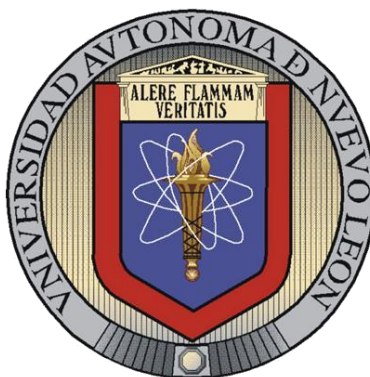


UNIVERSIDAD AUTÓNOMA DE NUEVO LEÓN
FACULTAD DE INGENIERÍA MECÁNICA Y ELÉCTRICA



CERIUM OXIDE NANOPARTICLES WITH CAPPING AGENTS BY SUPERCRITICAL
PROCESS

POR

ING.CECILIA PAMELA MARTÍNEZ ALVARADO

TESIS

EN OPCIÓN AL GRADO DE MAESTRÍA EN CIENCIAS DE LA INGENIERÍA CON
ORIENTACIÓN EN NANOTECNOLOGÍA

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UNIVERSIDAD AUTÓNOMA DE NUEVO LEÓN
Facultad de Ingeniería Mecánica y Eléctrica
Posgrado

Los miembros del Comité de Evaluación de Tesis recomendamos que la Tesis "Cerium Oxide Nanoparticles with Capping Agents by Supercritical Process ", realizada por el estudiante Cecilia Pamela Martínez Alvarado, con número de matrícula 1794062, sea aceptada para su defensa como requisito parcial para obtener el grado de Maestría en Ciencias de la Ingeniería con Orientación en Nanotecnología.

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The members of the thesis committee, recommend that the thesis "*CERIUM OXIDE NANOPARTICLES WITH CAPPING AGENTS BY SUPERCRITICAL PROCESS*", written by student Cecilia Pamela Martinez Alvarado, student ID 1794062, be accepted for defense as a requirement for the Master of Science in Engineering degree orientation in Nanotechnology.

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CON PROFUNDA GRATITUD A QUIENES INCULCARON EN MÍ LA PACIENCIA, LA INSPIRACIÓN Y EL APOYO NECESARIOS PARA ALCANZAR ESTA META. ESTE TRABAJO ES UN REFLEJO DE SU GENEROSIDAD, COMPAÑÍA Y CONSTANTE ALIENTO.

A MIS PADRES, MARIA DEL REFIGIO ALVARADO Y PEDRO MARTINEZ - POR SU APOYO INCONDICIONAL Y POR ENSEÑARME QUE EL TRABAJO DURO Y LA RESPONSABILIDAD SIEMPRE TE LLEVAN A LOGRAR TUS OBJETIVOS, SIN SU GUIA Y MOTIVACION EN CADA MOMENTO ESTO NO HABRIA SIDO POSIBLE.

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1. Introduction

The field of nanotechnology has revolutionized numerous sectors such as semiconductors, gas sensors, energy storage, catalysis, pharmaceutical and biomedicine, with a particular emphasis on the development and application of nanomaterials exhibiting size and structure dependent properties. Controlling the intricate interactions between component materials and their medium is paramount in the formation of nanoscale structures, especially given their extremely large interaction energy.

Cerium oxide (ceria) nanoparticles are highly versatile materials attracting immense interest in the biomedical field. Their therapeutic potential is rooted in their unique, self-regenerating antioxidant properties. This functionality is due to the reversible switch between the Ce^{3+} and Ce^{4+} oxidation states, enabling the scavenging of reactive oxygen species (ROS) and mitigation of oxidative stress damage associated with diseases like neurodegenerative disorders and cancer.

Successful biomedical application requires enhanced stability and biocompatibility, as ligand free ceria nanoparticles typically exhibit poor water solubility and aggregation issues. Capping agents are therefore essential to defining the particle's biological reactivity and improving colloidal stability and bioavailability.

The supercritical fluid process, particularly using supercritical water, offers an efficient and fast synthesis route, allowing deliberate control over nucleation and crystal growth. This technique enables the direct formation of organic and inorganic hybrid nanomaterials, incorporating capping agents to optimize surface chemistry for advanced biomedical applications, such as targeted drug delivery and tissue engineering.

1.1. Background

Cerium oxide nanoparticles have attracted significant and growing attention across various fields, particularly in the biomedical domain, due to their inherent biological properties. These characteristics position cerium oxide nanoparticles as highly promising candidates for a wide range of medical applications. The present study sources on the ability of these nanoparticles to modulate oxygen levels within intracellular environment which significantly contributes to their biological activity.

Among the various synthesis techniques available for producing CeO₂ nanoparticles, the subcritical water method stands out as a viable alternative. This approach enables the formation of nanoparticles with unique morphological features and dimensions, attributed to the distinct physicochemical conditions that differ markedly from those of conventional precipitation methods.

The use of capping agents during the synthesis confers key properties to the nanoparticles including control over size, morphology and stability. The incorporation of capping agents influences the interaction of the nanoparticles with biological systems, thereby affecting their toxicity and therapeutic efficacy. Functionalization of the nanoparticles with capping agent's facilities formation of covalent bonds between the organic and inorganic components of the hybrid structures, leading to the development of interfacial charge transfer (ICT) complexes.

Cerium oxide nanoparticles functionalized with coating agents synthesized via the supercritical water technique exhibit remarkable biomedical potential. Among their prospective applications, they have shown promise in wound by promoting tissue regeneration. Their antioxidant capacity renders them viable candidates for the treatment of diseases associated with oxidative stress, including neurodegenerative disorders such as Parkinson disease, where antifibrillar activity against the α -synuclein protein has been demonstrated. Additionally, their antimicrobial efficiency against various pathogens suggests their potential as alternative to conventional treatment methods.

The strategic selection of coating agents to fine tune toxicity and biocompatibility is a critical factor for ensuring safe biomedical applications. This study represents an innovative approach to the design of the CeO₂ nanoparticles with optimized properties, thereby expanding their utility within biomedical field.

1.2. Scope

This research analyzed CeO₂ nanoparticles synthesized through the supercritical fluid's technique, incorporating capping agents as surface modifiers within their structures. The study lies at the intersection of nanoscience, chemistry, material science, and biomedicine. The integration of supercritical fluid synthesis and capping agents presents significant potential for biomedical applications. The incorporation of acids, polymer and neurotransmitters as capping agents, combined with the redox activity of the material and biocompatibility of cerium oxide nanoparticles, enhances their stability and opens new options for the treatment and diagnosis of various diseases associated with degenerative stress. This analysis specifically focuses on evaluating the interaction between cerium oxide nanoparticles and different capping agents. A comparative analysis is conducted to assess differences of size, shape, and control graft density of the capping agents.

1.3. Hypothesis

The synthesis of Cerium Oxide Nanoparticles using a supercritical fluid process in the presence of capping agents (organic acids, polymers and neurotransmitters) yields chemically stable nanostructures with a fluorite type crystal structure, controlled size and morphology, and high dispersibility in water media.

1.4. Objective

1.4.1. General Objective

To produce cerium oxide nanoparticles by supercritical fluids incorporating organic acids, polymers or neurotransmitters as capping agents to evaluate, through their instrumental characterization, their morphology and size.

1.4.2. Specific Objectives

Extracted from the general objective:

- To synthesize CeO₂ nanoparticles using the supercritical fluid (SCF) process in a neutral environment mediated by KOH, systematically applying organic acids, polymers, and neurotransmitters (dopamine) as capping agents, to control nucleation.
- To determine the morphology and microstructure of the synthesized CeO₂ NPs using (TEM) and (XRD) to confirm the structure and morphology and size.
- To analyze the surface chemical composition and thermal stability of the functionalized nanoparticles, through Thermogravimetric Analysis

(TGA), to evaluate how their presence influences the protection of the inorganic surface.

- To evaluate the colloidal stability and dispersion degree of the functionalized CeO₂ nanoparticles in water media, employing Dynamic Light Scattering (DLS), to measure the hydrodynamic diameter and the level of agglomeration.

2. Cerium Oxide

2.1. Fundamentals of Cerium Oxide

Cerium is the most abundant element of the lanthanide series and the most prevalent rare earth metal in the Earth [1–3]. As a member of the 4f series, its unique electronic configuration allows it to exist in two stable oxidation states trivalent (Ce^{+3}) and tetravalent (Ce^{+4}) see Figure 2.1.1 [4,5].

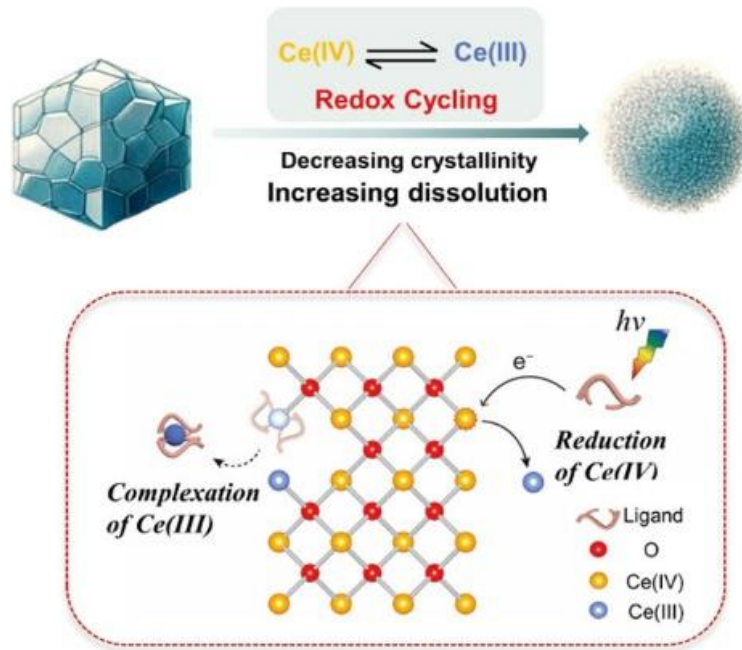


Figure 2.1.1 Dissolution mechanism of Ce in response to crystalline and oxygen vacancy[6].

In its oxide form CeO_2 , it typically crystallizes in a fluorite type face centered cubic (FCC) lattice structure within the Fm^3m space group [7]. In this arrangement, each cerium cation is coordinated by eight oxygen anions, while each oxygen anion is surrounded by a tetrahedron of four cerium cations see Figure 2.1.2 [8].

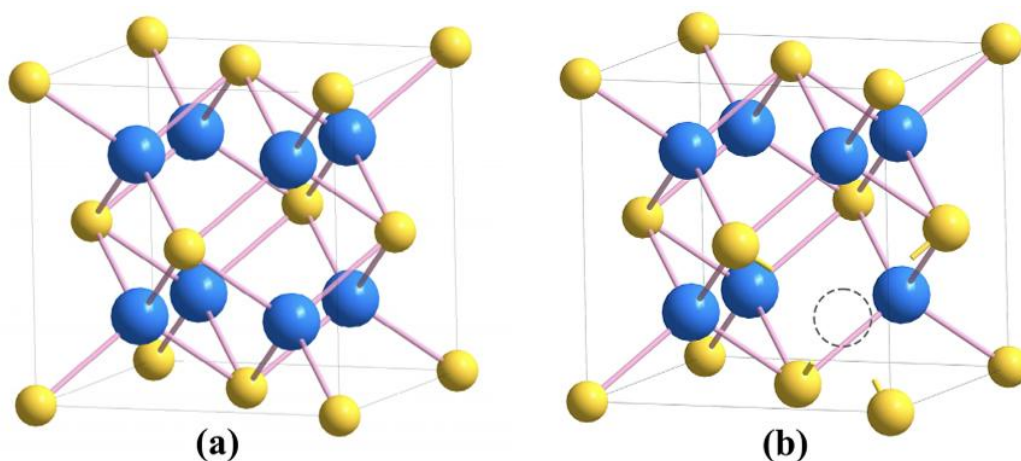


Figure 2.1.2 Diagrammatic representation of CeO₂ lattice structure. (a) Ideal CeO₂ lattice with the fluorite-type structure. (b) Defective CeO₂ with an oxygen vacancy. The yellow spheres: cerium atoms, blue spheres: oxygen atoms, and virtual sphere: oxygen vacancy.

One of the most distinctive features of CeO₂ is its redox flexibility, characterized by the dynamically reversible of Ce⁴⁺ to Ce³⁺ couple. The reduction of Ce⁴⁺/ Ce³⁺ is accompanied by the formation of oxygen vacancies in the crystal lattice to maintain charge neutrality, leading to non-stoichiometric cerium oxide (CeO_{2-x} where 0 < x ≤ 0.5) [7,9,10]. This process grants the material an exceptional Oxygen Storage Capacity (OSC) see Figure 2.1.3, allowing it to act as an oxygen buffer by absorbing or releasing oxygen depending on the surrounding environment [11,12]. Furthermore, the formation of these defects is thermodynamically favored due to an increase in system entropy [11,13].

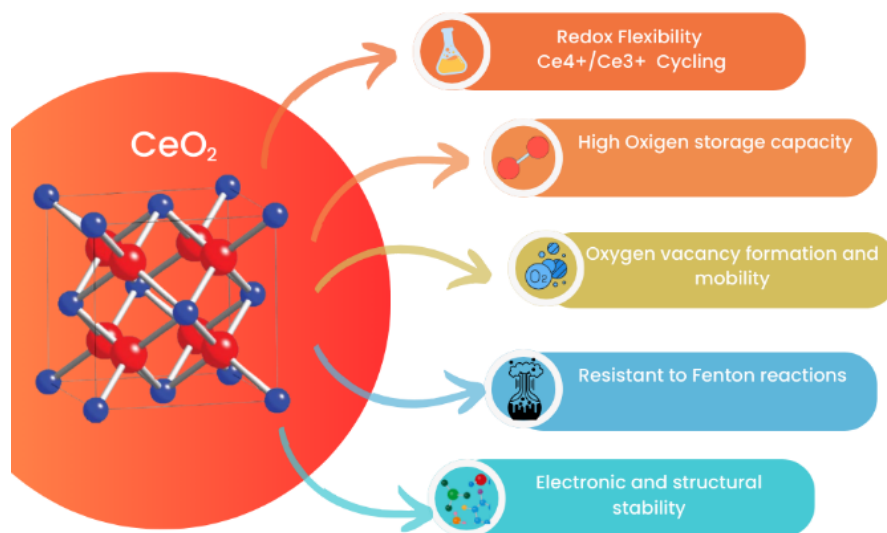


Figure 2.1.3. Characteristics of CeO₂

The versatile chemical properties of CeO₂ NP's have led to their widespread adoption across several critical fields, prioritizing biomedical applications. This is currently the most prominent area of research, driven by the fact that CeO₂ NP's acts as a nanozyme, mimicking the activity of natural enzymes such as superoxide dismutase (SOD), catalase, and peroxidase [12,14,15]. Surface associated Ce³⁺ ions are primarily responsible for SOD mimetic activity, scavenging superoxide radicals, while the Ce⁴⁺ state is linked to catalase-like activity for decomposing hydrogen peroxide [2,12,15,16]. This results in a stronger antimicrobial effect; infiltrate more easily into the cells and hindering the growth of germs as shown in Figure 2.1.4 [7]. As such, the mechanism of antimicrobial action of CeO₂ NPs is attributed to the production of reactive oxygen species (ROS) inducing damage in bacteria [17]. A

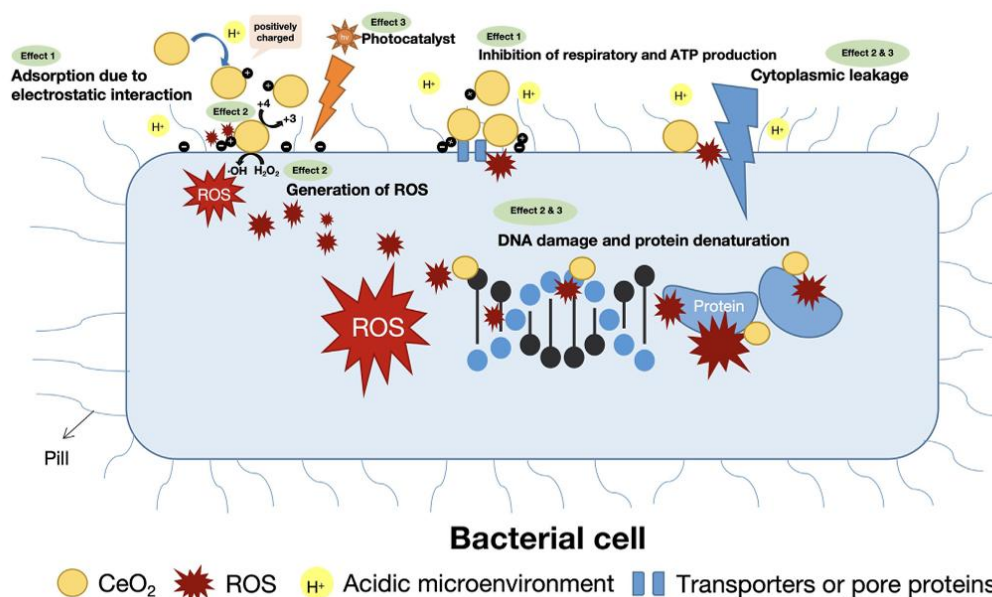


Figure 2.1.4. The mechanisms of antibacterial activities exhibited by CeO₂ NPs. Note that the bacterial cell and molecular structure are not shown to the scale but rather randomly for symbolic reasons [7]

As relevant results, it was demonstrated that CeO₂ NP's protect cardiac progenitor cells from oxidative stress [12,15]. It was observed that cerium oxide and lithium oxide nanoparticles are neuroprotective [13,18]. Recently, there were studies that prove that CeO₂ protects against the toxicity produced by B-AMINOID (A-B) peptide associated with Alzheimer's disease which conjugates antibodies against AB modulating neuronal survival [19]. CeO₂ NP's inhibits the accumulation and cellular toxicity of alpha synuclein protein associated with Parkinson's disease [15]. Another characteristic of this material that has been studied in recent years is the ability to cross the blood brain barrier, allowing it to reach the brain and exert therapeutic effects in neurological diseases [15].

Consequently, it is being extensively investigated for the treatment of neurodegenerative diseases (such as Alzheimer's and Parkinson's), cancer, diabetes,

chronic inflammation, and radiation protection [14,16,20,21]. Furthermore, its ability to promote angiogenesis and reduce oxidative stress at wound sites makes it a promising candidate for accelerated wound healing see Figure 2.1.5 [2,14,22].

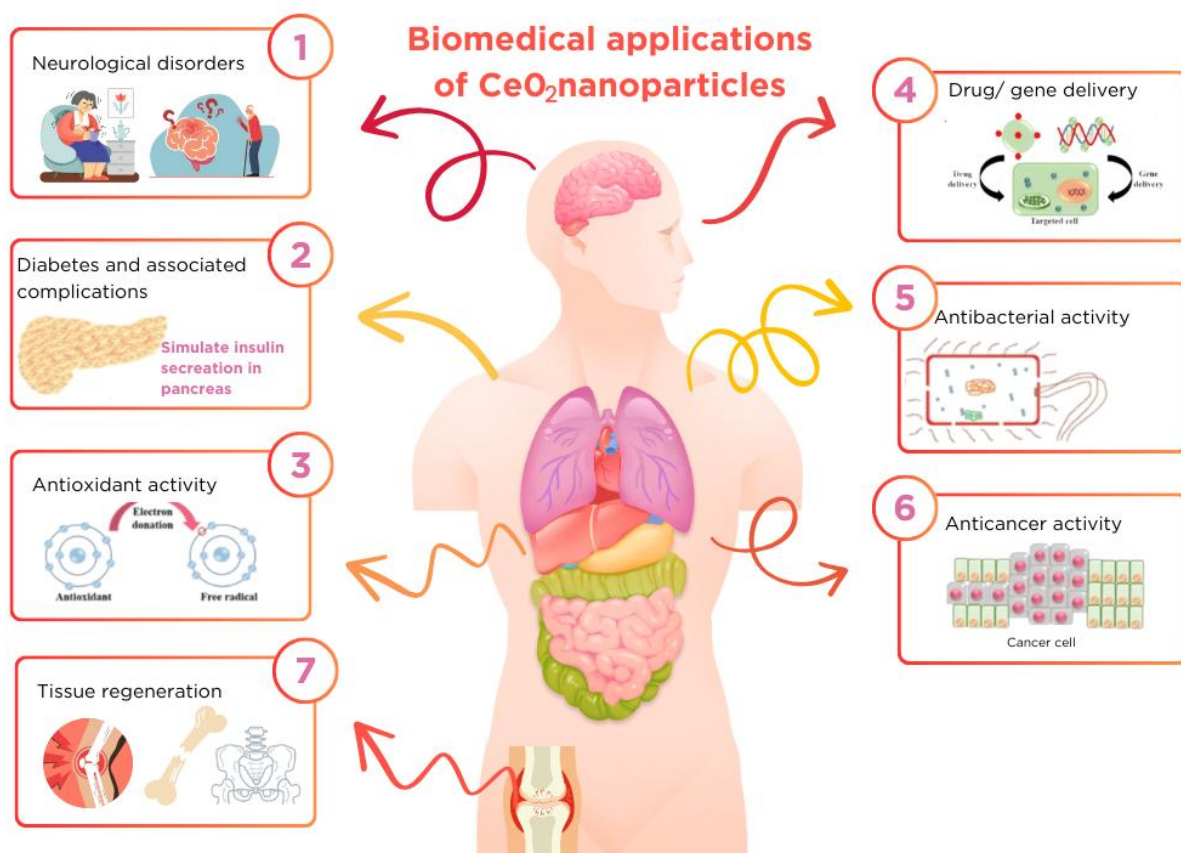


Figure 2.1.5. Biomedical applications of nanoparticles.

Additionally, another application of CeO₂ is industrial catalysis, traditionally is a fundamental component in automotive catalytic converters used for the oxidation of carbon monoxide (CO) and hydrocarbons, as well as the reduction of nitrogen oxides (NO) as shown in Figure 2.1.6 [1,2,4,19,23]. Its high (OSC) and redox activity also make it highly effective in solid oxide fuel cells (SOFC), where it acts as an excellent oxide ion conductor,

and in various organic transformations including the oxidation of volatile organic compounds [1,2,11].

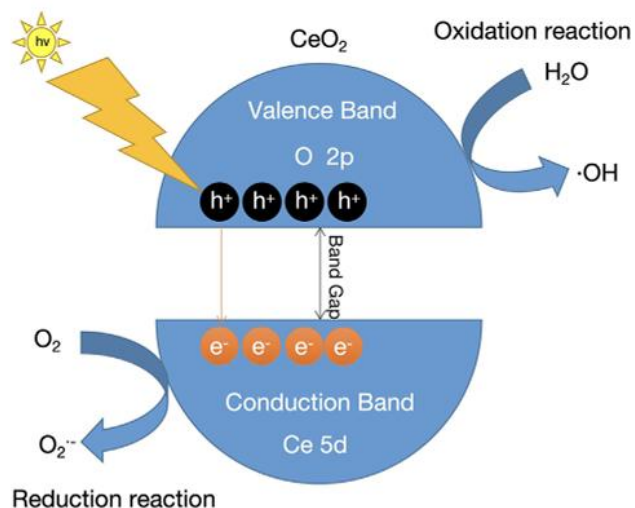


Figure 2.1.6. Schematic diagram of photocatalytic oxidation mechanisms of CeO₂ NPs [7]

Furthermore, CeO₂ is employed in energy and electronics as a high-performance chemical mechanical planarization agent for polishing silicon wafers in semiconductor manufacturing [19]. The surface Ce³⁺ species form strong Ce–O–Si bonds that facilitate material removal [1,2,11,19]. Additionally, it is used in gas sensors for detecting oxygen, moisture, and biomarkers, as well as in the development of solar cells and supercapacitors [[1,11,24–27].

Another important application of CeO₂ is its environmental remediation, serves as an efficient photocatalyst for the degradation of organic dyes (e.g., methylene blue, methyl orange) and pollutants in wastewater [2,3,16,20,28].

Due to its strong absorption of ultraviolet (UV) radiation, CeO_2 NP's is also utilized as a stable and transparent UV filter in sunscreens and cosmetic products [28]. It should also be emphasized that this material has higher absorption in the UV than the synthesized CeCO_3OH , in some hydrothermal processes facilitate the formation of a crystalline cerium carbonate hydroxide as intermediate [18].

2.2. Synthesis of cerium oxide Nanoparticles

There are several types of synthesis for inorganic nanoparticles which are classified into physical and chemical methods [2]. It should be noted that the choice of synthesis method has a relative influence on the final properties of the nanoparticles such as size, morphology, crystalline structure and surface properties [29].

There are multiple techniques used for the synthesis of cerium oxide nanoparticles see Figure 2.2.1, to have a better comparison between the techniques used and the offered characteristics [7,22,30].

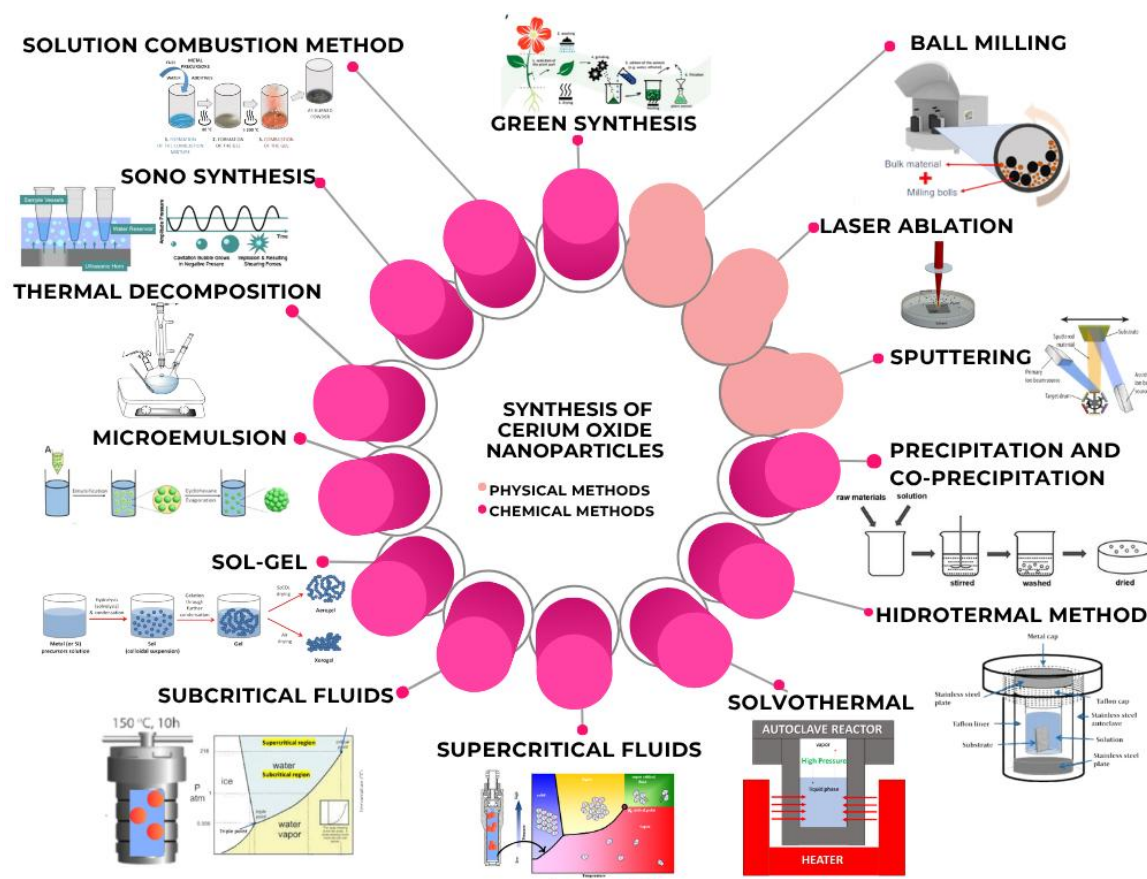


Figure 2.2.1 Synthesis methods of CeO₂ NPs.

Although several physical techniques have been historically for CeO₂ NP's as shown in Figure 2.2.1. Ball Milling, a simple mechanical technique used to fracture and reduce particle size by friction between grinding media and powder [22]. It is fast, environmentally friendly, reproducible and cost effective. However, it has disadvantages such as the possibility of contamination and the tendency of nanoparticles to agglomerate [22,29]. It is also possible to introduce the laser ablation technique characterized by a high purity process, but difficult size distribution, agglomeration, crystalline structure control where the size of the material is reduced by laser irradiation and production of the nanoparticle [3,31]. Another synthesis also called sputtering technique where the interactions of inert

gas ions with an empty metal form the nanoparticles on a surface [32]. Although it is a very versatile technique that allows depositing different metallic materials generally relates to a lack of interdiffusion during the deposition thus creating a poor interface by the lack of mixing in the deposited layer and the substrate [8]. These top-down approaches are frequently characterized as inconvenient and expensive, often resulting in nanoparticles with imperfect surface structures and requiring enormous energy consumption [33].

In the case of chemical methods, see Figure 2.1.1 is highly beneficial due to its simplicity, cost and effectiveness, and scalability, allowing for the facile and rapid production of pure, consistent, and uniform cerium oxide nanoparticles with precise control over their size, shape, and composition; in comparison to physical methods [14].

Highly technique used in CeO₂ NP's co-precipitation, is a variation where two or more precursors aggregate simultaneously instead of remaining scattered, which is particularly useful for creating doped or multi constituent nanozymes [1,7]. Among its main advantages could be higher purity, it allows great nucleation and homogeneous growth of nanoparticles, although it is generally complex and slow [22]. These syntheses generate substantial chemical waste and often involve the use of toxic solvents this is a limitation for biomedical applications [22]. Compared to supercritical fluid synthesis, co-precipitation reactions are slow paced, often requiring hours of stirring and aging [22].

Another synthesis is precipitation the most established and widely used, the principle is the same as co-precipitation but with a single metallic precursor, is a cheap route for fabricating, because the reactions are well mastered and easily operated, the method is highly suitable for large-scale and high throughput production [7]. But presents lack precise control over the final shape and particle size distribution, compared to more advanced methods like super critical fluids synthesis [15].

Hydrothermal synthesis occurs sealed vessel, the water is heated above its boiling point under high pressure, facilitating the recrystallization of metal ions into oxides [22]. It allows for high crystallinity and precise morphology control with a low temperature near to 70 °C, enabling the creation of specialized shapes like nanorods, nanocubes, and octahedrons [10,34]. But the disadvantages are the process is energy intensive and requires long reaction times near 12–24 hours, which limits its scalability [35]. Following the principle of hydrothermal method, solvothermal method utilizes non-aqueous solvents (alcohols or glycols) instead of water under high temperature and pressure [10,34]. Provides exceptional control over particle growth and crystallinity; viscous solvents like 1,4-butanediol can prohibit excessive growth upon nucleation, but it involves the use of organic solvents that can be expensive, toxic, and require longer reaction times [10,34] . Compared to other techniques such as supercritical fluids, these two methods are more expensive, and generates waste [35].

In addition, the supercritical fluid and subcritical fluids synthesis have the same principle as hydrothermal method, but the only difference is the parameters of use [36]. Reactions in super critical fluids are conducted at temperatures and pressures above the critical point of the solvent [35,37]. A key advantage of supercritical fluids synthesis is the ability to precisely modulate its physical properties and phase behavior [35,37]. This process has the characteristic of being a very fast process in comparison to hydrothermal, solvothermal and subcritical synthesis [38]. Disadvantages are requiring expensive high-pressure equipment, complex reactor designs to prevent system corrosion [37,38]. But eliminates the need for post treatments like calcination or milling [39]. Furthermore, subcritical synthesis occurs in fluids at temperatures and pressures slightly below the critical point [34]. Requires less extreme operating conditions, simpler equipment, higher solubility and less uniform distributions[2]. And the time of synthesis in subcritical is 12 and 24 hours, supercritical fluid achieves high nucleation and crystallization rates in short time [38].

Another sol gel technique offers precise control for the chemical composition, purity, and particle size of the resulting nanoparticles [22]. Characteristics of precursors act in hydrolysis and polycondensation to form a colloidal sol that transitions into a solid gel network It ensures high homogeneity, because the precursors are mixed at a molecular level in a liquid phase [22]. However, requiring several days for aging and drying and reproducibility, is challenging because it demands meticulous regulation of reaction conditions, such as pH, precursor concentration, and thermal profiles during calcination [2].

Hydroxide synthesis often involves the use of surfactants to control size and morphology and improve stability, such as microemulsions [34]. In Microemulsion micelles are used as nanoreactors to control the size and shape of the nanoparticles [22,40]. It is a spontaneous self-assembly of the surfactant molecules at the interface reducing the interfacial tension and promoting the formation of small droplets in dispersed phase (micelles) [13,22]. There is high control in morphology, homogeneity (identical to one another in size, shape, chemical) and surface area but presents a high agglomeration of nanoparticles and the use of surfactants effect removal and increase the cost and risk of impurities in the products [2,13].

Similarly, the thermal decomposition (Pyrolysis) method is commonly used for the synthesis of various metal oxides including CeO₂. Accordingly, the chemical decomposition of reagents at high temperature is used to prepare nanoparticles in the presence of surfactants that control their growth [41]. Allows thermal decomposition method enables the synthesis of diverse CeO₂ nanostructures by using pre-synthesized precursors as structural templates[22,31]. This two-step approach allows the final product to inherit the morphology of the precursor, although the high temperatures required (above 400 °C) typically promote grain growth [35]. Specifically, increasing the temperature from 500 to 1000 °C leads to thermal sintering, which significantly reduces the specific surface area and results in a subsequent loss of catalytic activity [28,41].

Likewise, sonochemical synthesis involved the production of cerium oxide nanoparticles employing sound waves to facilitates the nucleation and growth of nanoparticles. This

method generally uses inorganic salts such as cerium nitrate hexahydrate and a coating agent. Moreover, this route is ecological and simple since it uses green capping agents during the synthesis process, thus having a precise morphology and size control avoiding agglomeration [1,28].

Solution Combustion Synthesis (SCS) is a versatile and rapid approach for producing cerium oxide nanoparticles, utilizing cerium nitrate or cerium chloride as precursors. This process involves a self-sustained exothermic reaction where the generated heat drives the formation of NP's in seconds through successive stages of dehydration and decomposition, accompanied by the liberation of gases [1,9]. The introduction of organic fuels such as urea, glycine, glucose, or citric acid is critical, as the fuel type directly modulates the resulting crystalline structure and microstructure [1,9,11]. While SCS is characterized by its simplicity and low initiation temperatures, a final calcination step is typically required to ensure phase purity. Although the technique demands rigorous control of experimental conditions to mitigate high particle agglomeration [13,22].

The green synthesis of CeO_2 is typically characterized by using biological materials such as plant extracts, microorganisms, or bioproducts as reducing and stabilizing agents[1,7]. While this method is highly scalable and biocompatible, precise regulation of parameters like pH, extract concentration, and reaction time is essential [3,18,42]. These factors significantly dictate the final crystallite size and morphology, which can complicate large scale reproducibility [43]. Mainly we can highlight the following plant extracts most used

for cerium oxide: *Melastoma* sp, *Mollugo*, *Fusarium solani*, *Aspergillus niger*, orange peel, *Mentha*, *Acorus calamus*, *Syzygium cumini*, *Elaeagnus angustifolia*, *Eucalyptus globulus*, *Ocimum majorana*, *Ceratonia siliqua* and *Prosopis farcta* [3,9,17,22,28,42,44,45]. For a comparison for all the techniques used for cerium nanoparticles observed Table 2.2.1.

Table 2.2.1 Comparison between the synthesis methods of CeO₂ nanoparticles.

Technique	Size (nm)	Purity	Reaction time	Disadvantages
Co-precipitation	<100	Medium	8 h	Poor morphological control and agglomeration
Precipitation	<21	Medium	8 h	Unsuitable for particles < 10 nm
Hydrothermal	>3	High	14-24 h	Slow kinetics; require high-pressure autoclaves.
Solvothermal	>70	High	14-24 h	Use of expensive organic solvents.
Supercritical fluids	>10	High	<10 min	Requires robust high-pressure equipment.
Subcritical fluids	<10	High	24 h	Strict equipment design and high energy consumption.
Sol gel	>50	High	<24 h	Condition sensitivity; low reproducibility.
Microemulsion	>2	Medium	12 h	Complex removal of residual surfactants.
Thermal decomposition	>40	Medium	>4 h	Use of highly toxic precursors and chemicals.
Sono synthesis	>35	Low	1 h	Difficult control and low large-scale throughput.
Solution Combustion Method (SCS)	>20	Low	<5 min	Instantaneous reaction that limits crystallization.
Green synthesis techniques	>5	Low	2 h	Not scalable; risk of microbial contamination.

2.3. Super critical process (SCF)

Alternative synthesis methods for the preparation of nanomaterials have gained importance in recent years because nanostructures exhibit unique optical, electrical and magnetic properties compared with their bulk counterparts, due to their high surface-area-to-volume ratio and quantum confinement effects [3,40]. Therefore, the technology involved in the supercritical fluid process presents a promising approach for the synthesis of nanoparticles [35,40]. This synthesis process is characterized by using substances above the thermodynamic critical point. This technique is used for surface design with an effective approach in the formation of nanostructures and has better results than conventional processes [40].

A supercritical fluid is understood as a liquid that is in a state with temperature and pressure higher than its critical point. It should be noted that each substance has triple points and critical points [29]. As a generalized definition it is understood that a critical point is the state beyond which a fluid exists as a single phase without a specific distinction between a liquid and a gas; they have physical and chemical properties that differ from traditional fluids [29].

Supercritical fluids, including water, possess unique properties that make them suitable for nanoparticles synthesis [35]. While water at room conditions has a density of approximately 1.0 g cm^{-3} , its density significantly to about 0.2 g cm^{-3} when it reaches the supercritical state inside a reactor at 25MPa [29,36]. Moreover, the solubility of inorganic metal oxides in supercritical water is extremely low because the dielectric constant of water

decreases considerably upon reaching the critical point, thereby reducing the solubility of these compounds [36]. Accordingly, supersaturation is reached instantaneously, leading to rapid nucleation and nanoparticles formation [29,39].

It is essential to emphasize that while gases possess low density and viscosity and liquids exhibit high values for both, the supercritical state occupies a unique hybrid regime [35]. Supercritical water is characterized by high density and low viscosity; consequently, its kinematic viscosity (μ/ρ) is extremely low, which promotes high Reynolds numbers and enhances the rapid mixing necessary for uniform nanoparticle nucleation [29]. An extremely high Reynolds' number causes kinetic control of nanoparticle synthesis, triggering the particle size to decrease and be close to a constant value as the sample velocity increases, the strategy used to force the system into a kinetic control regime [35]. The low kinematic viscosity also causes a high Gasthof number with significant natural convection [39]. It is also important to note that as near the critical point is, the critical water acts as an organic solvent due to its low dielectric constant, thus having high miscibility with organic molecules [36].

Supercritical fluids (SCF) present multiple advantages compared to other traditional synthesis methods [29,46]. Mainly it can be mentioned by the reaction rate of the technique which is extremely fast [38]. Supercritical hydrothermal synthesis achieves reaction rates of four orders of magnitude higher than conventional methods with reaction times of less than 2 seconds [35]. This allows synthesis in less than 10 seconds while other coprecipitation techniques would require hours [35]. Low solubility of the precursor materials since they reach a high saturation instantaneously, thus exhibiting a high nucleation rate and favoring

the preparation of ultrafine particles in the range of 5 to 10 nm [29,36]. Allowing to have a uniform particle size distribution, narrower distribution, high purity and high yield rate compared to other techniques [34,36,38].

The supercritical water technique displays great synthetic flexibility due to the control of the phase and reaction behavior of supercritical water solving problems of conventional methods by more easily controlling the formation of nanostructures, tuning the interaction between nanoparticles and nanoparticle solvent [29,35]. The use of aqueous solvents helps to control properties such as size, geometry, morphology, homogeneity, crystallite growth and surface area of the products by this technique [22,29,39]. It is important to note that this technique is quite simple and generally uses water or other solvents as a reaction medium, which allows it to be an environmentally friendly process without causing secondary contamination and with a low production cost of between 5% to 10% of traditional methods [29,34,38]. The reaction rate is improved in supercritical fluid reactive nanofabrication processes by drastically reducing the required scale of the reactor and therefore the cost of the equipment is more economical compared to the other options mentioned above [3,29].

The synthesis of nanoparticles via SCF technology requires precise regulation of process parameters, as these directly dictate essential particle properties such as size, morphology, and crystallinity, as well as the overall reaction yields [29,35].

It is worth mentioning that the reaction temperature in these processes is an important parameter since metal oxide nanoparticles are synthesized at temperatures above the critical temperature [22,29]. It is specific for water critical hydrothermal synthesis temperatures above 400°C are necessary for the transformation of precursor materials such as lanthanum nitrate and praseodymium nitrate [3,13,22]. Another key parameter to consider in this technique is the pressure, which together with the temperature determines the supercritical state, since increasing the temperature also increases the pressure in the reactor [29,30,34]. Pressure control is highly important as it influences fluid properties such as density and solubility of the metallic precursors [34,38]. The efficiency of SCF relies heavily on the reaction time, which for CeO₂ synthesis, involves rapid kinetics that facilitate near instantaneous nucleation and controlled particle growth[29]. As well as the concentration of the precursor materials since it determines a significant effect on the crystallite size and synthesis yield. In the case of CeO₂ the concentration is ranged from 0.1 to 0.5 molar [29,35,38].

The architectural outcome of CeO₂ nanostructures is dictated by a synergistic interplay between the reaction medium and surface-active agents[35]. Specifically, the selection of solvents such as supercritical water, methanol, or ethanol modulates the phase equilibrium and reaction kinetics by drastically altering the dielectric constant and solubility of precursors [38]. While water often promotes the formation of stable octahedral crystals, alcohols act as in-situ surface modifiers, establishing alkoxide and carboxylate bonds that regulate the physical properties and crystallite dimensions [35]. This solvent driven control

enables the synthesis of varied geometries, including plates, spheres, and porous assemblies [35]. Furthermore, the addition of capping agents serves as a structure directing mechanism; by achieving high surface coverage (grafting density), these molecules effectively block active surface sites through steric hindrance[29]. his quenching of the growth phase results in significantly smaller, monodispersed nanoparticles with a small specific surface area to bare environments.[35].

Supercritical fluid synthesis can be performed in either batch or continuous flow reactors [29]. One of the most used is the continuous flow reactor which differs by having the following parts such as a feed tank which allows the mixing of the precursors and solvents that are kept in agitation during the synthesis [38]. There are also high-pressure pumps that allow the fluids to the reactor [36,38]. Is necessary to keep the solvent heat at supercritical set temperatures, which can use a coiled heating element that allows temperature control [29,31].

Another characteristic element is that where the solvent and the precursor solution are mixed is crucial since it allows us to have an instantaneous and fast mixture affecting the distribution and grain size [35]. For SCF synthesis uses different mixers, been designed such as the T, countercurrent swirl and refined jet [36]. Another important element is the reactor which consists of a stainless steel tube with characteristics outer diameter (OD) of 3.18 mm and an inner diameter (ID) 1.57 mm [29,36]. Consider the volume and length of this one

since it is what allows the residence time of the reaction mixture in subcritical conditions [36,38].

In the case of this equipment, the cooler part is also integrated to stop the growth of nanoparticles and terminate the reaction. It also includes a back pressure regulator [35]. Back Pressure Regulator (BPR), that is located after the reactor in which the pressure inside the reaction system is maintained with high precision control [38]. It is important to emphasize that the precursors and solvents are in separate lines under this equipment [36]. There are also solvent and precursor solution flow rates controlled by pumps, thus optimizing the residence time [29]. In the case of the challenge of this equipment is high temperatures and pressures require integrated equipment with cooling reaction mixing reducing costs and improving results [29,35].

Alternatively, the batch reactor system (or intermittent reactor) allows for the synthesis of nanoparticles by loading precursors into a high temperature and high-pressure environment[46]. For this purpose, a pressure resistant vessel, such as a Hastelloy-C autoclave with a 5 mL capacity, is typically employed [29]. Once the precursors are introduced and the vessel is hermetically sealed, it is placed into a heat source, such as a fluidized sand bath or a preheated electric furnace [31]. As the temperature rises, the thermal expansion of the internal fluid generates significant autogenous pressure, facilitating the reaction under supercritical conditions [29,39].

After the reaction time has elapsed, reactor is removed from the heat source and cooled by immersing it in cold water to stop the reaction [29,39]. The reaction product is then collected from the reactor and centrifuged to remove impurities, and the product is dried to better obtain the nanoparticles [31,35]. The key components of the batch supercritical fluid equipment include a high-pressure reactor that must be resistant to high temperatures, generally Hastelloy C or 316 L stainless steel alloys are used for these reactors [29,39]. A heating system that allows temperature elevation including a sand bath or preheated oven [39]; and a cooling system that allows for growth arrest such as a cold-water bath or an ice and water tank [29,39].

Separation and washing equipment, which allows the recovery of the nanoparticles produced, can include filtration equipment, centrifuges and washing solvents [24,35]. It's important to consider drying equipment for powder production such as a freezing oven or a vacuum oven [35]. Finally, the typical operating conditions include temperatures ranging from 300 to 500 °C and pressures between 25 and 40 MPa [29,38,46].

2.4. Capping Agents

Surface functionalization mechanisms refer to the modification of nanoparticles by capping agents [13,32]. These surface modifying substances are of paramount importance in colloidal synthesis, as they stabilize the interface where nanoparticles interact with their preparation medium, effectively inhibiting overgrowth and preventing uncontrolled

aggregation or coagulation [27,32]. By providing precise regulation of growth and physicochemical characteristics, these coatings modulate the interaction between different nanostructures and mediate critical properties for cell targeting and charge transfer [27,32]. The attachment of capping agents to the nanoparticle surface can occur through covalent or non-covalent interactions, as shown in Figure 2.4.1, and the process may be implemented either in situ during synthesis or through post-production stages, such as ligand exchange or encapsulation[27]. Recent studies emphasize that this level of surface tailoring is essential for enhancing the stability and biological reactivity of nanotherapeutic systems [32].

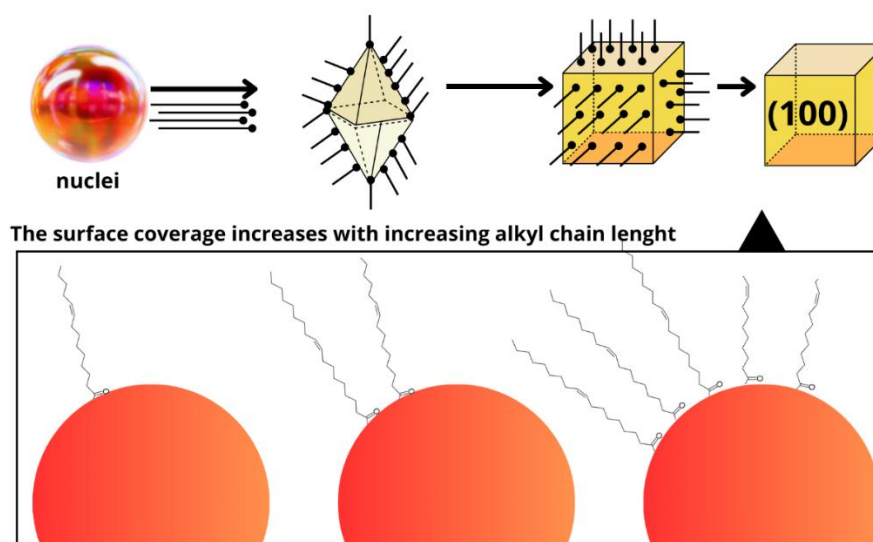


Figure 2.4.1 Grafting of capping agents

These substances play a crucial role in altering biological activities, the steric effects of capping agents adsorbed on the surface are responsible for physics-chemical and biological characteristics [27].

Classification of capping agents can also be given by mechanisms of action:

- Steric agents. They provide stability by creating steric hindrance around nanoparticles [27]. It is the covalent or non-covalent bonding between the ligand chains of the capping agent and the surface of the nanoparticle creating a steric hindrance, obtaining an optimal stability to the nanocomposite [27,32].
- Electrostatic agents. Generate electrostatic repulsion forces that prevent agglomeration, provide surface charge on the nanoparticles[30,32].

Types of Capping Agents

- Surfactants [32].
- Small ligands [27].
- Polymers [32].
- Dendrimers [27].
- Cyclodextrins [27].
- Polysaccharides [27].
- Lipids [32].
- Other Biomolecules [32].

It is important to understand the absorption mechanisms, in the case of the non-covalent ones they include dipole interactions, ionic exchange, hydrogen bonds and conformational effects [15,32]. In the case of these interactions, they are strongly linked to the pH of the solution, thus affecting the charge of the atoms [32]. In the case of the formation of physical bonds, it involves the physical interaction of the nanoparticles, resulting in the trapping of the nanoparticle [15,32]. The absorption of this capping agent is established through hydrophilic interactions, Van der Waals forces and hydrogen bonds,

this acquisition does not cause changes in the native structure of its active site [15,32]. Non-covalent bonds several responses are obtained such as hydrophilic interactions between the alkyl chains thus having an increase of the surface coverage linked to the length of the alkyl chain of the carboxylic acids [39]. Of anionic agents they are absorbed against the positively charged cerium and stabilize it while with cationic surfactants a repulsive response is received against the cerium cations [2].

Covalent bonds, these are involved in the bonds to metal atoms on the surface of the particle, thus comprising the union of chains linked to the coating and surface of the nanoparticles, causing steric hindrance and providing stability to the nanocomposite [27,32]. For the formation of a covalent bond the matrix must be biocompatible and not alter the biological activity of the enzyme [15]. The most common response between covalent groups such as surface molecules and amino-carboxyl through EDC/NHS (carbodiimide/N-hydroxy succinimide) reactions and between small molecules such as benzene derivatives result in cerium oxide nanoparticles in surface passivation and alteration of biological properties [32,47]. The selection of capping agents is a fundamental process as this can affect the properties of the nanoparticles such as relevant biological activity, increased biocompatibility and potential performance of the capping agents [32].

Most relevant effect of the use of capping agents is improving their colloidal stability, preventing the growth of the nanoparticles and avoiding their agglomeration [27,32]. In the case of cerium oxide nanoparticles, the use of capping agents influences high thermal

stability [17,22]. Capping agents also affect the final size of the nanoparticles and control their overgrowth, in the case of nano therapeutics the size has a vital influence [21,27,35,40]. Types of coating also have a significant influence on the final morphology of the nanoparticle [27,32]. Finally, the coating agents, by conferring stability, favor the good dispersion of the nanoparticles, thus having a uniform distribution [32].

The use of capping agents interacts notoriously as biological systems being fundamental in biomedical applications [27,32,47]. For this, capping agents stabilize the interface of the interaction of nanoparticles with their medium [27]. A simple way to explain these interactions is that the non-polar amphiphilic end of the agent interacts with the surrounding medium while the polar starting part interacts with the metal atom of the nano system [27]. The coated nanoparticles have been shown to interact with the cell membrane and rapidly internalize through the interaction of cell membrane receptors and internalize [32,48].

The use of capping agents in metallic nanoparticles [MG39.1][CM39.2] can enhance their biocompatibility for biological applications [1,20]. Since these capping agents usually exhibit desirable properties such as biodegradability, good dispersion, bio-soluble, bio-compatible and low toxicity, they enable the use of capped nanoparticles in living beings [1,13,27,32,48].

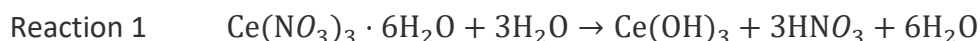
Similarly, introducing capping agents in the preparation of metal oxide nanoparticles synthesis can reduce their toxic [13,27]. Depending on the nature of the coating employed during the nanoparticle synthesis, it could influence in reactivity and surface charge [27,32,47]. Although the reduction of cytotoxicity of metal oxide nanoparticles is an important challenge to overcome, the incorporation of capping agents such as dopamine and PEG onto cerium oxide has been shown to decrease their cytotoxicity, as previously reported in the literature [27,32,47].

Regarding the bioavailability of metal oxide nanoparticles, it is important to consider biodistribution as it is strongly linked to toxicological effects [12,13,40]. Surface charge and its functionalization are critical for cellular uptake and subcellular localization [30]. Therefore, the introduction of coating agents is shown to significantly improve bioavailability in living cells [13,32]. The concept of bioavailability is fundamental to the concept of toxicology [13,15,27].

2.5. Synthesis of CeO₂ NPs with capping agents by supercritical processes

Supercritical fluid processes have shown advantageous results producing cerium oxide nanoparticles in recent years [32,35]. They have mainly been characterized by their rapid fabrication of nanostructures with high purity, using elevated temperature and pressure conditions [29,32,38].

The crystallization of CeO₂ nanostructures in hydrothermal or supercritical environments is a multi-step process highly sensitive to the precursor's nature and the reaction conditions [7,35]. The formation mechanism generally proceeds through three fundamental stages [38]. Hydrolysis; the cerium precursor (cerium nitrate) reacts with water to form intermediate cerium hydroxides (Ce³⁺ or Ce⁴⁺) or hydrated metal oxides [38].



Oxidation, in systems utilizing trivalent cerium (Ce³⁺), the intermediate Ce(OH)₃ is oxidized to the stable tetravalent state (Ce⁴⁺) required for pure ceria. This step is often driven by nitrate anions (NO₃⁻) acting as oxidizing agents or by dissolved oxygen in the medium [8,36,38].



Dehydration and nucleation, the final step involves the dehydration of the tetravalent hydroxide intermediates into cerium oxide. This transition occurs rapidly under supercritical conditions due to the sharp decrease in the dielectric constant of water, which triggers instantaneous supersaturation and fast nucleation [2,38].



Following nucleation, the growth and final morphology of the nanocrystals are dictated by the selective adsorption of ions on the crystal facets. For instance, nitrate anions preferentially adsorb onto the CeO₂ nuclei surfaces, promoting anisotropic growth that typically results in polyhedral or cubic nanostructures [38].

CeO₂ NPs synthesized by supercritical processes and functionalized with coating agents have the potential for biomedical applications [1]. They have been explored for their antioxidant, antibacterial, and antitumor properties, among others [1]. Their unique regenerative ability to remove reactive oxygen/nitrogen species (ROS/RNS) has made them promising candidates for reducing cellular and tissue damage [5]. Incorporating these nanoparticles into scaffolds has helped prevent their aggregation and provided sustained release systems that reduce the potential toxicity of CeO₂ NPs in wound healing [22].

The biocompatibility and behavior of CeO₂ NPs in biological environments have been crucial [12]. It has been demonstrated that synthesis and post-synthesis modifications, including the use of capping agents and biocompatible biodegradable stabilizers, have been necessary to obtain nanoparticles capable of therapeutic effects [27]. For example, ethylenediamine as a capping agent has resulted in ultrathin, water miscible CeO₂ nanoparticles with mixed valence on the surface, suitable for biomedical applications [2]. The use of polymeric coatings, such as PEG, has also been applied to modify the surface of CeO₂ NPs and to explore their activity against neurodegenerative diseases [12,13].

Most documented biomedical applications of surface modified nanoparticles rely on conventional synthesis routes, such as forced hydrolysis, precipitation, solvothermal methods, and biosynthesis [13,30,47]. Consequently, while CeO₂ nanoparticles (NPs) produced via supercritical fluid (SCF) synthesis and capping CeO₂ NPs have independently shown biomedical relevance, their synergistic combination specifically the biomedical assessment of CeO₂ NPs functionalized during or after supercritical processing has not been comprehensively detailed. [5,7,38,39]. This specific intersection represents a significant research gap and a promising frontier for developing advanced nanotherapeutic systems [43].

The interaction of CeO₂ NP's with capping agents is essential to control their properties and behavior [2]. These agents play crucial roles in the synthesis process and determine the subsequent properties of the NPs [2].

The architectural tailoring of CeO₂ nanostructures is primarily driven by the selective adsorption of coating agents onto specific crystallographic planes, which quenches growth in certain directions and promotes oriented attachment[2]. Coating agents like polyphenolic groups in plant extracts, polymers such as PEG or polymeric materials in general, and hydrophilic stabilizing agents can prevent undesired particle agglomeration, ensuring good dispersibility and uniform size distribution [2,9,13,27,32].

Usually, capping agents help to control and reduce particle size and narrow the size distribution [27]. Surfactants used in the microemulsion method have limited NP size between 2 and 21 nm, predominantly spherical [13]. Leads to surface modification, influencing surface chemistry, surface charge, and zeta potential [7]. Modification with catechol type ligands may result in the formation of interfacial charge transfer complexes [47]. Zeta potential can be stabilized over time [27]. Use of biocompatible and biodegradable coating agents is necessary for biomedical applications. Capping agents can alter the toxic effects of NP's [27]. The toxicity of CeO₂ NPs can be influenced by the capping agent used [13,27]. Polymer coatings can affect cellular uptake mechanisms and subcellular localization [7]. The electrostatic interaction between positively charged CeO₂ NP's (possibly due to the coating) and the negatively charged bacterial cell surface can improve antibacterial activity [7].

There are several types of compounds that can function as a capping agent, and each offers different advantages and disadvantages therefore the strategic selection of the capping agent is essential to control the properties of CeO₂ nanoparticles [32]. Factors such as dispersion stability, biocompatibility and catalytic activity should be considered [49]. The variety of capping agents shown in Figure 2.5.1 include propionic acid, citric acid, 3,4-dihydroxybenzoic acid (DHBA), gallic acid, lactic acid, PEG 4,000, oleic acid, and dopamine utilized to optimize the physicochemical properties [7,27,32].

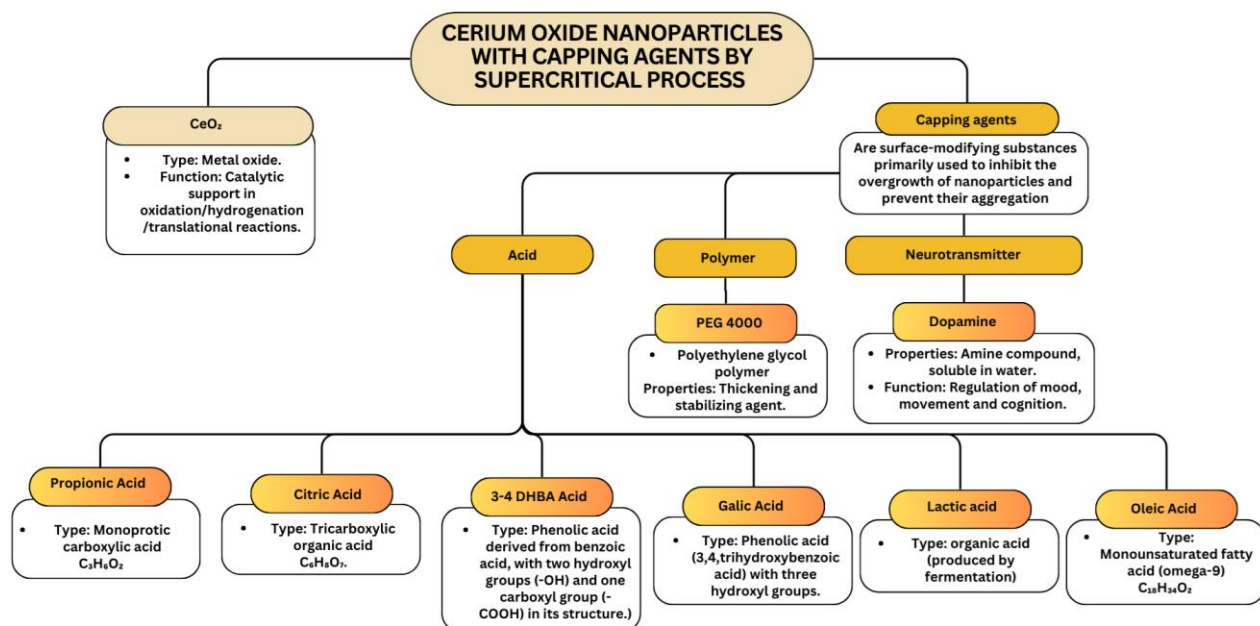


Figure 2.5.1 Comparison of capping agents.

In the medical field propionic acid is commonly used as a pH stabilizer and complexing agent for metal oxides, which affects growth during synthesis and results in different nanoparticle structures exhibiting antimicrobial properties [27]. Likewise, citric acid is a tricarboxylic acid containing three functional carboxyl groups in its structure [27]. It acts as a reducing and stabilizing agent. The carboxylic groups bind to metal ions on the surface of nanoparticles preventing agglomeration by helping electrostatic dispersion due to the negative charge provided by the protective agent [50]. For biomedical applications stand out exhibiting higher antioxidant activity compared to other particles [39].

Otherwise, 3,4-dihydroxybenzoic acid (3,4-DHBA) binds as a coating agent through the catechol functional group leaving the carboxylate group free, forming one of the strongest bonds on the nanoparticle surface, ensuring a stable and well-defined surface [51]. Same as

gallic acid is another stabilizing agent that exhibits excellent antioxidants and antibacterial properties [32,49].

The impressive properties of complexing and buffering agent by the lactic acid, make it react with the metal oxides surrounding the nanoparticles, preventing the oxidation of the metal forming a stable oxide coating [30]. Working almost the same way, polyethylene glycol (PEG) is a polymer of ethylene oxide as part of hydrophobic polymers, it is biocompatible, non-toxic and non-immunological helps to improve their stability, biocompatibility and functionalization of nanoparticles. It acts as a reducing and stabilizing agent improving the water affinity and biodegradability of nanoparticles. It also influences their surface charges, allowing negative, neutral and positive charges [2,30]. PEG provides low toxicity and immunogenicity of the particles, improves colloidal stability, prevents aggregation. Moreover, PEG is commonly used for drug delivery in cancer treatments and as a protective agent since does not degrade under *in vivo* conditions, ensuring prolonged stability of nanoparticles in the body [2].

Oleic acid is a monounsaturated fatty acid that acts as an effective capping agent. It contains a carboxyl group that binds to the particle surface and a long hydrocarbon chain that extends outward. This structure provides stabilization and protection against oxidation for the nanoparticles while facilitating their dispersion in non-polar media [2,41]. As a protective agent dopamine offers catechol and amino groups, is biocompatible and less toxic than other coating agents [43,52]. The groups of these substances reduce metal ions

and stabilize nanoparticles by controlling growth and preventing agglomeration [52] It is noted for promoting cell proliferation, although at high concentrations is highly toxic [12,47].

The incorporation of protective agents into cerium oxide nanoparticles performed to have better control of size, morphology, colloidal stability, and physicochemical properties in a precise manner [7,51]. This surface modification is fundamental for the optimization of CeO₂ NP's properties for biomedical applications, influencing biological environments, biocompatibility enhancement, and cytotoxicity modulation [47].

3. Experimental

Cerium oxide nanocrystals were synthesized by rapid reaction of $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ and KOH in supercritical water. Figure 3.1 illustrates the experimental methodology followed in this investigation.

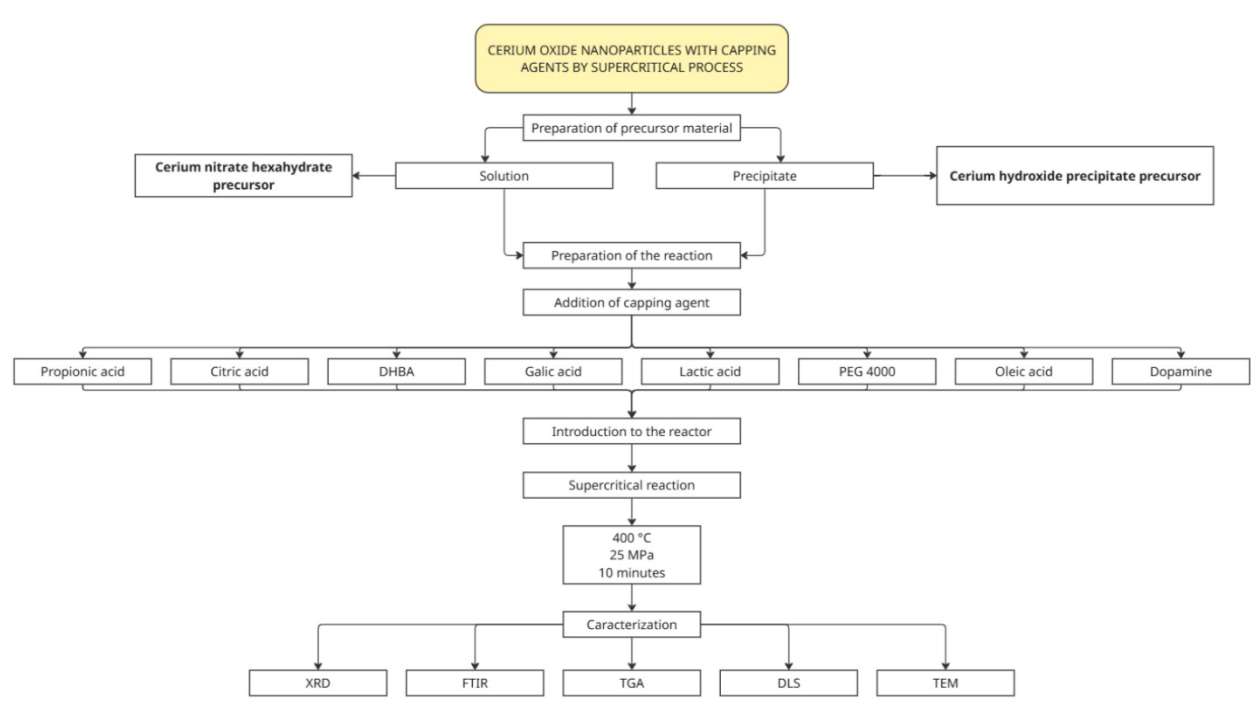


Figure 3.1 Experimental Process of Cerium oxide nanoparticles with capping agents by supercritical water

3.1. Materials

Cerium nitrate hexahydrate ($\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$, 99.99% purity, Wako Chemicals) and potassium hydroxide (KOH, 99.99% purity, Wako Chemicals) were used as reagents for the synthesis of cerium oxide (CeO_2) NP's. Distilled water was used as the reaction media. Additionally, organic acids such as propionic acid (PA, 99.99% purity, Wako Chemicals), citric acid (CA, 99.99% purity, Wako Chemicals), 3,4-dihydroxybenzoic acid (DHBA, 98.0% purity,

Wako Chemicals), gallic acid (GA, 97.5% purity, Sigma Life Science), lactic acid (LA, 94.05% purity, Wako Chemicals) and oleic acid (OA) (65.05% purity, Wako Chemicals), as well as polyethylene glycol 4000 (PEG 4000, 99.99% purity, Wako Chemicals) and dopamine (DA, 99.99% purity, Wako Chemicals) were used as surface modifiers, separately (see table 3.1.1).

Table 3.1.1 Chemical reagents used

	Substance Name	Chemical Formula	Reagent Brand
Precursor	Cerium nitrate hexahydrate	$Ce(NO_3)_3 \cdot 6H_2O$	Wako Chemicals USA Corporation
pH Control	Potassium hydroxide	KOH	Wako Chemicals USA Corporation
Capping agent	Propionic Acid	$C_3H_6O_2$	Wako Chemicals USA Corporation
	Citric Acid	$C_6H_8O_7$	Wako Chemicals USA Corporation
	3,4-dihydroxybenzoic Acid	$C_7H_6O_4$	Wako Chemicals USA Corporation
	Gallic Acid	$C_6H_2(OH)_3COOH$	Sigma Life Science
	Lactic Acid	$C_3H_6O_3$	Wako Chemicals USA Corporation
	PEG 4000	$(C_2H_4O)_nH_2O$	Wako Chemicals USA Corporation
	Oleic acid	$C_{18}H_{34}O_2$	Wako Chemicals USA Corporation
	Dopamine hydrochloride	$C_8H_{11}NO_2 \cdot HCl$	Wako Chemicals USA Corporation
	Distilled water	H_2O	Yamato WG203 Auto Still Laboratory Water Distiller QP
	Ethyl alcohol	C_2H_6O	Wako Chemicals

Respect to the synthesis of cerium oxide nanoparticles conducted using a supercritical water reaction process, it was two different types of precursor solutions chosen. To evaluate the pH of the solution, two experimental sets were considered. Table 3.1.2 explains the differences between the precursors between these two sets. During synthesis,

capping agents were incorporated to function as surface modifiers (a capping agent to precursor weight ratio of 0.5). Schematic workflow for the supercritical water synthesis of CeO₂ NPs with surface grafted capping agents is illustrated in Figure 3.1.2. The experimental design included the preparation of nine distinct samples; eight functionalized with different organic modifiers and one a pure plain CeO₂ NPs (control). Figure 3.1.3 provides a schematic representation of the CeO₂ NPs tailored with propionic acid, citric acid, 3,4-dihydroxybenzoic acid, gallic acid, lactic acid, polyethylene glycol (PEG) 4000, oleic acid and dopamine.

Table 3.1.2 Experimental set

(Note: ✓ indicates the addition of KOH during the precursor treatment, while × denotes its absence.)

#	PRECURSOR MATERIAL	ID	KOH	CAPPING AGENT
1	Cerium nitrate hexahydrate precursor	A	×	PLAIN
2		B	×	PROPIONIC ACID
3		C	×	CITRIC ACID
4		D	×	3-4 DHBA
5		E	×	GALLIC ACID
6		F	×	LACTIC ACID
7		G	×	PEG 4000
8		H	×	OLEIC ACID
9		I	×	DOPAMINE
10	Cerium hydroxide precipitate precursor	A	✓	PLAIN
11		B	✓	PROPIONIC ACID
12		C	✓	CITRIC ACID
13		D	✓	3-4 DHBA
14		E	✓	GALLIC ACID
15		F	✓	LACTIC ACID
16		G	✓	PEG 4000
17		H	✓	OLEIC ACID
18		I	✓	DOPAMINE

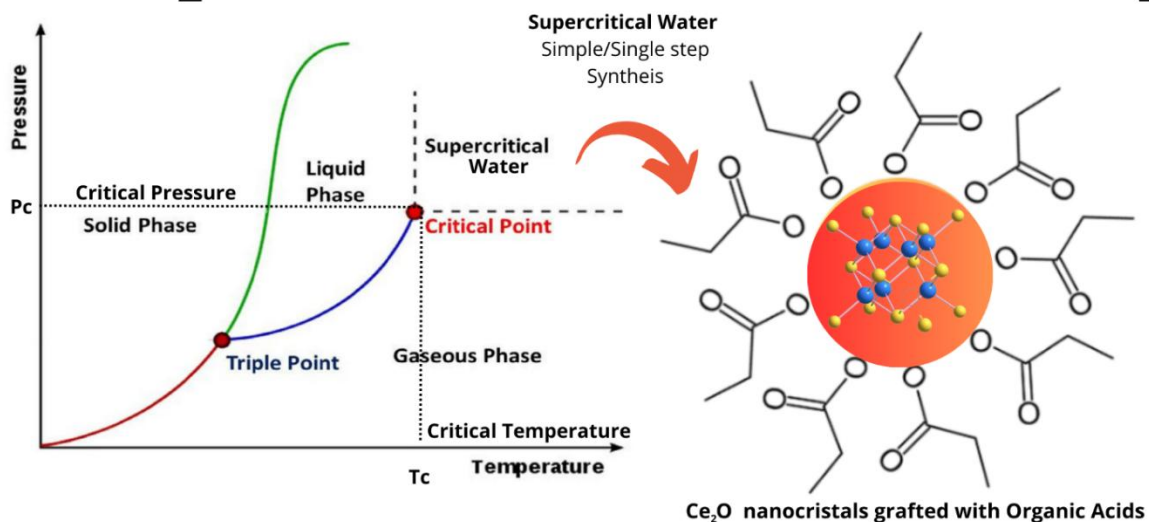
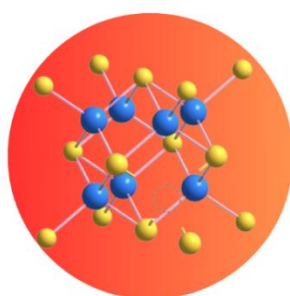
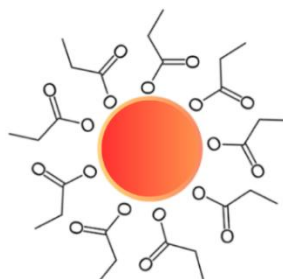


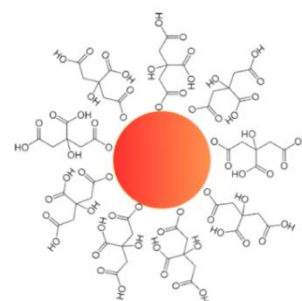
Figure 3.1.1 Supercritical water cerium oxide with capping agents.



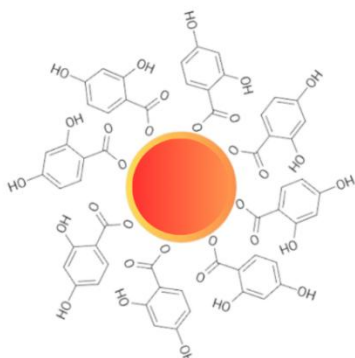
Cerium Oxide



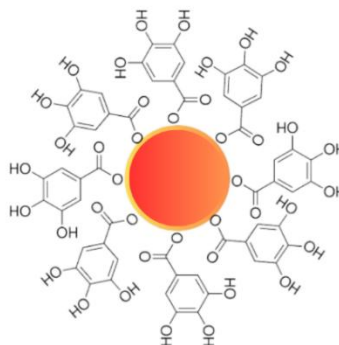
Propionic acid



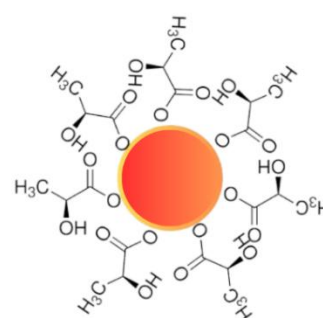
Citric acid



DHBA



Galic acid



Lactic acid

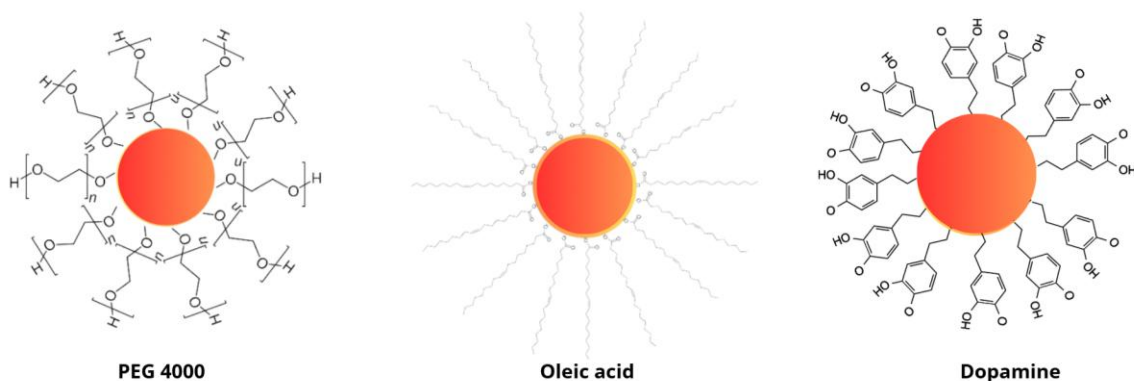


Figure 3.1.2 Cerium oxide is grafted with organic acids.

Precursor Solution

Preparation of the Cerium Nitrate Precursor Solution

In the first experimental setup, cerium nitrate hexahydrate ($\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$) was dissolved directly in deionized water. For one reactor batch 0.108 g of ($\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$) was weighed using an analytical balance and subsequently dissolved in 2.5 mL H_2O using a micropipette to achieve a precise concentration of 0.1 mol/L. This primary aqueous phase served as the starting precursor solution for the systematic incorporation of the various capping agents, as shown in Figure 3.1.4.

Subsequently, 0.054 g of the specific capping agent was weighed on a precision balance and incorporated into the starting precursor solution. The process was maintained for 5 minutes at 5 °C to ensure controlled surface functionalization while strictly adhering to the standardized 0.5 mass ratio relative to the initial cerium precursor solution.

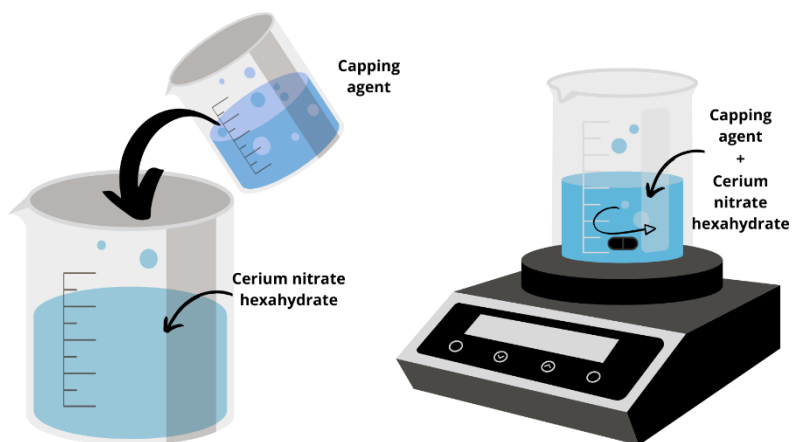


Figure 3.1.3 Preparation of the Cerium Nitrate Precursor Solution with Capping Agents

Preparation of Cerium Hydroxide Precipitate as a Precursor Solution

In the second experimental configuration, a precipitation method was employed to prepare the inorganic base prior to functionalization see Figure 3.1.5. For one reactor, 0.108 g $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ was weighed using an analytical balance and dissolved in 2.5 mL H_2O to maintain a concentration of 0.1 mol/L. Simultaneously, an aqueous solution 0.1 mol/L; of potassium hydroxide was prepared by dissolving 0.0108 g KOH of the base in 1.925 mL deionized water. The KOH solution was added dropwise to the cerium precursor using Pasteur pipette to ensure optimal pH control and the formation of a cerium hydroxide ($\text{Ce}(\text{OH})_4$) precipitate without disturbing the medium. The resulting precipitate was collected and washed by centrifugation three times (5 minutes per cycle at 120 rpm) with distilled water to effectively remove residual nitrates and reaction byproducts. Following the

washing steps, the pH of the suspension was adjusted to a value of 9 to stabilize the surface environment.

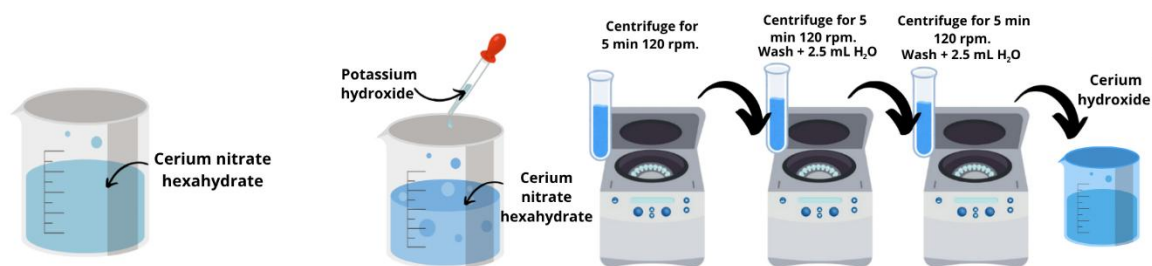


Figure 3.1.4. Cerium hydroxide process.

Subsequently as shown in Figure 3.1.6; 0.054 g of the specific capping agent was weighed on a precision balance and incorporated into the cerium hydroxide precipitate. The mixture was agitated using a hotplate magnetic stirrer to facilitate the dissolution of modifiers with low solubility; the process was maintained for 5 minutes at 5 °C to ensure controlled surface functionalization while strictly adhering to the standardized 0.5 mass ratio relative to the mass of the initial cerium nitrate precursor.

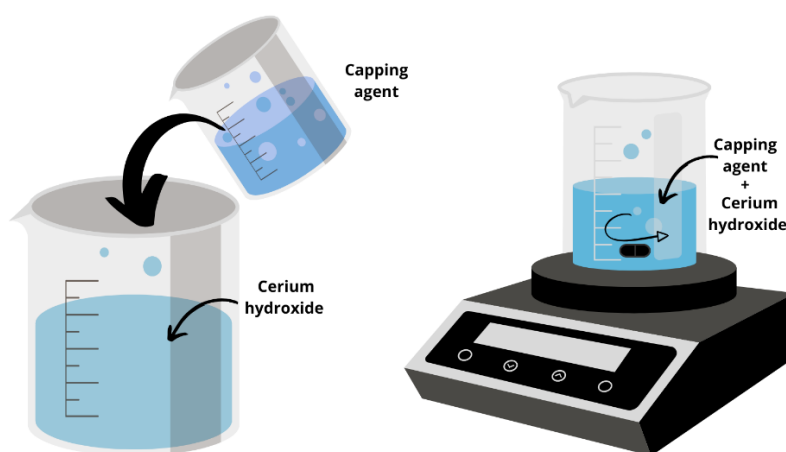


Figure 3.1.5. Cerium hydroxide process with capping agents.

3.2. Supercritical Water Synthesis Process

A schematic diagram of the experimental apparatus (AKICO Co. Japan) used for synthesis of CeO_2 NPs in supercritical water is shown in Figure 3.2.1. After obtaining precursor substance (Cerium hydroxide and the capping agent with distilled water), 2.5 mL of precursor solution was introduced into a batch type Hastelloy-C reactor, with an internal volume of 5 mL and electric furnace). The reactor was hermetically sealed using a torquemeter at 20 kN until a "click" heard, ensuring an adequate seal for supercritical conditions.

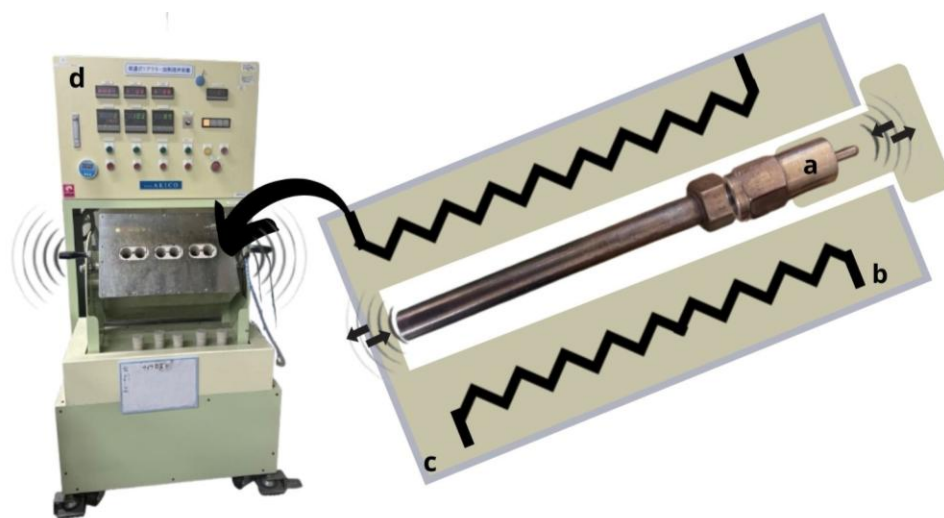


Figure 3.2.1. Schematic diagram of experimental apparatus used for synthesis of CeO_2 NPs in supercritical water. a. batch reactor, b. electric furnace c. ceramic box, d. AKICO Co. Japan

The electric furnace was preheated for 20 minutes until it reached a temperature of 400 °C. Once the furnace reached the desired temperature, the sealed reactor was inserted into the furnace. The reactor's design allows the system to reach the desired temperature and thus the pressure above the critical point in relatively short times. The reaction was carried

out for 10 minutes at 400 °C and 25 MPa, keeping the reactor under constant agitation during the synthesis process (see Figure 3.2.2).

Post-Synthesis Treatment and Purification

After 10 minutes of reaction, agitation was stopped. The reactor was removed from the furnace and rapidly cooled by immersing it in a water bath for 8 minutes to reduce the temperature. After cooling and depressurization, the reactor was opened using the torquemeter to extract the reaction products. To ensure complete material recovery, 2.5 mL of distilled water was introduced into the reactor, and a spatula was used to scrape the walls, collecting all the product into a Falcon tube.

The samples were purified by centrifugation for 5 minutes at 120 RPM and washed with distilled water to eliminate residual reactants. This centrifugation and washing process with 2.5 mL of distilled water were repeated twice. If the substance contained a capping agent, an additional wash was performed for 5 minutes at 120 RPM with ethanol to ensure the elimination of organic reagents.

After the final wash, 2.5 mL of distilled water was added, and the samples subjected to sonication for 30 minutes to achieve the dispersion of CeO₂ nanoparticles.

Freeze-Drying

To facilitate the handling and preservation of the nanoparticles, a freeze-drying process was performed. The sample was placed on a tray, frozen with liquid nitrogen, and introduced into the freeze-drying equipment for 12 hours for drying and its subsequent preparation for characterization.

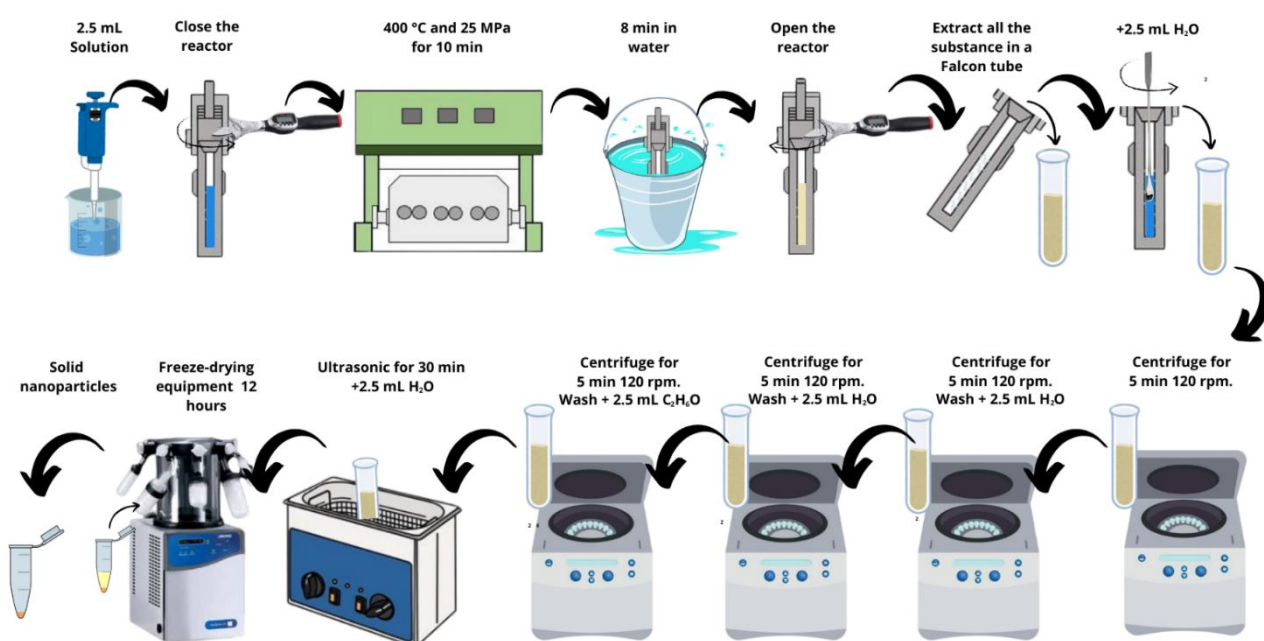


Figure 3.2.2. Cerium oxide Nanoparticles by supercritical process synthesis

3.3. Characterization

X-ray Diffraction (XRD)

XRD technique was employed to identify the crystalline structure of the synthesized nanoparticles, as well as to verify the absence of secondary crystalline phases in the

samples. The recorded patterns were also used to determinate the crystallite size by the Scherrer equation. The PANalytical X-ray diffractometer was used to record the patterns of the products, employing Cu-K α radiation and 2 θ values ranging from 10° to 70° (see Figure 3.3.1).



Figure 3.3.1. MALVERN PANALYTICAL BENCHTOP X-RAY DIFFRACTOMETER - AERIS 600 W WITH GI-XRD OR HEATING STAGE

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR was employed to characterize surface functional groups and to validate the chemical grafting of capping agents onto the nanoparticles. Measurements were performed using a Thermo Scientific Nicolet iS5 FTIR Spectrometer (see Figure 3.3.2) in transmittance mode over the wavenumber range of 1900–500 cm⁻¹. This system, equipped with OMNIC software and an auto-alignment diode laser, ensured a precise analysis of the interfacial chemical interactions and the successful binding of stabilizers during synthesis.

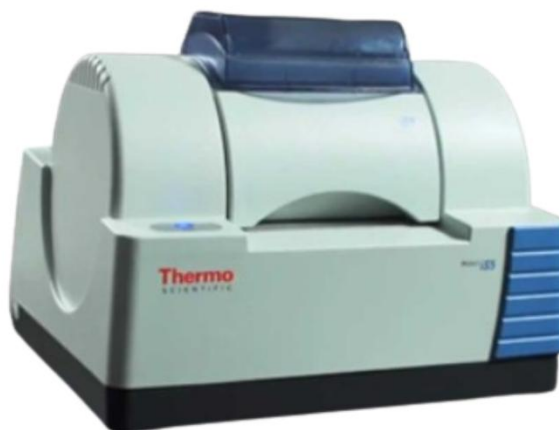


Figure 3.3.2. Thermo Scientific Nicolet iS5 FT-IR Spectrometer

Thermogravimetric Analysis) (TGA)

Analysis determines the stability of the nanoparticles and the amount of organic materials present during the synthesis of capping agents, revealing the decomposition of substances or oxidation reactions as the temperature increases. TGA analyzer is depicted in Figure 3.3.3. The measurements were performed by introducing a powdered sample into a 0.1–0.5 g cuvette. The analysis consists of comparing how the weight of the sample reduced during the temperature exposure. In this case the equipment has a temperature ramp where it increases to one hundred degrees, stabilizes, and starts measuring from 200 to 600 °C at 10 °C/min.



Figure 3.3.3. STA 2500 Regulus - NETZSCH Analyzing & Testing

Dynamic Light Scattering (DLS)

DLS was used to determinate the nanoparticle size distribution and its stability in dispersion. Moreover, the hydrodynamic size of the nanoparticles was obtained to evaluate their aggregation in liquid media. The DLS equipment Figure 3.3.4 was used by introducing a small amount of sample in a transparent cuvette with water up to the indicated line.



Figure 3.3.4. Zetasizer Nano ZS Malvern Panalytical

Transmission Electron Microscopy (TEM)

This technique is one of the most important since it allows us to obtain atomic-level images with high resolution to compare the morphology, size, and arrangement of nanoparticles. Transmission Electron Microscopy as shown in Figure 3.3.5 helps to determine the optimal morphology for antioxidative effects in internal structures and detect defects in nanomaterials during CeO₂ production. The characterization procedure involved dispersing the powdered samples in isopropyl alcohol, depositing an aliquot of this dispersion onto a lacey-carbon copper grid, allowing the solvent to evaporate and subsequently introducing the specimen into the microscope.



Figure 3.3.5. TEM/STEM Titan 300/80

4. Results and Discussion

4.1. Cerium oxide nanoparticles via solution

X-ray Diffractograms of Cerium oxide nanoparticles via solution

According to the literature, the CeO_2 crystallize into a fluorite-type structure, corresponding to the $F\bar{m}3m$ space group, characterized by the presence of well-defined X-ray diffraction peaks, attributed to the planes (111) (200) (220) (311) (222) (400), as shown in Table and Figure 4.1.1. In this study, the diffraction patterns of all synthesized samples index perfectly with the standard reference pattern JCPDS No. 34-0394, confirming the successful formation of highly crystalline and phase CeO_2 . The characteristic reflections of the fluorite structure are clearly observed in all diffractograms, demonstrating that the robust inorganic CeO_2 crystalline core remains unaltered after the chemical grafting and surface modification with the various capping agents. This stability is expected, as the organic modifiers primarily interact with the active surface coordinates of the nanoparticles via chemisorption without being incorporated into the inner crystal lattice.

Table 4.1.1 Bragg diffraction angles and corresponding interplanar spacing for CeO_2 NP's with SCW

Plane (hkl)	2 θ Angle	Interplanar distance d (Å)
(111)	28.56	3.12
(200)	33.09	2.71
(220)	47.50	1.91
(311)	56.34	1.63
(222)	59.09	1.56
(400)	69.42	1.35

A significant broadening of the Bragg reflections is selectively observed for the samples modified with 3,4-DHBA, gallic acid, and dopamine. According to the Debye-Scherrer equation ($D = \frac{K*\lambda}{\beta*\cos\theta}$), the FWHM of a reflection plane is inversely proportional to the average crystallite size. Thus, the broader profiles of these specific samples signify a pronounced reduction in the crystallite core size compared to the plain, unmodified CeO₂ NP's.

This crystalline restriction is explained by a "selective quenching effect" operating during the single-step supercritical water synthesis.[37]. In this mechanism, the polyphenolic and catecholate-type ligands (3,4-DHBA, gallic acid, and dopamine) exhibit an exceptionally high coordination affinity toward the surface cerium ions of the newly nucleated particles. By rapidly coordinating these active metal centers, these capping agents effectively saturate the solid-liquid interface almost immediately after the primary nucleation burst, blocking further solute diffusion and crystal growth.

In contrast, the samples modified with propionic acid, citric acid, lactic acid, and oleic acid exhibit peak profiles and widths almost identical to those of plain CeO₂. This indicates that, under the highly dynamic conditions of this supercritical synthesis, these specific molecules exert a limited or subtle effect on the growth kinetics of the inorganic core. For these agents, the thermodynamic interaction with the growing ceria nuclei was not strong enough to quench the growing crystallites as effectively as the catecholate-type ligands,

allowing the domains to reach sizes comparable to those obtained in the control sample synthesized without any capping modifier.

Interestingly, a distinct behavior is observed for the sample modified with PEG 4000, where the diffraction peaks exhibit a slight shift toward lower 2θ angles compared to the reference pattern. According to Bragg's Law, a shift toward lower diffraction angles corresponds directly to an increase in the interplanar spacing (d), indicating a minor lattice expansion. This lattice dilation (tensile strain) is attributed to the steric and surface relaxation effects induced by the physisorbed PEG 4000 polymer chains.

The high molecular weight and dense polymeric layer of PEG 4000 physisorbed on the hydrophilic surface of the newly formed CeO_2 nuclei exert a tensile pull on the surface planes, leading to a minor distortion and relaxation of the unit cell volume at the surface interfaces. This structural behavior highlights the distinct physics of polymeric capping agents compared to small organic molecules, where steric hindrance and surface tension relaxation dominate over the chemical quenching of the crystalline core.

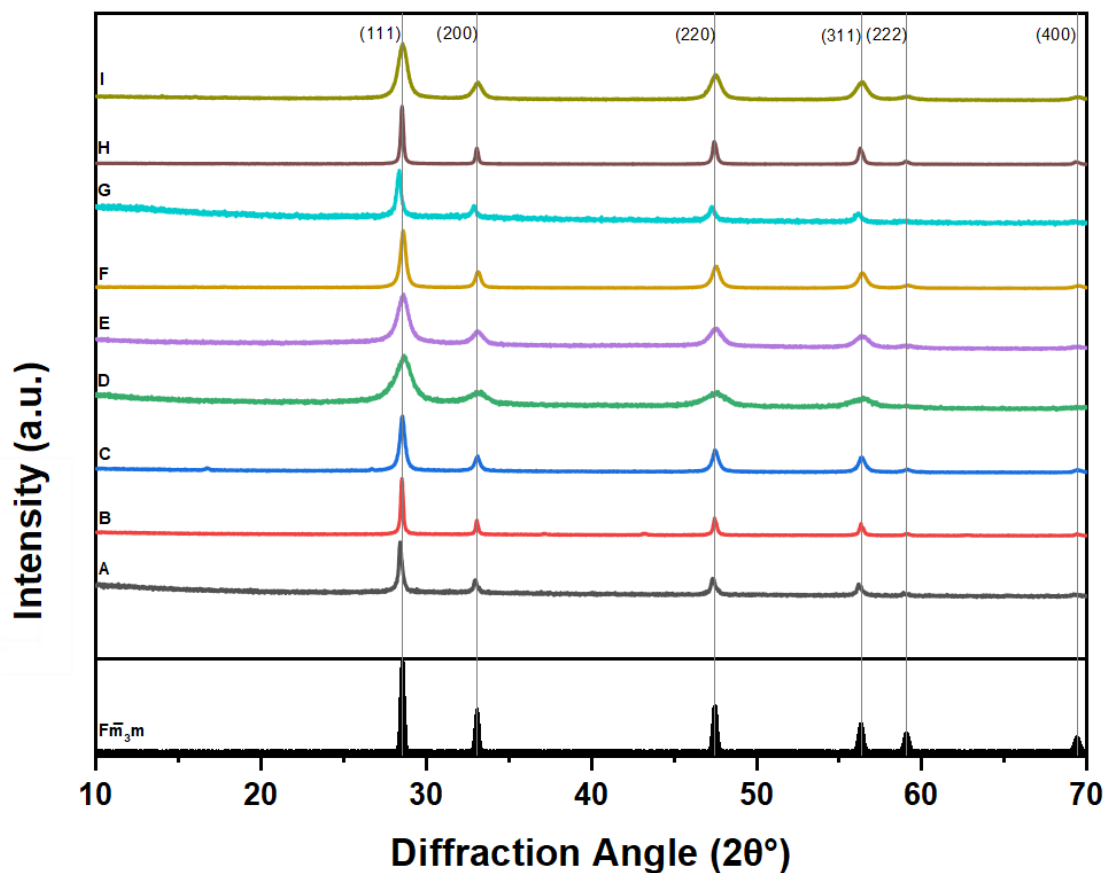


Figure 4.1.1 X-ray Diffractograms of cerium oxide nanoparticles via solution of cerium nitrate hexahydrate precursor by Supercritical Fluids A. Plain CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Propionic Acid, C. CeO₂ NPs grafted with Citric Acid, D. CeO₂ NPs grafted with 3,4-dihydroxybenzoic acid, E. CeO₂ NPs grafted with Gallic Acid, F. CeO₂ NPs grafted with Lactic Acid, G. CeO₂ NPs grafted with PEG 4000, H. CeO₂ NPs grafted with Oleic Acid, I. CeO₂ NPs grafted with Dopamine. The file used to identify the structure is JCPDS No. 34-0394[53]

FTIR Spectra of cerium oxide nanoparticles via solution

The comparative analysis of the FTIR spectra, conducted within 2000 to 500 cm⁻¹ spectra, demonstrates successful surface interaction of CeO₂ NP's synthesis through SCF process Figure 4.1.2 all the analysis were compared to reference criteria [54] . By utilizing plain CeO₂ NP's (Sample A) as a pristine control, the chemical shifts and structure rearrangement's introduced by diverse capping agents (Samples B-I) were systematically analyzed.

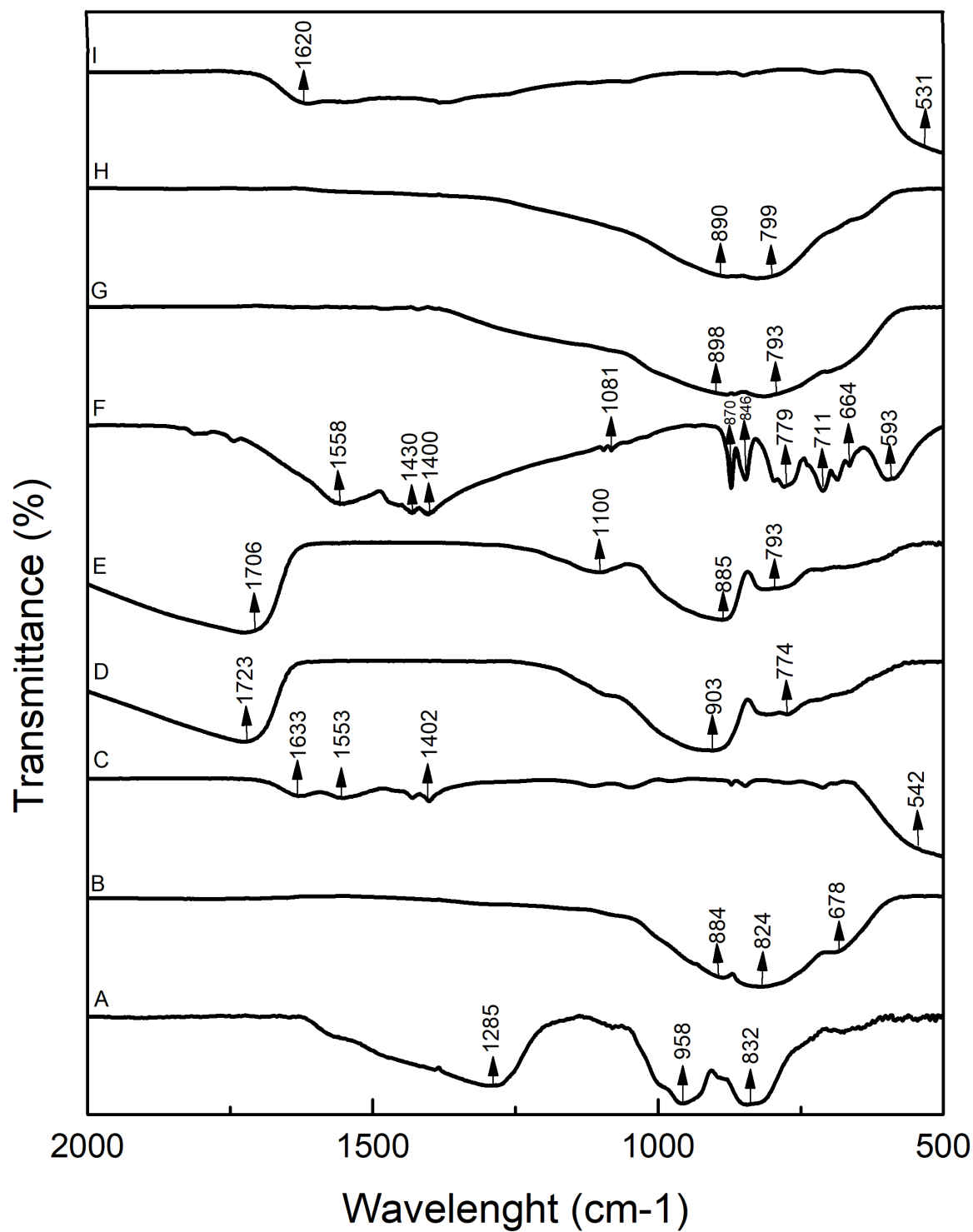


Figure 4.1.2 FTIR Spectra of cerium oxide nanoparticles via solution of cerium nitrate hexahydrate precursor by Supercritical Fluids A. Plain CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Propionic Acid, C. CeO₂ NPs grafted with Citric Acid, D. CeO₂ NPs grafted with DHBA, E. CeO₂ NPs grafted with Galic Acid, F. CeO₂ NPs grafted with Lactic Acid, G. CeO₂ NPs grafted with PEG 4000, H. CeO₂ NPs grafted with Oleic Acid, I. CeO₂ NPs grafted with Dopamine.

Spectrum of Sample A see Figure 4.1.2 establishes the fundamental inorganic baseline for the nanoceria in the analyzed region. The band at 1285 is attributed to the asymmetric stretching of nitrates (νNO_3^-) representing residual nitrates from the precursor. The band at 958 corresponds to the asymmetric stretching of the metal-oxygen lattice ($\nu \text{Ce-O-Ce}$). Additionally, the band at 832 is assigned to the surface peroxide bond stretching (νO_2^{2-}), indicating active oxygen species adsorbed on the oxygen vacancies of the Ce [54].

Results of functionalization with Propionic Acid see Figure 4.1.2 B, the band at 884 represents the aliphatic skeletal stretching ($\nu \text{C-C}$) corresponding to the C-C segments of the short ethyl chain of the propionate. The band at 824 is assigned to the methylene bond rocking ($\rho \text{C-H}$) representing the bending and deformation modes of the aliphatic chain. Finally, the band at 678 is attributed to the metal-oxygen bond vibration ($\nu \text{Ce-O}$) indicating the inorganic lattice perturbed by the chemisorption of the carboxylate [54].

In contrast, the spectrum of Citric Acid Figure 4.1.2 C reveals four key features. The band at 1633 represents the stretching of uncoordinated carbonyl/carboxyl groups ($\nu \text{C=O}$). Additionally in the band at 1553 represents the asymmetric stretching vibration of the carboxylate group ($\nu_{\text{as}} \text{COO}^-$) which confirms chemical grafting onto the CeO_2 . In band 1402 is assigned to the symmetric stretching vibration of the coordinated carboxylate ($\nu_{\text{s}} \text{COO}^-$). Observed at band 542 corresponds to the pure stretching of the crystalline lattice ($\nu \text{Ce-O}$) [54].

Outcomes FTIR spectra of 3,4-dihydroxybenzoic acid (DHBA, Figure 4.1.2 D) reveals two key features. At the band 1723 corresponds to the free carbonyl stretching (ν C=O of -COOH), indicating that the carboxylic group is free, and that the DHBA anchors to the ceria via the catechol group (phenols). In addition, the bands at 903 and 774 are assigned to the out-of-plane aromatic bending (γ C-H) serving as a diagnostic signal of the meta-substitution of the benzene ring [54].

Also, spectrum of Gallic Acid (Figure 4.1.2 E) exhibits remarkable similarities as 3-4 DHBA and shows three characteristic bands. First band in 1706 is attributed to the free carboxylic carbonyl stretching (ν C=O) representing free acid physisorbed on the surface. Furthermore, the band at 1100 corresponds to the phenolic bond stretching (ν C-O), representing the phenolic ether bond coordinated directly to the cerium sites on the surface. As well the bands at 885 and 793 are assigned to the C-H out-of-plane bending of the aromatic ring, confirming the symmetrically substituted benzene ring structure of the gallate [54].

Another spectrum is lactic acid (Figure 4.1.2 F) characterized by several vibrational modes. Moreover, the band at 1558 is assigned to the asymmetric carboxylate stretching (ν_{as} COO⁻), representing the coordinated covalent bond of the lactate on the Ce. Also, bands at 1430 and 1400 correspond to the symmetric carboxylate stretching (ν_s COO⁻) and C-H bending, where the low difference confirms a bidentate chelating/bridging coordination. Additionally, band at 1081 is attributed to the stretching vibration of the secondary alcohol

group (ν C-O), and the band at 870 represents the aliphatic skeletal stretching (ν C-C) of the lactate backbone. Also, band at 846 corresponds to the rocking/bending of methyl groups, and the bands at 779 and 711 are assigned to the methyl rocking modes (ρ CH₃). Finally, the band at 664 is assigned to the skeletal chain deformation or surface coordination modes, and the band at 593 represents the inorganic lattice stretching modes (ν Ce-O) [54].

The result of PEG 4000 see Figure 4.1.2 G, displays two prominent signals. As shown in band at 898 corresponds to the aliphatic ether bond stretching (ν C-O-C), serving as an unequivocal spectral fingerprint of the polyethylene glycol polymer skeleton. Moreover, the bands at 793 and 671 represent the torsional bending of methylene segments (δ CH₂), indicating repeating ethylene oxide segments on the nanoparticle surface [54].

In addition, FTIR spectrum of Oleic Acid (Figure 4.1.2 H) shows two defined bands. Remark band at 890 is assigned to the skeletal (C-C) stretching of the hydrocarbon chain, representing the signal of the long lipophilic skeleton; and observed band at 799 is attributed to the in-phase rocking modes of methylene groups (ρ -(CH₂)_n-) confirming the long hydrophobic chain that generates the capping agent [54].

The most striking mechanistic revelation emerges from the evaluation of Dopamine grafted CeO₂ NP'S (Figure 4.1.2 I), shows two characteristic bands. Note the band at 1619

corresponds to the primary amine group bending $\delta(\text{N-H})$ and aromatic ($\nu \text{ C=C}$) stretching, indicating a close interaction of the terminal nitrogen of dopamine when coordinating with Ce. And observed band at 531 is assigned to the intrinsic lattice stretching ($\nu \text{ Ce-O}$) [54].

Comparative analysis within the $1900\text{--}500 \text{ cm}^{-1}$ spectral region demonstrates the versatility and high efficiency of the supercritical fluid (SCF) synthesis for the targeted functionalization of CeO_2 NP's. This wide array of spectroscopic responses confirms the successful displacement of precursor materials and validates the development of an advanced colloidal platform, whose ultimate interfacial affinity is strictly dictated by the chemical nature of the grafted ligand.

TGA results of Cerium oxide nanoparticles via solution

Thermogravimetric analysis (TGA) was employed to evaluate the thermal stability of modified CeO_2 nanoparticles and to precisely quantify the total surface-associated organic fraction (Figure 4.1.3). The assay was conducted under an oxidizing atmosphere of oxygen (supplied from an oxygen tank), governing thermal decomposition via direct combustion. Under these conditions, the plain CeO_2 sample Figure 4.1.3 A remained completely stable at 100% weight throughout the run, since its low specific surface area prevents significant chemisorption and reactive vacancy exposure.

Only the samples modified with 3,4-DHBA and gallic acid exhibited a sharp and highly significant weight drop above 200–250 °C, associated with the combustion of the dense catecholate-type organic shell. Physically, this thermal range provides the energy required to cleave the chemical coordination bonds between the adjacent phenolic hydroxyl groups and the surface cerium cations. The 3,4-DHBA Figure 4.1.3 D curve dropped continuously and cleanly to a residual mass of 82.33% at 350 °C. Furthermore, gallic acid Figure 4.1.3 E curve dropped to a local minimum of 82.30% at 346 °C, but immediately after, experienced an anomalous weight gain, rising back up to 83.43% at 350 °C (a net weight gain of 1.13% within a narrow 4 °C interval). At 346 °C, the decomposition of the ligand is nearly complete, suddenly exposing the nanoparticle surface. This uncovers a large density of highly reduced surface-active sites (Ce^{3+} ions) and oxygen vacancies generated during the supercritical synthesis. The bare ceria surface (CeO_{2-x}) activates its Oxygen Storage Capacity (OSC), vigorously scavenging molecular oxygen from the oxygen tank flow, re-oxidizing surface sites ($\text{Ce}^{3+} \rightarrow \text{Ce}^{4+}$) and incorporating oxygen atoms directly into the fluorite crystal lattice vacancies.

The citric acid modified sample Figure 4.1.3 C showed a slight but measurable weight increase exceeding 99.5% within the 100 °C to 200 °C range. Being coordinated to highly dispersed, oxygen-deficient nanoparticles, the material utilizes its OSC at low temperatures to scavenge oxygen from the oxygen tank flow. This net weight gain is also influenced by the desorption of physically adsorbed moisture from the air prior to the run, alongside the instrumental buoyancy effect caused by gas density changes with temperature.

Unlike citric acid, the samples modified with PEG 4000, dopamine, propionic acid, lactic acid, and oleic acid showed a practically horizontal thermal profile with a very low and progressive weight decrease, remaining close to 100%. This behavior confirms that these organic agents form extremely thin, compact, and highly ordered monolayers on the cerium oxide surface. Due to the low molecular weight or low grafting mass fraction of these ligands compared to the dense and heavy inorganic CeO_2 , the burned organic fraction represents an insignificant mass contribution that scarcely affects the percentage weight in the overall thermogram.

It is essential to specify that TGA is a strictly quantitative mass-change characterization technique; therefore, it is not a suitable tool to prove whether the organic ligand is chemically anchored (grafted/chemisorbed) to the nanoparticle. TGA only records weight loss or gain upon heating, demonstrating the presence and mass percentage of the organic fraction within the solid, but it cannot identify the chemical nature of the interfacial interaction. To unequivocally prove the existence of actual chemisorption and chemical grafting of the capping agents on the nanoparticle surface, spectroscopic characterization techniques (such as FTIR) must be employed to identify the exact coordination modes and chemical bonds at the interface.

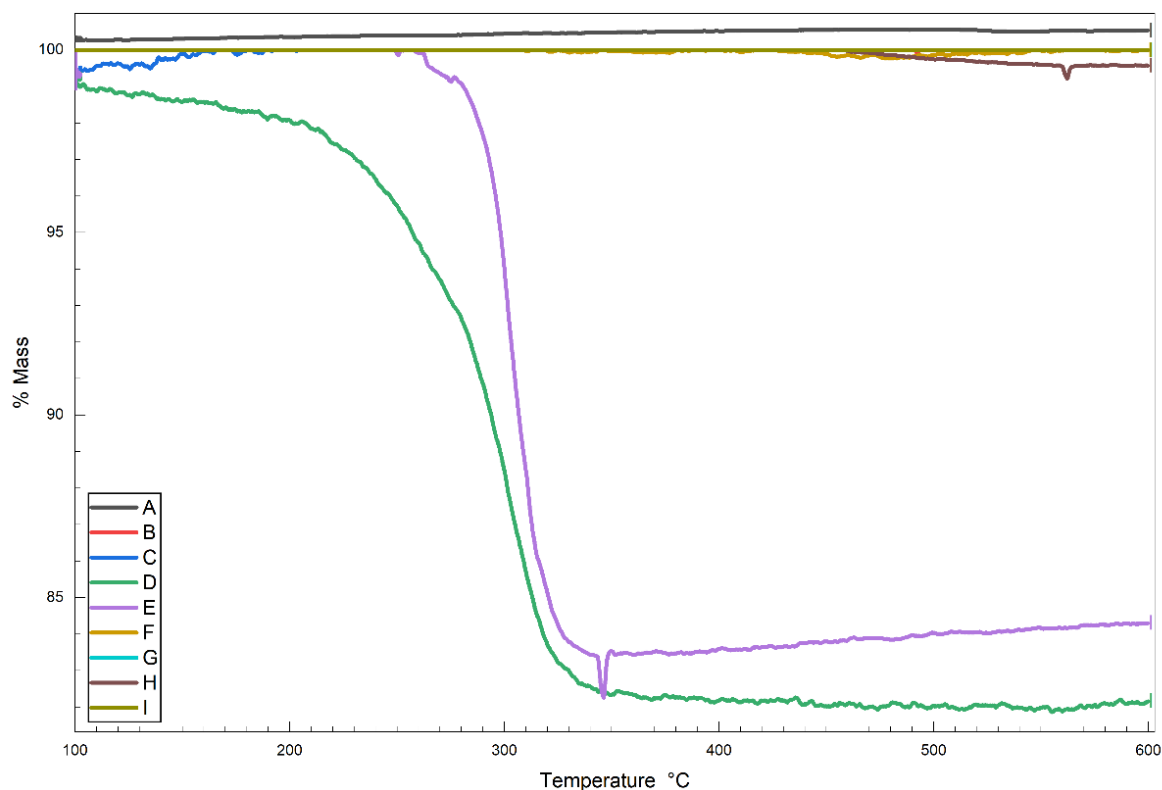


Figure 4.1.3 TGA results of Cerium oxide nanoparticles via solution by Supercritical Fluids A. Plain CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Propionic Acid, C. CeO₂ NPs grafted with Citric Acid, D. CeO₂ NPs grafted with 3,4-dihydroxybenzoic acid, E. CeO₂ NPs grafted with Galic Acid, F. CeO₂ NPs grafted with Lactic Acid, G. CeO₂ NPs grafted with PEG 4000, H. CeO₂ NPs grafted with Oleic Acid, I. CeO₂ NPs grafted with Dopamine.

DLS results of Cerium oxide nanoparticles via solution

Particle size distribution analysis using Dynamic Light Scattering is a fundamental tool for evaluating the degree of dispersion aggregation and colloidal stability of nanoparticles in aqueous suspension. In this study the signal of CeO₂ NP's synthesized by SCF and subsequently modified with capping agents evaluated. All measurements of Figure 4.1.4 show the size distributions by DLS show each grafting agent's effect on colloidal dispersion.

The samples modified with propionic acid (B), PEG 4000 (G), and oleic acid (H) present narrower and well-defined monomodal peaks located in regions below 1000 nm. This behavior reflects an excellent surface coating and outstanding colloidal dispersion stability in water media. For propionic and oleic acids, the well-packed carboxylate monolayer effectively isolates individual core domains. In the case of PEG 4000, the dense, highly hydrated polymeric "brush" shell surrounding the nanoparticles provides a robust steric barrier that successfully prevents close particle-particle approach and secondary aggregation.

In contrast, plain control (A), and the samples modified with citric acid (C), gallic acid (E), and dopamine (I) exhibit significantly broader peaks in their intensity curves less than 2000 nm. This broadening indicates polydispersity and lower colloidal stability in suspension. For plain control (A), the lack of stabilizer leads to spontaneous aggregation. For citric acid (C), gallic acid (E), and dopamine (I), although they possess functional groups with high affinity for the cerium sites (multidentate carboxylates or catechol's), the presence of intermolecular interactions, such as hydrogen bonding between neighboring free hydroxyl groups, promotes the formation of loose, polydisperse secondary clusters in the aqueous medium.

However, sample modified with 3,4-DHBA (Sample D) exhibits a unique bimodal distribution with two well-defined peaks; one at approximately 50 nm and another around

850 nm. This behavior is attributed to the presence of two distinct populations in equilibrium. The narrow peak in the low size range (50 nm) represents a highly successful population of isolated, primary nanoparticles effectively stabilized by the strong, covalent bidentate coordination of the catecholate group. The second peak (850 nm) corresponds to a coexisting population of small secondary aggregates held together by physical interparticle interactions in water.

Furthermore, discussing results displayed by the sample modified with lactic acid Figure 4.1.4 (Sample F), which also exhibits a bimodal distribution shifted toward extreme sizes, with one peak around 1500 nm and a second, larger population reaching 5000 nm. This profile is characterized by a highly broadened distribution of very low intensity. As a very short-chain α -hydroxy acid, the lactate ligand lacks the necessary molecular volume to provide effective steric hindrance, and its surface charge is insufficient to overcome van der Waals attraction. This leads to immediate, uncontrolled secondary coalescence and rapid sedimentation in the water suspension.

In conclusion, the Dynamic Light Scattering (DLS) analysis demonstrated the decisive influence of chemical functionalization on the hydrodynamic diameter and colloidal behavior of the CeO₂ nanoparticles in an water medium. The diameter reported by this technique is larger than the actual crystalline size because DLS measures the diffusive

motion of the particle surrounded by its corona of adsorbed ligands and its respective solvation shell [32].

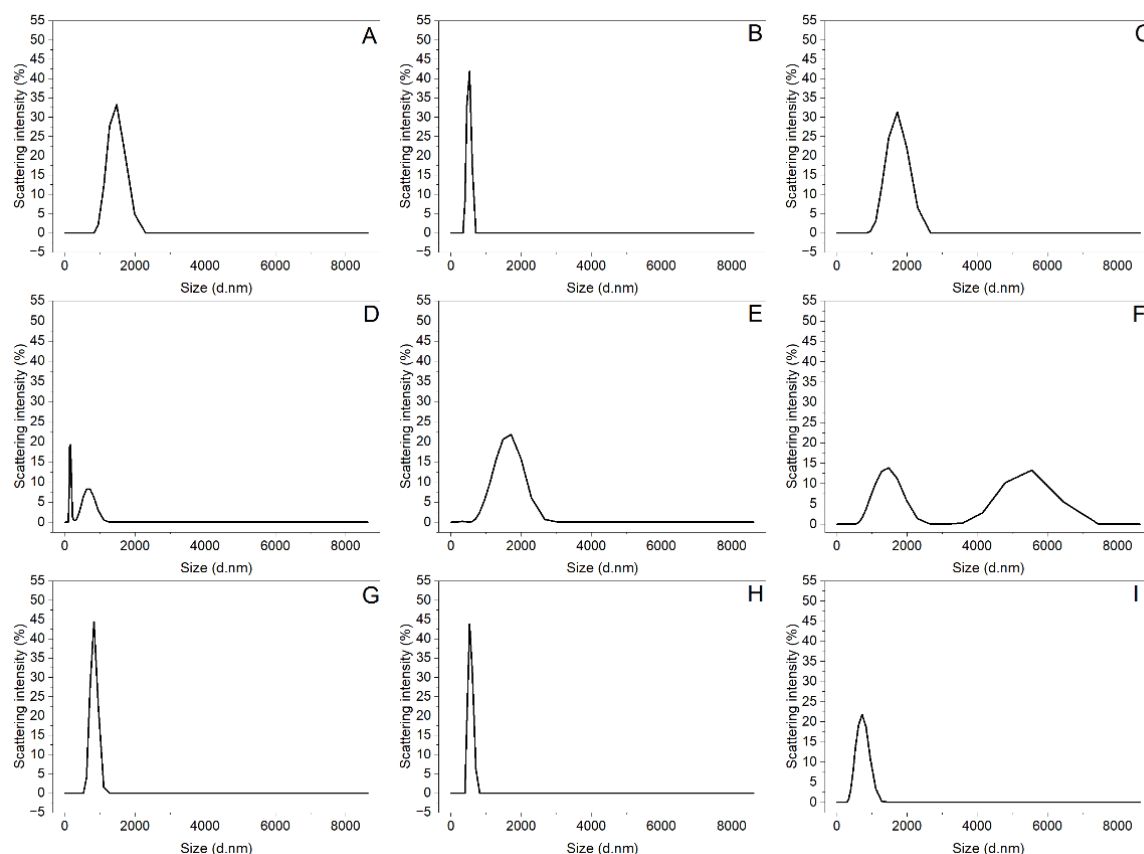


Figure 4.1.4 DLS results of cerium oxide nanoparticles via solution by Supercritical Fluids A. Plain CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Propionic Acid, C. CeO₂ NPs grafted with Citric Acid, D. CeO₂ NPs grafted with DHBA, E. CeO₂ NPs grafted with Galic Acid, F. CeO₂ NPs grafted with Lactic Acid, G. CeO₂ NPs grafted with PEG 4000, H. CeO₂ NPs grafted with Oleic Acid, I. CeO₂ NPs grafted with Dopamine.

Transmission Electron Microscopy micrographs of Cerium oxide nanoparticles via solution

Transmission electron microscopy (TEM) assists to identify the morphological and size distribution of CeO₂ nanoparticles synthesized by supercritical fluids and surface modified with different capping agents. This part of the investigation only considers the cerium oxide nanoparticles grafting with plane, lactic acid, oleic acid and dopamine. The sample without

surface modifier in Figure 4.1.5.A. represents the plain behavior of CeO_2 synthesized by SCF. The image shows small particles but with a strong tendency to uncontrolled agglomeration. The nanoparticle has a size of 58.46 nm with a quasi-spherical shape. For reference, the particles synthesized by SCF. The absence of clear spaces between particles indicates that the surface energy not passivated, allowing for structural reorganization and extreme proximity between primary units.

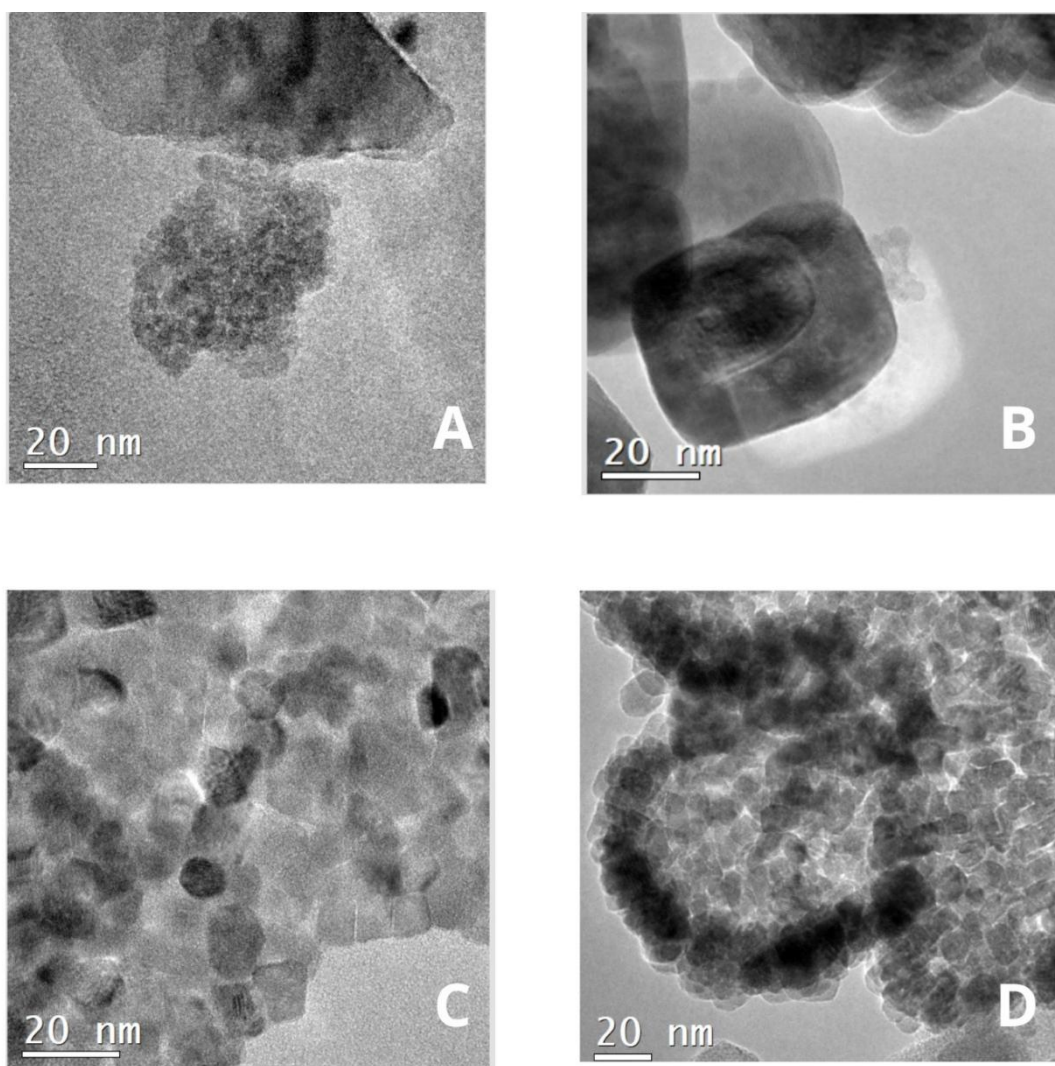


Figure 4.1.5 Transmission Electron Microscopy micrographs of cerium oxide nanoparticles via solution by Supercritical Fluids, A. CeO_2 NPs by SCF, B. CeO_2 NPs grafted with Lactic Acid, C. CeO_2 NPs grafted with Oleic Acid, D. CeO_2 NPs grafted with Dopamine.

In the case of Figure 4.1.5B for lactic acid, large particles with a clearly cubic morphology can be seen, which contrasts with the more amorphous texture of pure CeO_2 , confirming that the capping agent changes the morphology of the nanoparticle. This indicates that lactic acid favored more directed growth, stabilizing facets during nucleation. The presence of well-defined cubic structures measuring 44.65 nm suggests that the ligand allowed the oriented coalescence of small nuclei into more orderly shapes. Although sharp edges observed, there are also contacts between cubes that indicate surface interaction without steric hindrance, presenting agglomerations.

The micrograph in Figure 4.1.5C shows numerous small and uniform nanoparticles with estimated sizes of 8.36 nm. Unlike the unmodified sample, the particles are more clearly defined and separated from each other, although they still form groups. The shape tends to be fingerprints, with no obvious orientational growth. The separation between nanoparticles shows that during supercritical synthesis, the oleic acid capping agent functioned as a stabilizer. Such as Figure 4.1.5D displays a dense cluster of small nanoparticles, in the range of 4.74 nm, smaller than those observed in the unmodified sample. Smooth edges and spherical shapes observed, which is typical when a ligand preferentially inhibits oriented growth, blocking multiple crystalline facets. To compare the size presented in the TEM images see Figure 4.1.6 and observe the highest size is the CeO_2 plain and confirm that the capping agents reduce the size of the nanoparticles. Support that the different capping agents have a different size nanoparticle; as sample dopamine presents less size as the lactic and oleic capping agents NP's.

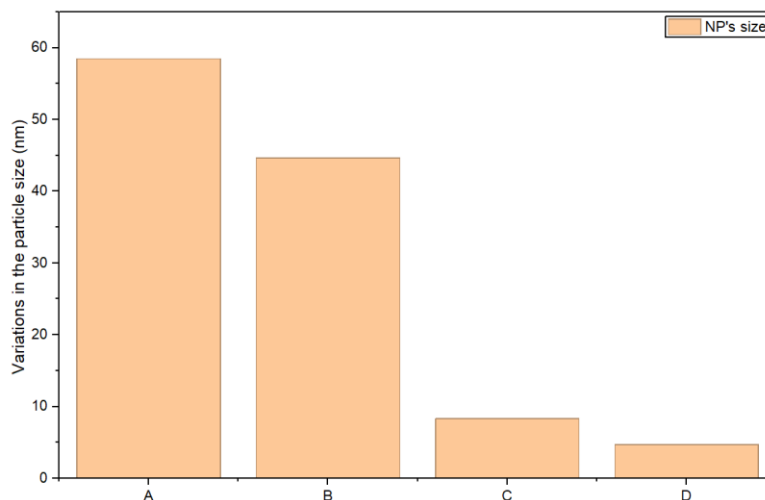


Figure 4.1.6 Histogram of the variation in the particles size (nm) via solution by Supercritical Fluids, A. CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Lactic Acid, C. CeO₂ NPs grafted with Oleic Acid, D. CeO₂ NPs grafted

4.2. Cerium oxide nanoparticles via precipitation using KOH.

X-ray Diffractograms of Cerium oxide nanoparticles via precipitation using KOH.

As observed in the reference pattern included at the bottom of the Figure 4.2.1, CeO₂ has the typical cubic fluorite structure corresponding to the $Fm\bar{3}m$ space group, whose characteristic peaks are located around (111), (200), (220), (311), (222), and (400) see the comparison Table 4.2.1. All the patterns presented share these reflections, indicating that the functionalization process does not alter the main crystalline structure of the oxide, maintaining the face centered cubic arrangement.

Table 4.2.1 Bragg diffraction angles corresponding interplanar spacing for CeO₂ NP's with SCW.

Plane (hkl)	2θ Angle	Interplanar distance d (Å)
-111	28.50	3.12
-200	33.19	2.69
-220	48.00	1.89
-311	56.21	1.63
-222	59.00	1.56
-400	69.01	1.35

Interestingly, a slight broadening of the diffraction peaks (indicated by a minor increase in the FWHM) is selectively observed for the samples modified with 3,4-DHBA, gallic acid, and dopamine. According to the Debye-Scherrer equation ($D = \frac{K \cdot \lambda}{\beta \cdot \cos \theta}$), a broader Bragg reflection indicates a slightly reduced average crystallite size compared to the plain, unmodified CeO₂ control sample.

This phenomenon can be explained by a mild "selective quenching effect" occurring during the supercritical fluid synthesis. In this mechanism, these specific organic molecules (3,4-DHBA, gallic acid, and dopamine acid) exhibit a high affinity for the cerium ions on the surface of the newly formed nuclei, partially blocking and restricting further crystal growth immediately after the primary nucleation burst [37].

In contrast, the samples modified with propionic acid, citric acid, lactic acid, PEG 4000, and oleic acid exhibit peak widths (FWHM) and patterns identical to those of the plain, unmodified CeO₂ reference. This suggests that, under the specific conditions of this supercritical synthesis, these agents had a very limited effect on the growth kinetics of the crystalline core.

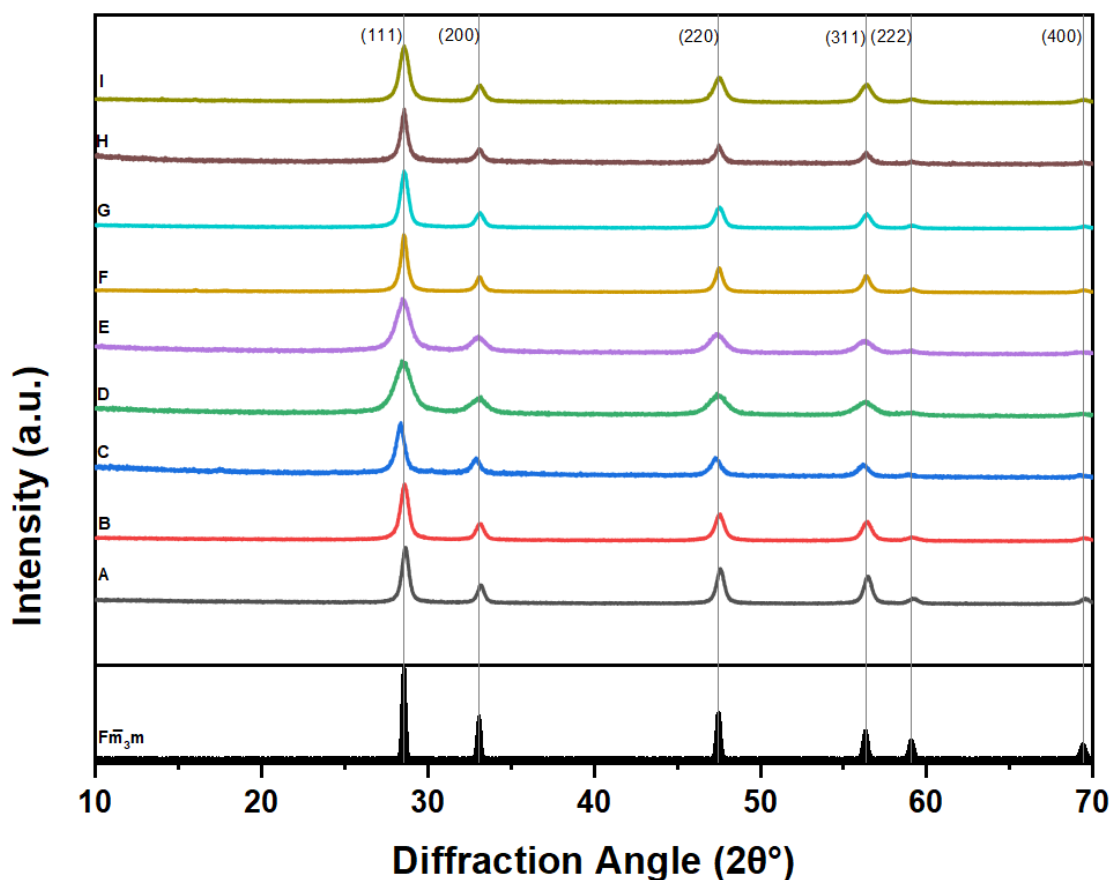


Figure 4.2.1X-ray Diffractograms of cerium oxide nanoparticles via precipitation using KOH by Supercritical Fluids A. Plain CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Propionic Acid, C. CeO₂ NPs grafted with Citric Acid, D. CeO₂ NPs grafted with 3,4-dihydroxybenzoic acid, E. CeO₂ NPs grafted with Gallic Acid, F. CeO₂ NPs grafted with Lactic Acid, G. CeO₂ NPs grafted with PEG 4000, H. CeO₂ NPs grafted with Oleic Acid, I. CeO₂ NPs grafted with Dopamine. The file used to identify the structure is JCPDS No. 34-0394[53].

FTIR Spectra of Cerium oxide nanoparticles via precipitation using KOH.

The comparative analysis of the FTIR spectra shows in Figure 4.2.2 all the analysis were compared to reference criteria [54], conducted within the 2000 to 500 cm⁻¹ spectral, demonstrates the successful surface interaction and functionalization of CeO₂ NPs synthesized through SCF synthesis and precipitation precursor. By utilizing plain CeO₂ nanoparticles via precipitation using KOH (Sample A) as a control, the chemical shifts and

structural rearrangements induced by the introduction of diverse capping agents (Samples B–I) analyzed.

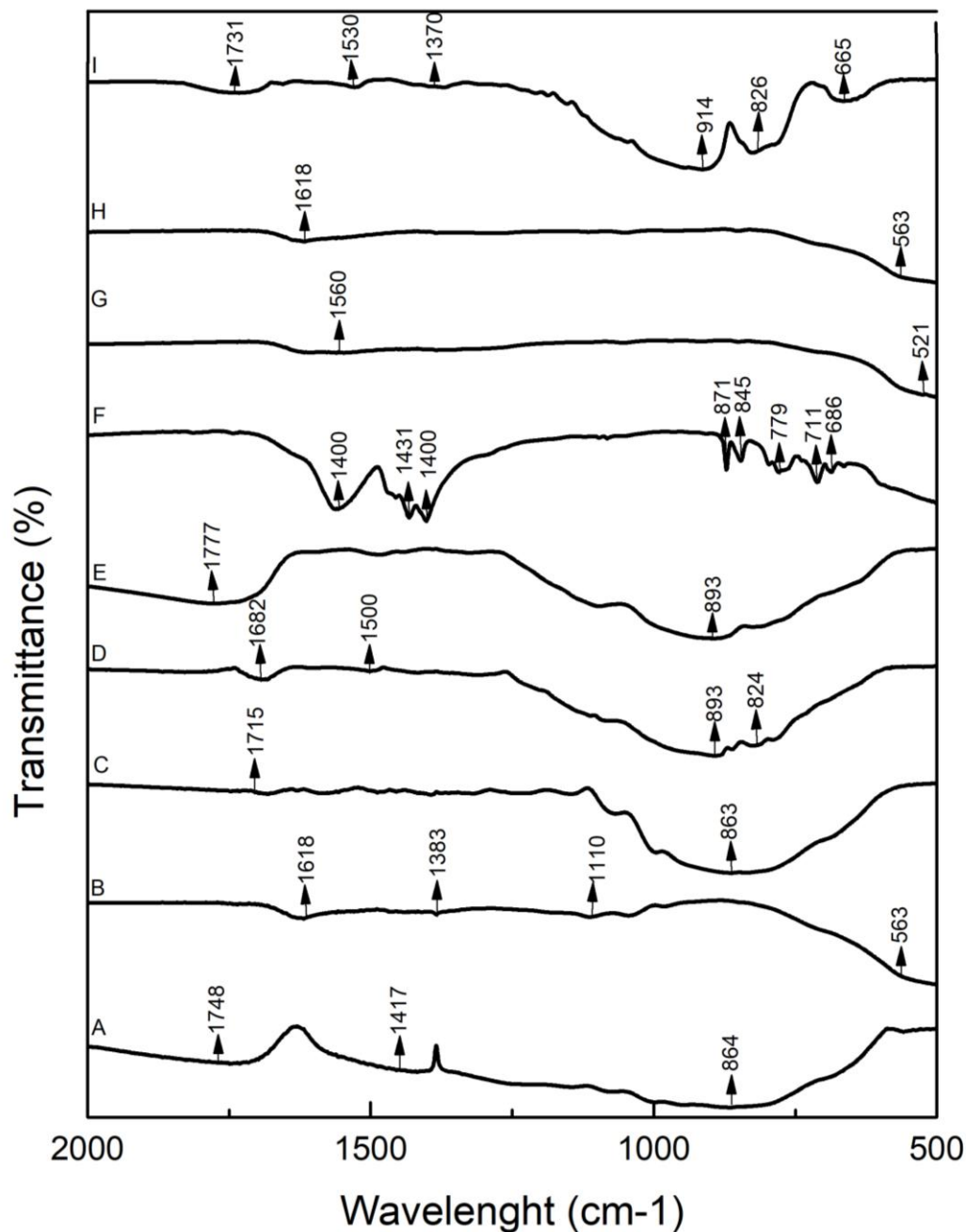


Figure 4.2.2 FTIR Spectra of cerium oxide nanoparticles via precipitation using KOH by Supercritical Fluids A. Plain CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Propionic Acid, C. CeO₂ NPs grafted with Citric Acid, D. CeO₂ NPs grafted with 3,4-dihydroxybenxonic acid, E. CeO₂ NPs grafted with Gallic Acid, F. CeO₂ NPs grafted with Lactic Acid, G. CeO₂ NPs grafted with PEG 4000, H. CeO₂ NPs grafted with Oleic Acid, I. CeO₂ NPs grafted with Dopamine.

The spectrum A in figure 4.2.2 exhibits the control of precipitation KOH solution. The peak at 1748 cm^{-1} is associated with the stretching vibration of the carbonyl group ($\text{C}=\text{O}$) originating from the physisorption of atmospheric carbon dioxide (CO_2). The prominent band at 1417 cm^{-1} , is attributed to the bending vibrations of surface hydroxyl groups ($\text{Ce}-\text{OH}$) and the symmetric stretching vibration of physisorbed carbonates. Lastly, the signal at 864 cm^{-1} is associated with the bending vibrations of carbonate groups (CO_3^{2-}) which are highly common in Ce NP's obtained through precipitation routes in strongly basic media[54].

Also, surface modification with propionic acid (a monocarboxylic acid) is evidenced by the appearance of bands associated with the carboxylate group see Figure 4.2.2 B. The peak at 1618 cm^{-1} is assigned to the asymmetric stretching of the carboxylate group ($\nu_{\text{as}}\text{COO}^-$) demonstrating the deprotonation of propionic acid and its subsequent chemisorption onto surface Ce cations. Furthermore, peak at 1383 cm^{-1} corresponds to the symmetric stretching of the carboxylate group ($\nu_{\text{s}}\text{COO}^-$). The frequency difference between both modes suggests a monodentate mechanism between the propionate and the Ce atoms on the surface. Additionally, the signal at 1100 cm^{-1} is associated with the stretching of the $\text{C}-\text{O}$ bond, while the peak at 563 cm^{-1} confirms the presence of the active inorganic CeO ($\nu\text{Ce}-\text{O}$)[54].

Furthermore, interaction of citric acid Figure 4.2.2 C presents polyfunctional tricarboxylic nature. The presence of the signal at 1715 cm^{-1} is highly relevant, as it is associated with the stretching vibration of the free carbonyl group of non-deprotonated carboxylic acids ($\nu\text{C}=\text{O}$). Indicating that, due to the multidentate nature of citric acid, not all of its carboxylic groups are coordinated to the nanoparticle surface, leaving some free acid groups oriented

toward the dispersing medium, which favors the dispersibility and colloidal stability of the sample in water. The signal at 863 cm^{-1} is related to the deformation vibrations of the carbon skeleton (C–C) of the ligand[54].

Also, Figure 4.2.2 D, incorporating 3,4 DHBA onto the surface of Ce is reflected in peaks at 1682, 1500, 893, and 824 cm^{-1} . The peak at 1682 cm^{-1} is attributed to the carbonyl stretching (C=O) of its carboxylic group. The band at 1500 cm^{-1} is characteristic of the aromatic ring stretching (C=C ar) of the ligand. The peaks at 893 and 824 cm^{-1} correspond to the out-of-plane bending of the aromatic C–H bonds and meta-substitution. This confirms the successful chemisorption of 3,4-DHBA, which can anchor to the ceria surface through its carboxylate functions via the catecholate group (bidentate)[54].

Compared to the other graphs Figure 4.2.2 G, gallic acid shows peaks in 1777 and 893 cm^{-1} . The high-frequency peak at 1777 cm^{-1} is assigned to the stretching of weakly interacting carboxylic group (C=O), indicating that the gallic acid molecule anchors to the surface preferentially through its adjacent phenolic hydroxyl groups (catecholate-type chemisorption), leaving the carboxylic functionality free toward the exterior. The peak at 893 cm^{-1} represents the out-of-plane bending vibrations of meta-substituted aromatic C–H groups[54].

Observing scattering in Figure 4.2.2 F, lactic acid, α -hydroxy acid, interacts in a coordinated manner through its carboxylic and hydroxyl functional groups. The peaks at 1400 and 1431 cm^{-1} correspond to the symmetric stretching of the deprotonated carboxylate ($\nu_s\text{ COO}^-$) and the bending vibrations of the methyl/methine group of lactates.

The series of peaks in the low-energy region (871, 845, 779, 711, and 686 cm^{-1}) represents the skeletal vibrations of the coordinated ligand, highlighting the coupling with the metal-oxygen stretching band of the coordinated Ce–O bond, which confirms the strong physisorption and chemisorption of lactate on Ce[54].

The physisorption of ligands Figure 4.2.2 G, Polyethylene Glycol 4000 a neutral polymer widely used to provide steric stability, is evidenced by peaks at 1560 and 521 cm^{-1} . The band at 1560 cm^{-1} is associated with the C–O–C stretching of the polymer ether modified by interaction with the hydrophilic surface of Ce. The sharp and highly intense peak at 521 cm^{-1} is the fingerprint of the Ce–O bond stretching, demonstrating unequivocally the successful stabilization of the CeO_2 [54].

In the sample modified with oleic acid (C_{18}), exhibits bands at 1618 and 563 cm^{-1} . The peak at 1618 cm^{-1} corresponds to the asymmetric stretching of the deprotonated carboxylate ($\nu_{\text{as}} \text{COO}^-$) of the oleate, demonstrating the chemisorption of the polar head of the fatty acid onto the nanomaterial surface. The intense band at 563 cm^{-1} belongs to the Ce–O bond stretching, confirming the formation of monodispersed Ce nanoparticles coated with a hydrophobic monolayer of oleate[54].

Looking at Figure 4.2.2 I, dopamine yields an interfacial charge-transfer (ICT) complex due to the strong bidentate interaction of its catechol groups with the active metallic sites of Ce. The obtained signals are located at 1731, 1530, 1370, 914, 823, and 665 cm^{-1} . The peak at 1731 is assigned to C=O and C–N stretching vibrations of partially oxidized dopamine residues on the surface (such as quinone species formed by interfacial auto polymerization).

The band at 1530 is associated with the aromatic ring stretching ($C=C$ ar) of the dopamine molecule and the bending of the amino group ($N-H$). The peak at 1370 cm^{-1} corresponds to the stretching of the phenolic $C-O$ bond, whose shift with respect to free dopamine confirms the covalent coordination of surface catechol groups to the metal. Moreover, the lower frequency peaks at 914, 823, and 665 cm^{-1} correspond to the out-of-plane deformations of aromatic $C-H$ bonds and the coordinated vibration of the $Ce-O$ -Catechol chelate bonds, demonstrating the successful formation of the bifunctional hybrid[54].

In summary, the implementation of KOH as a precipitating agent under supercritical fluid (SCF) conditions dictates a competitive and chemical surface reconstruction mechanism on CeO_2 NPs within the $1900-500\text{ cm}^{-1}$ spectrum. These results confirm that the KOH mediated route alters traditional binding affinities, providing a methodology to synthesize highly specialized CeO NP's interphases with customizable molecular orientations.

TGA results in Cerium oxide nanoparticles via precipitation using KOH.

Thermogravimetric analysis (TGA) was used to evaluate the thermal stability of the modified CeO_2 nanoparticles synthesized from a cerium hydroxide precipitate and to quantify the organic fraction associated with their surfaces (Figure 4.2.3). The assay was conducted under an oxidizing atmosphere of oxygen (supplied from an oxygen tank), which

promotes the thermal decomposition of the capping agents via direct combustion. Under these conditions, the plain CeO₂ sample remained completely stable at 100% weight throughout the run, since its severe aggregation and low specific surface area limit both the adsorption of organic species and the exposure of reactive active sites.

In this essay, the samples modified with 3,4-dihydroxybenzoic acid (3,4-DHBA) and lactic acid were the only ones that exhibited a sharp and pronounced drop in their weight percentage due to the combustion of their organic fraction. In addition, 3,4-DHBA Figure 4.2.3 D curve showed a sudden and highly marked decrease above 250 °C, reaching a residual mass of 82.72% at 343 °C (a net loss of 17.28%). This is due to the complete combustion of the dense aromatic shell coordinated strongly via catecholate-type linkages to the surface cerium cations. Moreover, lactic acid Figure 4.2.3 F curve exhibited a well-defined drop, reaching a value of 91.27% at 357 °C (a net loss of 8.73%). This decay corresponds to the combustion of the coordinated lactate ligands on the inorganic core, requiring a slightly higher temperature to complete its oxidative degradation due to the nature of its surface packing.

Alternatively, lactic acid is the sample with the highest total mass loss, making it the least thermally stable and therefore the worst result. This is because its hydroxyl group facilitates strong interaction with the surface, accumulating more molecules that subsequently degrade. 3,4-Dihydroxybenzoic acid also shows remarkably similar behavior, but its degradation is slightly less severe.

The sample modified with dopamine Figure 4.2.3 I exhibited an anomalous behavior characterized by a continuous weight increase, rising from 97.84% at 100 °C to recover 100% at 150 °C. This net increase is attributed to the outstanding (OSC) of the reduced non-stoichiometric Ce phase (CeO_{2-x}) obtained from the hydroxide precipitate. Following the initial loss of residual moisture at 100 °C (which placed the mass at 97.84%), the flow of pure oxygen from the tank triggered a vigorous and accelerated re-oxidation in this temperature range (100–150 °C). The surface Ce^{3+} cations were rapidly oxidized to Ce^{4+} , incorporating oxygen atoms from the gaseous environment directly into the fluorite crystal lattice vacancies, resulting in a measurable weight gain that offset any potential combustion loss in that thermal region.

In contrast to the previous samples, the nanoparticles modified with propionic, citric, gallic, oleic acids, and PEG 4000 presented practically horizontal thermal profiles with minimal weight decreases, remaining very close to 100% throughout the run. This confirms that under these specific synthesis conditions from cerium hydroxide, these ligands form extremely thin protective layers or monolayers of very low mass fraction relative to the heavy CeO_2 inorganic core, so their combustion does not generate a significant percentage impact on the overall thermogram.

It is essential to specify that TGA is a strictly quantitative mass-change characterization technique; therefore, it is not a suitable tool to prove whether the organic ligand is chemically anchored (grafted/chemisorbed) to the nanoparticles. TGA only records weight loss or gain upon heating, demonstrating the presence and mass percentage of the organic fraction within the solid, but it cannot identify the chemical nature of the interfacial interaction. To unequivocally prove the

existence of actual chemisorption and chemical grafting of the capping agents on the Ce surface, spectroscopic characterization techniques (such as FTIR) must be employed to identify the exact coordination modes and chemical bonds at the interface.

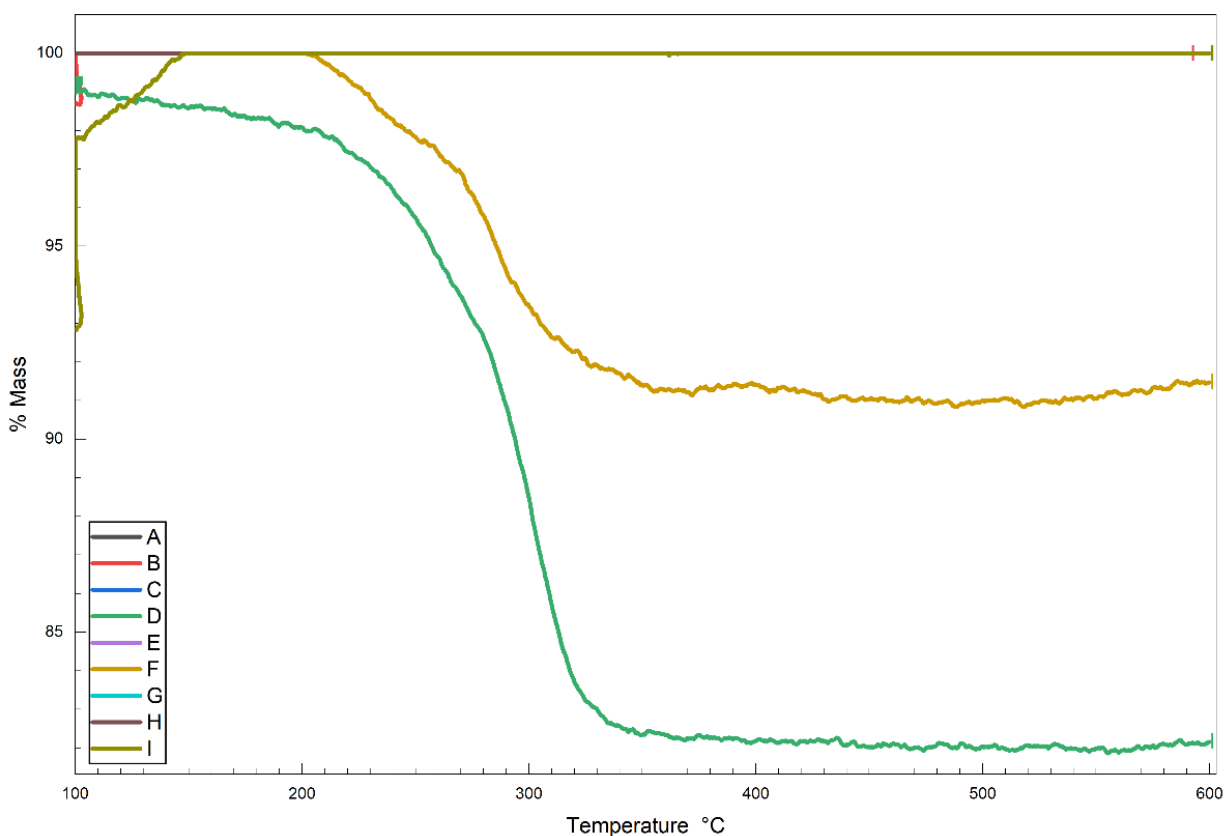


Figure 4.2.3.TGA results of cerium oxide nanoparticles via precipitation using KOH by Supercritical Fluids A. Plain CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Propionic Acid, C. CeO₂ NPs grafted with Citric Acid, D. CeO₂ NPs grafted with 3,4-dihydroxybenzoic acid, E. CeO₂ NPs grafted with Galic Acid, F. CeO₂ NPs grafted with Lactic Acid, G. CeO₂ NPs grafted with PEG 4000, H. CeO₂ NPs grafted with Oleic Acid, I. CeO₂ NPs grafted with Dopamine.

DLS results of Cerium oxide nanoparticles via precipitation using KOH.

The analysis of particle size distribution using dynamic light scattering (DLS) is an essential tool for evaluating the colloidal behavior of SCF synthesized CeO₂ nanoparticles. The

differences observed Figure 4.2.4 in the intensity curves are direct indicators of the ligand's efficiency in coating the CeO_2 surface, as well as its ability to prevent agglomeration phenomena, which are particularly relevant in alkaline media and under the KOH conditions used in the precipitation process. In the case of these results, could be highlighted with single peak curves. Separating the graphs, is possible to observe how A, E, G, and moderate H and D present narrower and well-defined peaks in areas below 1000 nm, reflecting high basic stability and dispersion. In the case of results with greater hydrodynamic size dispersion and slight stability, graphs B, C, F, and I stand out, showing greater heterogeneity in size and lower colloidal stability. The worst result is F, due to its wider distribution and low intensity.

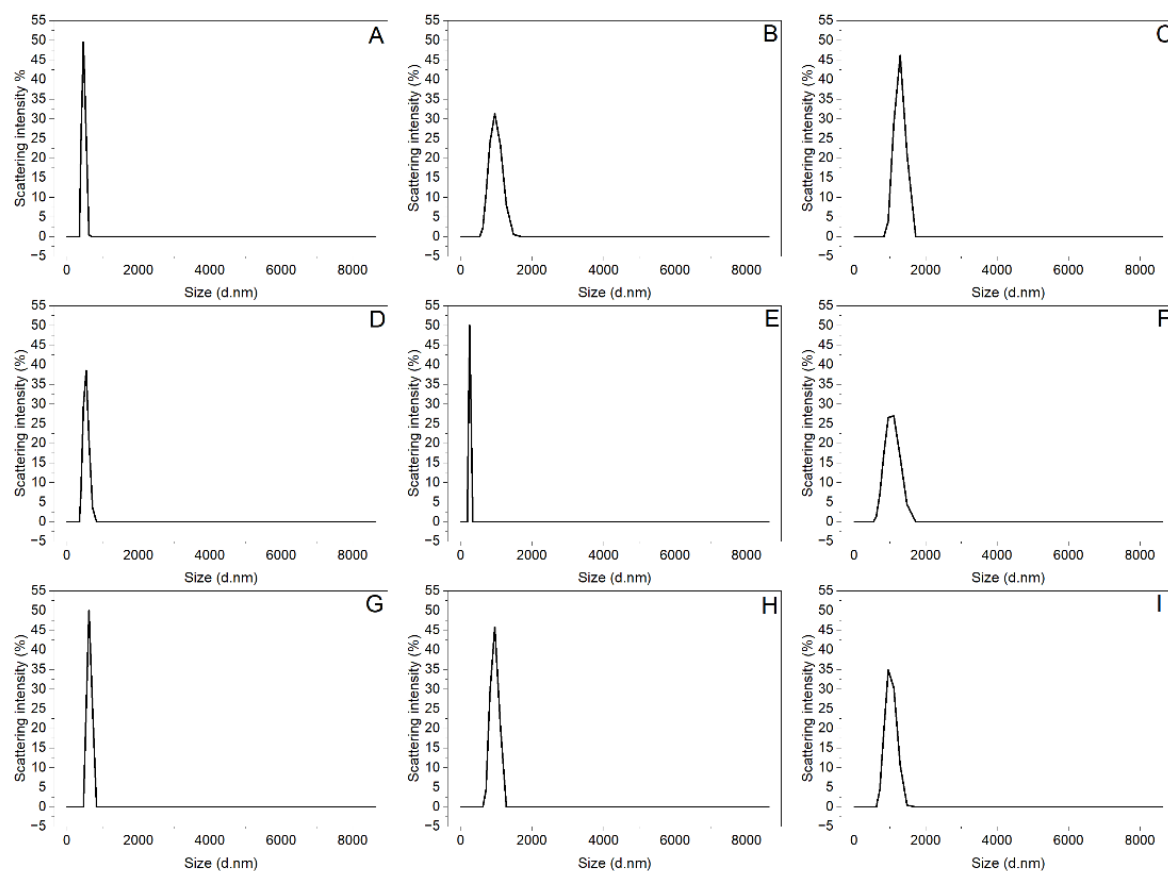


Figure 4.2.4 DLS results of cerium oxide nanoparticles via precipitation using KOH by Supercritical Fluids A. Plain CeO₂ NPs by SCF, B. CeO₂ NPs grafted with Propionic Acid, C. CeO₂ NPs grafted with Citric Acid, D. CeO₂ NPs grafted with 3,4-dihydroxybenzoic acid, E. CeO₂ NPs grafted with Gallic Acid, F. CeO₂ NPs grafted with Lactic Acid, G. CeO₂ NPs grafted with PEG 4000, H. CeO₂ NPs grafted with Oleic Acid, I. CeO₂ NPs grafted with Dopamine.

5. Conclusions

In this study, the hypothesis was successfully corroborated since the synthesis of cerium oxide nanoparticles using a supercritical fluid process in the presence of capping agents (organic acids, polymers and neurotransmitters) yields chemically stable nanostructures with a fluorite type crystal structure, controlled size and morphology, and high dispersibility in water media.

Shape controlled synthesis of unique CeO₂ nanoparticles has been successfully implemented in water under supercritical conditions with organic acid and polymeric molecules grafted on the surface of the nanoparticles. The capping agents grafted on the surface confer the potential to produce CeO₂ nanomaterials with advanced applications as they have the capability of tailoring the interaction of the nanostructures to specific media in which they can be applied; there are still many options among possible configurations of surface modification and nanoparticles structures. These capping agents not only modify the surface of the nanoparticles but also control and change the morphology of the nanoparticles through a cooling effect that blocks nanoparticle growth during synthesis. X ray diffraction showed that cubic fluorite CeO₂ NPs were effectively synthesized in this simple one step process.

The nanoparticles obtained showed morphologies of different sizes with controlled shapes; further research could improve the adaptation of these morphologies for biomedical applications. The molecules of the capping agents interact directly with the surface of the nanoparticles through carboxylate, catechol, and gelato bonds and hydrogen bridges, as demonstrated by FTIR, while the integrity of the grafted capping agents has also been validated by this technique. Through DLS analysis, we observed the aggregation of CeO₂ NPs interestingly. The CeO₂ nanoparticles synthesized and grafted with capping agents dispersed in water, demonstrating their dispersibility and agglomeration in aqueous media, which opens the door to possible biomedical applications for use with other media such as ethanol and blood.

Based on thermogravimetric analysis, it can be inferred that thermal stability and the number of molecules anchored to the nanoparticle are strongly influenced by the molecular structure of each capping agent. The mass loss profiles suggest that the active sites available on the surface of the nanoparticles become progressively saturated as functionalization progresses. This is reflected in early thermal destabilization and greater organic loss.

Regarding the importance of this study, it has been established that measuring the pH of the solution prior to synthesis is important for cerium oxide nanoparticles, thus allowing for more uniform nanoparticles to be obtained in comparison with results where there is no pH control measurement of the solution. Furthermore, the capping agents selected for this analysis have different qualities that have never been studied for cerium oxide nanoparticle grafting, opening new opportunities for study in biomedical and catalytic applications.

According to the limitations presented in this study, the main one would be the TEM micrographs, which was one of the studies that was most delayed due to the lack of grids to analyze all the nanoparticles and the lack of nitrogen in the equipment. Another important limitation would be the lack of incorporation of multidisciplinary areas in biomedical studies for nanoparticles synthesized by supercritical fluids.

The synthesis of CeO₂ nanoparticles functionalized with capping agents using supercritical fluids is an effective and controlled process for obtaining advanced materials with potential applications in the catalytic, optical, environmental, and biomedical industries.

For future research, and as a recommendation, these CeO₂ NPs should be evaluated using MTT analysis to assess cell viability and proliferation; NIH 3T3 to evaluate cytotoxicity, proliferation, adhesion, and safe doses of compounds; hemolysis analysis to evaluate whether a nanoparticle causes erythrocyte rupture and determine the level of cell damage; also, detailed kinetic studies of the interaction of CeO₂ NPs with specific proteins such as alpha synuclein are suggested to determine the details of this interaction.

6. References

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