological responses in the presence of nanoparticles. [263]

Aashima et.al fabricated L-lysine coated the ultra-small gadolinium oxide nanoparticle with the size of ~2 nm via ultrasonication method. In this paper authors proposed the calculation of thermodynamics parameters of ΔG, ΔH and ΔS using three different heating rates. The negative value of ΔG indicates that the binding interaction of BSA protein shows the spontaneous in nature. [264]

Nazia Nafsin et al. use detailed experimental data to show how the dopant affects process thermodynamics and kinetics. The paper also uses microcalorimetry to show that the dopant lowers yttria stabilized zirconia (YSZ)'s grain boundary energy and growth driving force. The results suggest that the dopant acts largely thermodynamically and offer good prospects for coarsening control based on system energetics. The report also reviews relevant research and emphasizes assumptions' weaknesses. [265] In the study conducted by Bhakta et al. the authors highlight the significant potential of reactive nanoparticles in several fields, such as catalysis and energy storage. Nevertheless, the ability to establish a correlation between cluster size and thermodynamic stability and chemical reactivity in several microporous templates is hindered by the wide range of pore sizes and the lack of well-characterized chemical environments. [266]

2.4.3 Computation of nucleation rate and interfacial energy of nanomaterial

Calculating nucleation rates and interfacial energies at low temperatures (ranging from 0 to 100 ºC) was one of the major technologies developed specifically for the purpose of gaining a deeper comprehension of the processes that lead to the development of ultra-small clusters. [248] The preceding strategy relied on the application of the Classical Nucleation Theory (CNT) to arrive at its conclusion regarding the nucleation rate. The CNT postulates that nucleation can commence either at a predetermined value of supersaturation or by the influence of high temperature on amorphous solid-state particles. [249] Homogeneous nucleation encompasses growth, crystallization, aggregation, and phase shift processes. [249] The nucleation process is characterized by a significant amount of the interfacial surface, which is crucial in facilitating many synthetic procedures that rely on interfacial interactions. [251]

These procedures include CO_2 sequestration, biomineralization, battery operations, and scaling control processes. [251] In order to accurately estimate the nucleation rate, it is essential to have a comprehensive understanding of the two barriers involved: kinetic and thermodynamic. The nucleation rate (J_o) can be expressed as the product of two factors: $A \exp {}^{Ea}/_{RT}$ for the kinetic barrier and $\exp {}^{\Delta G}/_{RT}$ for the thermodynamic barrier. Here, Ea represents the activation energy for nucleation, ΔG represents the Gibbs free energy barrier, and T represents the temperature, which is subject to change and R is universal gas constant. [248, 251]

Several experiments were conducted at standard room temperature in order to determine the value of Jo for the intent of determining homogeneous nucleation. Jo was calculated using the formula (D)/(5d), where D represents the diffusion coefficient of the monomer and d represents the diameter of the monomer. [267] Moreover, further investigation was

carried out at ambient temperature to determine Jo, employing an atomic force microscope (AFM). [258] As an illustration, the observed Jo values for silica nucleation on NH_3/COO and carboxyl mixed composite platforms are notably high, reaching 1014.81.4 and 1013.50.7 nuclei per square meter per minute, respectively. [268] The experimental investigation of nucleation rate kinetics for heavy hydrocarbon gases and alcohols with varying temperatures and specific supersaturations was conducted using the SAXS (Small Angle X-ray Scattering) technology. [269] The utilization of molecular dynamics simulations (MDS) was employed as an additional methodology to investigate the mechanisms underlying nucleation rate phenomena. The primary theoretical framework behind the MD simulations focused on the interactions and physical characteristics of the nucleating entities. [270]

The molecular dynamics (MD) simulation conducted in this study yielded multiple methodologies for the computation of nucleation rates in diverse condensation systems. The Stillinger criteria was developed as a theoretical framework to estimate the nucleation rate of clusters in condensing systems through the utilization of molecular dynamics (MD) simulations. [249] Moreover, it was postulated that clusters could be found in liquid systems exhibiting greater local density in comparison to gas densities. Ultimately, the characterization of a liquid cluster necessitates the fulfilment of two specific conditions: the validation of the Stillinger criterion and the presence of a minimum of five adjacent particles. The scientific community developed several methods to compute nucleation rate based on nanomaterials identification which devised the aforementioned approaches to determine the nucleation rate of nanoclusters and ultra-small gas molecules at low temperatures, specifically at 100 °C and 100-200K. one of researchers Chkonia et al. employed Argon gas condensation as a means to compare several approaches for the determination of nucleation rates. [270]

Nevertheless, when exposed to elevated temperatures exceeding 100 °C, the primary factors contributing to the lack of knowledge regarding kinetic parameters in the calculation of nucleation rates for ultrasmall solid nanoclusters are the presence of significant complexity and limitations in microscopic functions, as well as the incorporation of bulk components. [248] Further investigation is necessary to determine J0 for nanoclusters at elevated temperatures (>100 °C) through a meticulous evaluation of A (pre-exponential kinetic factor) and E (nucleation activation energy). [267] Hence The kinetic factors mentioned can be accurately determined by iso-conversional methods utilizing data acquired from a non-isothermal thermogravimetric analysis (TGA) instrument.

The determination of the activation energy for the dehydration process during the phase transition of amorphous calcium carbonate clusters to crystalline calcite at a temperature of 315°C has been conducted in prior research. Moreover, it has been observed that the nucleation rate of ultra-small osmium clusters increases from 78.8 pm/min at a temperature of 20 °C to nearly ~177 pm/min at a temperature of 100 °C. [271–273]

The surface and interfacial energy of nano-structured materials would have a substantial influence on the effective characteristics of these materials at the tiny length scales. [274] Yuhi Nagatsuma et al. examined the impact of temperature variations on the interfacial characteristics between solid and liquid phases during the process of crystal development in nickel. [275] This was achieved by employing ensemble Kalman filter (EnKF)-based data assimilation techniques. [275] Xiang Gao et.al have proposed a novel interface model and a linear small deformation interface stress model that incorporates the influence of curvature on interfacial energy. The work proposes the utilization of the Lagrangian description-based fundamental equations of the interface as a practical and advantageous approach for investigating interface difficulties, particularly the impact of residual interface stress. [274] The application of the created interface model and micromechanics approach

is utilized in the investigation of the effective modulus of composites reinforced with nanoparticles. The findings indicate that the impact of curvature on the effective modulus is significantly more pronounced, and the influence of particle size distribution becomes evident particularly in cases where there is a high degree of dispersion in the particle radius. [274] Joao M. P. Franca et.al investigated the interactions between ionic liquids and carbon nanomaterials, with a particular focus on understanding the impact of these interactions and the arrangement of ions in the interfacial layers on the thermal conductivity of composite systems. [276]

The decision was made to construct precise interatomic interaction models through the process of parameterization against electronic structure calculations. This choice was motivated by the recognition that employing simplistic mixing rules for dissimilar interactions and relying on pre-existing force fields designed for small organic molecules would not adequately capture the intricate interactions occurring between ions and highly polarizable substances, such as carbon nanotubes or graphene planes. [276]

2.5 General Biological Applications of Gadolinium Oxide NPs

The excellent physiochemical and optical properties of Gd_2O_3 with their low toxicity and high sensitivity make these nanoparticles very promising towards use in biological application. [277] The antibacterial study for these nanoparticles opens the door for better future to tackle the problem of multidrug resistance bacteria. Moreover, the upconversion nanoparticles of these nanoparticle provide other windows in the area of drug delivery in targets cell. [203] The excellent relaxivities and fluorescent properties of these gadolinium-based nanoparticles gives the window for multimodal imaging platform better diagnosis and treatments. [278]

2.5.1 Multimodal imaging

Wenlong Xu. et al. reported the water-soluble fluorescein polyethyleneimine functionalized Gd_2O_3 nanoparticles for T1 weighted imaging of N1S1 liver tumor in rat and cell labelling with the average size of 3.92 nm. The prepared nanoparticles show improve relaxivities of 6.76 $mM^{-1}S^{-1}$. [247] Maalej et al. trying to synthesized crystalline cubic nanoplatelets of Gd_2O_3 which, doped with varying concentration of europium (Er) from 2 to 10 % using polyol chemical procedure method. The strong red fluorescence (612 nm) of complex $Gd_2O_3:Eu^{3+}$ used for biological cell labelling for better visualization of cell morphology under fluorescence microscopy. [279] Fang et.al synthesised the PVP coated ultra-fine Gd_2O_3 nanoparticles for better MR imaging. The prepared nanomaterials give the three-time better contrast in comparison of commercially available Magnevist contrast agent. They also conduct the *in-vivo* cytotoxicity test and find very low toxicity in this nanomaterial. [280] Yi Pan et al. developed well-structured core shell GdFPNPs using RB encapsulated PMMA cores Gd^{3+} chelated conjugated breached PEI shells. The structural characteristics of Gd-FPNPs make them suitable for high-performance FL/MR dual-modal imaging phosphors. [281]

S.NO	Compound name	Size (nm)	cell viability	Multimodal Imaging	*r_1 ($mM^{-1}S^{-1}$)	Magnetization	Ref.
1.	Gd-chelated nanogels	50-85	> 90%	Only MR	09.70	1.41 T	[282]
2.	Gd FPNPs	4- 8	90%	FL/MR	56.72	3 T	[283]
3.	I-BSA-GdNPs	2.5	Good	MR/CT	12.03	3 T	[284]
4.	GdW10 nanoclusters	~3	85%	MR/CT	09.45	4.7 T	[285]
5.	(Gd-CQDs@N-Fe_3O_4)	2.25	N/A	FL/MR	05.16	0.5 T	[286]
6.	Gd-encapsulated CQDs	~15	> 80%	MR/FL	57.42	1.5 T	[287]
7.	BSA-Gd_2O_3/Au	3.3	Good	NIR/MR	13.10	0.55 T	[288]
8.	Gd_2O_3-OA-CTAB	2.9	~ 80%	Only MR	12.12	7 T	[280]
9.	Eu: Gd_2O_3	5.2	< 80%	RFL/MR	05.15	9.4 T	[289]
10.	PVP-coated Gd_2O_3 NPs	2.5	N/A	Only MR	10.28	3 T	[215]
11.	PEGylated Gd_2O_3	1.3	N/A	Labelling/MR	14.20	1 T	[210]
12.	PEI- Gd_2O_3	3.92	~ 65 %	MR/Cell Labelling	06.75	3 T	[229]
13.	Paramagnetic Gd_2O_3	1	> 90%	Only MR	09.90	3T	[196]
14.	PEG saline Gd_2O_3	3	N/A	Only MR	09.40	1.5 T	[290]
15.	**BSA@ Gd_2O_3**	**1.7**	**98%**	**FL/MR full visible range**	**07.9**	**3 T**	**This work**

Table 2.2: Relaxivity of various ligand coated gadolinium oxide nanoparticle with their size and cell viability distribution.

The r_1 value of Gd-FPNPs is higher than that of commercially available Gd contrast agents such as DTPA analogues Magnevists (3.2 mM^{-1} s^{-1}), ProHance (4.3 mM^{-1} s^{-1}), Omniscans (3.3 mM^{-1} s^{-1}), Gadobutrol (2.5 mM^{-1} s^{-1}), and Gadovist (4.34 mM^{-1} s^{-1}).

2.5.2 Antibacterial

Ashima et al. synthesize biocompatible L-ascorbic acid-coated gadolinium oxide nanoparticles as well-suited antimicrobial potential. [291] The synthesized nanoparticles were non-toxic to HaCaT cells and exhibited antimicrobial activity against E. coli, S. aureus, and S. typhimurium. The study concludes that the synthesized nanoparticles are safe and protective against pathogenic bacteria, and their non-toxic nature allows them to be investigated in biomedical applications. Selvaraju et.al discuss the co-precipitation synthesis and characterization of Gd-doped ZnO nanoparticles. [292] Using techniques such as XRD, FESEM, and photoluminescence analysis, the paper also investigates the structural, morphological, and optical properties of the synthesized nanoparticles. In addition, the nanoparticles' antibacterial efficacy against gram-positive and gram-negative microorganisms is investigated with the limit of potential toxicity of nanomaterials. K.dedkova synthesized gadolinium oxide nanoparticles with their antibacterial activity under daylight and dark conditions. [293] They also perform toxicity of these nanoparticles in aquatic environment This paper provides a protocol for creating these nanoparticles and describes the morphology of the final product. The authors utilized scanning electron microscopes to examine the morphology of the product.

2.5.3 Drug delivery

Shailja et al. synthesized microemulsion mediated synthesis of Polyethylene glycol Coated Gd2O3 nanoparticles loaded with the anti-cancer drug doxorubicin for drug delivery and optical and MR imaging purposes. The authors performed in vitro cytotoxicity assay on U-87, A549, and PANC-1 cell lines and demonstrated efficient drug delivery and cytotoxicity on these cells. [294] Hung-Wei Yang et al. developed poly(amidoamine) dendrimer-grafted gadolinium-functionalized nanographene oxide (Gd-NGO) as effective carriers to deliver both chemotherapeutic drugs and highly specific gene-targeting agents

such as microRNAs (miRNAs) to cancer cells. [295] Using human glioblastoma (U87 MG) cells as a model, they found that this conjugate of Let-7g and EPI (Gd-NGO/Let-7g/EPI) not only exhibited considerably higher transfection efficiency but also induced better inhibition of cancer cell growth than Gd-NGO/Let-7g or Gd-NGO/EPI. In another approach, Kewu He et al. developed pH-responsive polyelectrolyte-coated gadolinium oxide doped mesoporous silica nanoparticles for the anti-cancerous drug doxorubicin delivery and magnetic resonance imaging enhancement. [296] They reported that the coated polyelectrolyte underwent a charge reversal process at acidic pH. When the Gd_2O_3@MSN-DOX nanoparticles entered cells via folic acid (FA) receptor-mediated endocytosis, the mildly acidic pH within endolysosomes triggered the disassociation of the absorbed polyelectrolytes on the surfaces of the nanoparticles, thereby activating DOX release and exerting an anti-cancer effect using a sol-gel technique. [296] Xu et al. encased Gd_2O_3:Eu^{3+} nanospheres with nonporous silica and a further layer of ordered mesoporous silica. [297] To assess their effectiveness as drug nanocarriers, the Gd_2O_3:Eu^{3+}@$nSiO_2$@$mSiO_2$ composites were loaded with doxorubicin hydrochloride (DOX). [172] *In vitro*, HeLa cell assays revealed that DOX is shuttled into the cell from loaded composites and taken up by endocytosis. DOX emitted from core-shell-shell nanocomposites exhibited more cytotoxicity than DOX alone. Furthermore, the MTT experiment demonstrated that the nanocarriers had little cytotoxicity in fibroblasts.

Zhou et al. [17] used a simple wet-chemical method to create Eu^{3+} -doped mesoporous Gd_2O_3 nanorods, which were then modified with polyethylene glycol (PEG) to load the doxorubicin hydrochloride (DOX). TEM scans revealed a monodisperse rod-shaped Eu^{3+}-doped Gd $(OH)_3$ precursor with dimensions of 160 nm and 40 nm. *In-vitro,* the cytotoxicity of these nanorods in BXPC cells demonstrated no harmful effects. However, release studies revealed that Gd_2O_3: Eu@PEG-DOX was internalized by cells faster than the control

(DOX-free) and exhibited more cytotoxicity. Furthermore, the multifunctional nanorods were used as MRI contrast agents.

Aim and objective of the current work:

The major objectives of our research are as follows

Objective 1: White light-emitting, highly biocompatible, water-soluble gadolinium oxide nanoclusters (Gd_2O_3 NCs) for bioimaging applications

- One-pot facile synthesis of ultrasmall, multifluorescent BSA capped gadolinium oxide nanoclusters without mixing any dopants (Heavy metals, C-dots).
- Characterization of prepared nanoclusters through UV-Vis absorbance, TEM, XRD, XPS, FTIR, Fluorescence spectrophotometer, Lifetime decay, MALDI-TOF.
- Measurement of relative quantum yield of gadolinium oxide nanoclusters.
- Direct and indirect band gap measurement of gadolinium oxide nanoclusters using Tauc plot.
- *In-vitro* Confocal imaging of prepared gadolinium oxide nanoclusters in various cell.
- *In-vitro* cytotoxicity estimation of prepared Gd_2O_3 clusters in human cell line via MTT assay.

Objective 2: A novel approach for computation of nucleation rates and interfacial energy of Gd_2O_3 NCs at high temperature using Non-isothermal TGA Models

- Thermogravimetric raw data was extracted from Gd_2O_3 NCs (~1 nm).
- Precisely computation of high-temperature kinetic barrier (Jo) of nucleation using Vyazovkin AIC method.

- Apparent value of activation energy was calculated using various isoconversional methods such as KAS, FWO, Starink, Tang, Vyazovkin and Vyazovkin AIC.
- Frequency factor was computed using KAS derived equation.
- Nucleation rate of ultra-small Gd_2O_3 NCs at high temperature and respective conversions is estimated by adopting classical nucleation theory equation.
- Interfacial energy of ultra-small Gd_2O_3 NCs is also computed at high temperature and conversion.
- Thermodynamic parameters (ΔG, ΔH, and ΔS) are computed at all three heating rates (10 ºC/min ,15 ºC/min and 20 ºC/min) for Gd_2O_3 NCs.
- Four different models were proposed for the computation of nucleation rate and interfacial energy of Gd_2O_3 NCs.

Objective 3: Chitosan templated synthesis of biocompatible ultrasmall Gd_2O_3 NCs for multimodal imaging (MR imaging and fluorescence imaging).

- One-pot facile synthesis of multifluorescent, water soluble, chitosan templated Gd_2O_3 NCs nanoclusters.
- Characterization of prepared Gd_2O_3 NCs via several microscopic and spectroscopic techniques.
- Measurement of absolute quantum yield of Gd_2O_3 NCs.
- Stability measurement of prepared nanoclusters in terms of ionic strength, organic solvents, broad range pH and prolonged light exposure.
- *In-vitro* hemocompatibility assessment in rat blood and *In-vitro* biocompability measurement in human brain cells.
- CTCF analysis for measuring depth penetration of Gd_2O_3 NCs.
- *In-Vivo* toxicity assessment of prepared Gd_2O_3 NCs in rodents for 28 days.

- IVIS imaging in mice model.
- *In-vitro* relaxivity measurement and compared the value of relaxivity with conventional contrast agents.