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Synthesis of New Phosphate Nanomaterials "Pyrophosphates of Cerium" Application in Biomedicine

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Abstract. The use of effective contrast agents in magnetic resonance imaging (MRI) has become an international research challenge. The aim is to improve the diagnosis of some pathologies. The preparation of contrast agent by the solid-state method using efficient nanomaterials has attracted considerable attention due to its potential to interact with the physical stimulus, the objective is for the signal collected to be as intense as possible. Methods: This article proposes a simple method to prepare a nanomaterials based on pyrophosphates and doped with Gadolinium and Cerium from solid-state reagents. Firstly, the two phosphate nanomaterials (Pyrophosphate $SrMP_2O_7$) based on Gadolinium and Cerium ($SrMP_2O_7$ with M=Gd and Ce) were prepared at 1,000°C to develop pure phases, capable of increasing the contrast of the signal observed by MRI. The characterization of these nanomaterials was mad by several techniques: X-ray diffraction (XRD) to determine the mesh parameters; UV-visible to interpret optical properties and electronic properties; Fourier transform infrared spectroscopy (FT-IR) to characterize the functional groups of $SrGdP_2O_7$ and $SrCeP_2O_7$ nanomaterials. Results: The Gap energies values of two nanomaterials showed that the $SrCeP_2O_7$ has a better magnetic speed 1/T1 in comparison with the $SrGdP_2O_7$. Morever in T1 encoding, if the T1 relaxation time is short, the image is much clearer. However, T2 encoding implies that if the T2 relaxation time is short, the image is darker. Conclusion: Our nanomaterial based on Cerium $SrCeP_2O_7$ have a better longitudinal relaxation. then it can be an excellent positive contrast agent.

Keywords: Gap energy; Medicine; Nanomaterials; Positive contrast agent; Pyrophosphate.

I Introduction

Nanotechnologies constitute a field of multidisciplinary research and development, which is based on the crossing of several scientific disciplines such as mechanics, electronics, chemistry, and optics, biology while allowing the manipulation and characterization of matter at the nanometric scale.

The study and modification of matter at the nanoscale gives unexpected results and properties that are often totally different from those of the same materials at the micro or macroscopic scale, in particular in terms of mechanical resistance, electrical conductivity, fluorescence and chemical reactivity. Indeed, nanotechnologies allow us to manufacture materials whose fundamental properties can be controlled (1).

Due to their varied and often unprecedented properties, the application of materials in nanomedicine presents itself as a transversal field that promises to revolutionize therapy and diagnostics in the health field. « Nano-theranostic» (2), by allowing the development

of the principles of predictive medicine, personalized medicine and regenerative medicine (3).
In magnetic resonance medical imaging, some areas are difficult to visualize. Therefore, contrast agents needed to improve the diagnosis of some pathologies.
The nanomaterials used to formulate these contrast agents must choose to interact with the physical stimulus so that the signal collected is as intense as possible. These agents must exhibit zero or at least low toxicity with respect to the actual benefit (4).

The goal of contrast agent injection is to accelerate the 1 / T1 and 1 / T2 magnetic relaxation speed of protons in water molecules, that is, to shorten the time during which the spins of these protons return to their initial state after excitation by the radiofrequency wave. This is what increases the contrast of the signal observed by MRI (5).

Studies have shown that Gadolinium Gd^{3+} ion is the element of choice for manufacturing MRI contrast agents (6). Even today it is widely used in contrast agents. However, the high toxicity is the great inconvenience of this chemical element, this toxicity is due to its competition with the calcium ion (Ca^{2+}) which is involved in multiple functions essential to the body: blood clotting, muscle contraction, nerve conduction, release of hormones.
Researchers have shown that this toxicity can be considerably reduced by trapping it in ligand molecules: linear polyaminocarboxylates and macrocyclic. Gadolinium chelates are then obtained, they are also called contrastophores and many of which have been marketed (4).
However, other researchers have shown in a study, the existence of Gd^{3+} ions in skin biopsies of patients. Who underwent an MRI examination with injection of chelated Gadolinium in the months before the first symptoms, these ions would then precipitate in the form of Gadolinium phosphate, which would be phagocytosed by macrophages, which would then recruit circulating fibrocytes, triggering fibrosis (5).

Consequently, the competent bodies triggered the alerts. In the United States, the Food and Drug Administration (FDA) has issued an alert on the injection of all Gadolinium chelates, especially in patients with severe kidney failure; while in Europe, three of the least stable products (Omniscan®, Optimark® and Magnevist®) are contraindicated in these patients. The European Medicines Agency (EMEA) extends the prudence recommendation to the use of all other Gadolinium chelates in patients with severe kidney failure (7).

In addition, Cerium is the first element of the 17 lanthanides (rare earth elements) with a 4f orbital, which gives it physicochemical properties that are required in wide fields of application, such as: light, electricity, magnetism and other fields were witnessed (8) (1). Indeed, the therapeutic applications of Cerium are numerous, thanks to its catalytic properties and its relevant pharmacological properties, for example, it is used as antiemetics, bacteriostats and antitumors (9). Currently, efforts are focused on future applications of Cerium, in particular in nanomedicines (10) (11).
The objective of our study is to manufacture a stable and effective contrast agent based on Cerium. Indeed, we adopted a rational approach, starting from the solid method, of two phosphate nanomaterials (Pyrophosphate $SrMP_2O_7$) based on Gadolinium and Cerium ($SrMP_2O_7$ with M = Gd and Ce), to make a study of characteristics and comparison between the two nanomaterials.

II Experimental

2.1 Synthesis of materials based on Gadolinium and Cerium $SrMP_2O_7$ (M= Gd or Ce)

For our study, the pyrophosphates $SrGdP_2O_7$ and $SrCeP_2O_7$ were synthesized by the solid-state method.
The reagents chosen for the synthesis are: Gadolinium oxide (Gd_2O_3) at 99.999%, 99.99% of $SrCO_3$ (strontium carbonate) and ammonium phosphate $(NH_4)_2HPO_4$ and Hydrated Cerium Acetate ($C_6H_9CeO_6$ .H_2O) to 99.9%
The synthesis reaction is as follows:

$$SrCO_3+0.5Gd_2O_3+2(NH_4)2HPO_4 \rightarrow SrGdP_2O_7 +CO_2+ 3H_2O+4NH_3+0.25O_2$$

$SrCO_3+C_6H_9CeO_6.xH_2O+2(NH_4)_2HPO_4 \rightarrow SrCeP_2O_7+CO_2+2CH_3CO_2H+2NH_3+7.5H_2$

The white phase of pyrophosphates: $SrGdP_2O_7$ (to the left) and $SrCeP_2O_7$ (to the right)

Fig. 1. Picture of the two nano-materials $SrMP_2O_7$ (M = Gd or Ce) inside the alumina crucible at 25 °C.

The reagent mixtures in stoichiometric proportions being carefully ground in a mortar, in order to obtain a homogeneous mixture. Then introduced into a platinum crucible and placed in an oven to undergo a decomposition treatment: evaporation of structural water at 160 °C, then decomposition of the organic material at 450 °C (See Figure 2).

$SrCeP_2O_7$ Almond color **And** $SrGdP_2O_7$ White color

Fig. 2. Picture of the two nano-materials $SrMP_2O_7$ (M = Gd or Ce) at 300 °C.

Before grinding

After grinding

Fig. 3. Picture of of the two nano-materials $SrMP_2O_7$ (M = Gd or Ce) at 1000 °C.

This decomposition follows a heat treatment according to the diagram below.

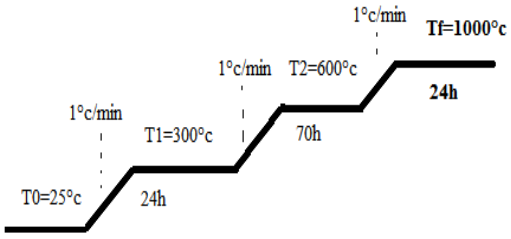

Fig. 4. Reagent decomposition with heat treatment cycle

III Results and Interpretation

3.1 X-Ray Diffraction

The spectra of the nanomaterials were made at room temperature using a Philips Xpert MPD diffractometer, in CuKα radiation stepwise scanning mode, its step value is 0.02°.

X-ray analysis of $SrGdP_2O_7$ shows that this phase crystallizes in the monoclinic system (Space group: P2 / m) with the following unit lattice parameters: a = 17.824 Å; b = 3.0517 Å; c = 17.330 (5) Å. X-ray analysis of $SrCeP_2O_7$ shows that this phase crystallizes in the monoclinic system (Space group: P2 / m) with the following unit lattice parameters: a = 18.941 Å ; b = 9.690 Å ; c = 14.238 Å.

The Rietveld coefficients obtained reveal a good agreement between the profiles of the observed and calculated diagrams.

Figure 4 gives the X-ray diffraction spectrum, refined by the FullProf software of the two nanomaterials $SrGdP_2O_7$ and $SrCeP_2O_7$.

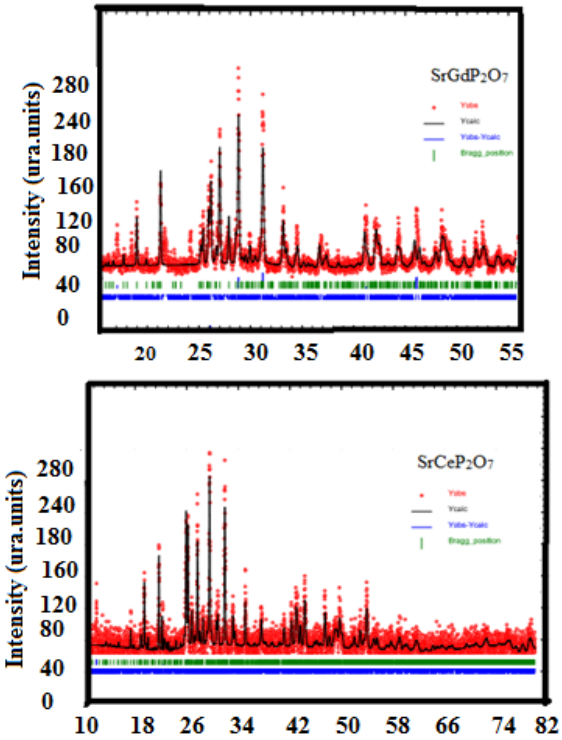

Fig. 5. X-ray Diffraction Spectrum SrGdP2O7 et SrCeP2O7

Samples	$SrGdP_2O_7$	$SrCeP_2O_7$
Cristal system	Monoclinic	Monoclinic
S.Group	P 2/M	P 2/M
a(Å)	17.8243	18.9416
b(Å)	3.0517	9.6907
c(Å)	17.3305	14.2384
v(Å)	907.2986	2489.1472
Alpha(°)	90.000	90.00
Beta(°)	107.750	96.078
Gama(°)	90.000	90.00
u	0.0100	0.0100
V	-0.0100	-0.0100

w	0.0050	0.00500
Rp	59.4	97.9
Rwp	62.5	61.5
Rexp	35.7	58.1

Table. 1. Structural data of $SrGdP_2O_7$ and $SrCeP_2O_7$ nanomaterials

3.2 Optical properties of pyrophosphates $SrMP_2O_7$ with M = Gd and Ce

Transmittance Spectra

The pure pyrophosphates based on Gadolinium and Cerium ($SrMP_2O_7$ with M = Ce and Gd) are presented in figure 6, they were analyzed by UV-Visibile absorption spectroscopy in order to demonstrate the absorption of Cerium and Gadolinium ions in this wavelength range.

The Gadolinium spectrum is composed of a contribution centered at 310 nm. Our results are similar to a study by Shadab Ali and All (12). Indeed, it is possible to distinguish the absorption of Gd ions, having an absorption band around 320 nm. This pyrophosphate $SrGdP_2O_7$ has a transmittance greater than 35% in the visible range ranging from 400 nm to 600 nm. This band signifies an electronic transition of Gadolinium.

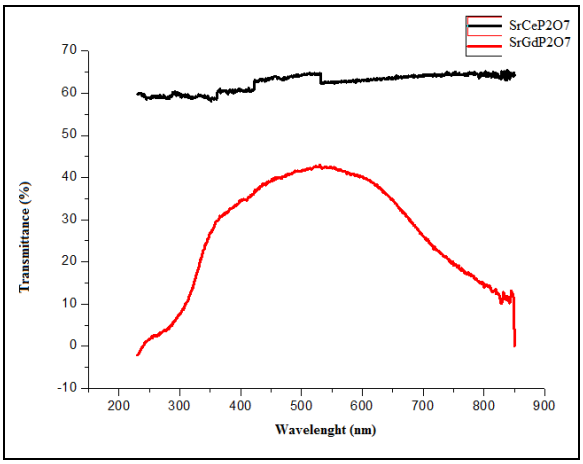

Fig. 6. Transmittance spectra of $SrMP_2O_7$ pyrophosphates with M = Ce and Gd

We note that the $SrGdP_2O_7$ nanomaterial is a semiconductor with a direct gap. We also have a transmittance equal to 40% in the near UV-visible-infrared region (from 400 to 850nm). In addition, we have an absorption band which is due to the presence of free e-electron or that of conduction in the nanomaterial $SrGdP_2O_7$, which is naturally moves in all directions throughout the solid, under the effect of electromagnetic fields generated by other charged species. Indeed, this interaction of electromagnetic waves with matter can clearly explain the optical properties of the material.

In the case of the $SrCeP_2O_7$ nanomaterial, we have a wide electronic transition band; the transmittance is greater than 65% in the near UV-visible-infrared region (from 400 to 850nm).

The Gap: To determine the optical band gap of our nanomaterials we used TAUC's law and the Uv-visible spectrum.

$$\alpha h\nu = \alpha_0 (h\nu - Eg)^n \text{ with } n = 2 \text{ in the case (direct gap)}$$

With α: absorption coefficient, h: Planck constant, α0: constant; Eg: gap energy;

Then the method consists in representing the $(\alpha h\nu)^2$ in function (hν) the value of the gap is obtained by the extrapolation of the linear part of the curve on the abscissa axis (hν), figure 7.

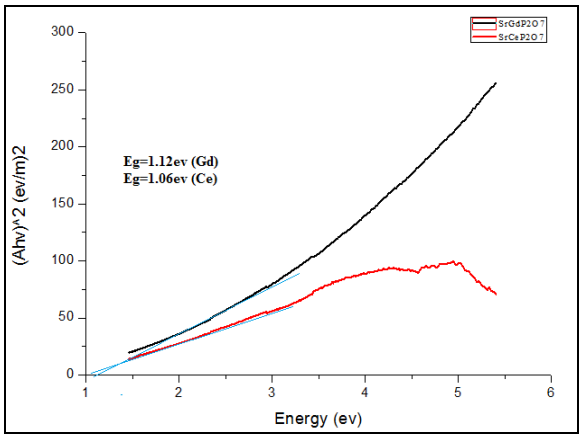

Fig. 7. Dependence $(\alpha h\upsilon)^2$ of the nanomaterials $SrGdP_2O_7$ and $SrCeP_2O_7$ in terms of the photon energy in eV

The figure 7 shows the curves of the nanomaterials SrGdP2O7 and SrCeP2O7. Their optical gap energy values are:

- Eg^{opt} = 1.12 eV for the $SrGdP_2O_7$ nanomaterial
- Eg^{opt} = 1.06 eV for the $SrCeP_2O_7$ nanomaterial.

The Urbach Energy (Disorder) : The energy of Urbach reflects the disorder state of the material; it is related to the absorption coefficient by the following expression :

$$\alpha = \alpha_0 e^{(h\nu/Eu)}$$

With α: absorption coefficient and photon energy (hν) and Eu is energy of Urbach.

Important Urbach energy values are shown in Figure 8 and Table 2.

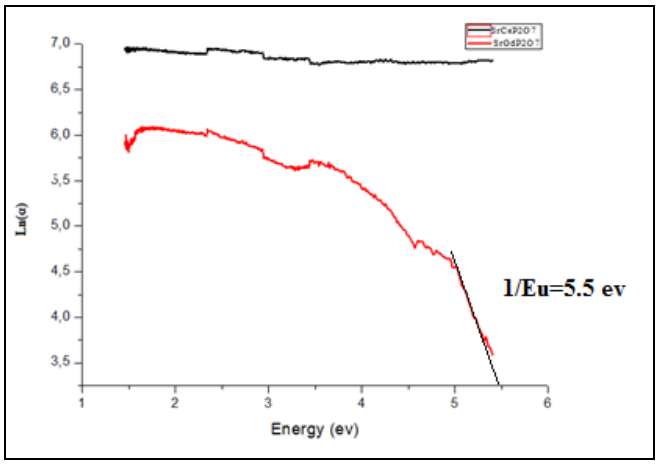

Fig. 8. Disorder by extrapolation from the variation of ln(α) in terms of hν for the both nanomaterials $SrGdP_2O_7$ and $SrCeP_2O_7$

Pyrophosphates	$SrGdP_2O_7$	$SrCeP_2O_7$
Eg^{opt} (ev)	1.12	1.06
Eu (ev)	0.18	0.0
Ion Radius(pm)	94	101

Table. 2. The gap energy and the Urbach energy value for the pyrophosphates $SrGdP_2O_7$ et $SrCeP_2O_7$

3.3 Infra-Red Spectroscopy

The vibrational study by infrared spectroscopy of $SrGdP_2O_7$ and $SrCeP_2O_7$ nanomaterials provides structural information, in particular the identification of the different basic groups forming the phosphate material. In fact, the number and frequency bands distribution depend on the nature of local symmetry of the $P_2O_7^{4-}$ anion. The spectrum of $SrGdP_2O_7$ and $SrCeP_2O_7$ nanomaterials (Figure 9) shows the existence of a band around 741.82cm-1 for $SrGdP_2O_7$ pyrophosphates and at 745.96cm^{-1} for $SrCeP_2O_7$ pyrophosphates attributed respectively to asymmetric stretching vibrations and symmetrical with the P-Ô -P bridge. These bands are characteristic of pyrophosphate groups ($P_2O_7^{4-}$). In the 450-1300 cm^{-1} range, frequencies related to symmetrical and antisymmetric vibration modes of end groups $(PO3)^{2-}$ have been highlighted. The bands around 400-700 cm^{-1} have been attributed to the deformation and tilting modes of the PO_3 groups. In addition, the existence of frequencies Vs(PO_3) in the infrared spectrum indicates that the ring [P_2O_7] adopts a bent configuration.

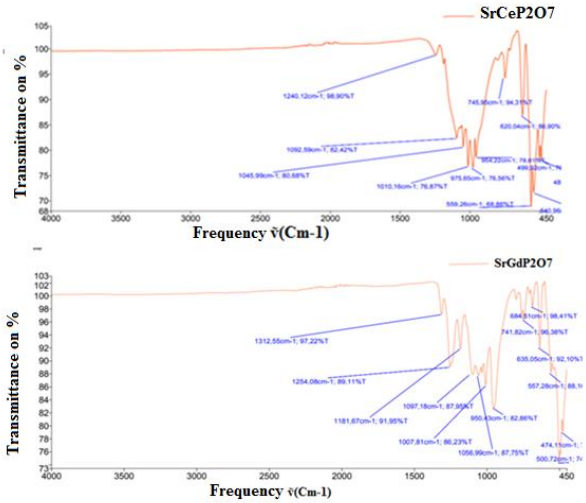

Fig. 9. Transmittance Spectra of $SrGdP_2O_7$ and $SrCeP_2O_7$ Nanomaterials

Frequency value(cm^{-1})	Transmi-ttance (%)	Assignm-ent	Frequency value (cm^{-1})	Transmi-ttance (%)	Assignm-ent
$SrGdP_2O_7$		-	$SrCeP_2O_7$		-
474,11	80	ν_sPO3	459,92	72	ν_sPO3
500,72	74	ν_sPO3	540,96	66,66	ν_sPO3
557,26	88,11	ν_sPO3	620,04	86,9	ν_sPO5
635,28	92,1	ν_sPO3	745,96	94,3	ν_sP-O-P
654,51	98,41	ν_sPO3	954,22	87,56	ν_sPO7
741,82	96,38	ν_sP-O-P	975,65	76,56	ν_sPO3
950,43	82,85	ν_sPO3	1010,16	76,87	$\nu_{as}PO_3$
1007,81	86,23	$\nu_{as}PO_3$	1045,99	60,68	$\nu_{as}PO_3$
1056,43	87,75	$\nu_{as}PO_3$	1002,56	62,42	$\nu_{as}PO_3$
1097,18	87,95	$\nu_{as}PO_3$	1240,12	96,9	$\nu_{as}PO_3$
1181,67	91,95	$\nu_{as}PO_3$	-	-	-
1254,06	89,11	$\nu_{as}PO_3$	-	-	-
1212	97,22	$\nu_{as}PO_3$	-	-	-

Table. 3. Allocation of bands to $SrGdP_2O_7$ and $SrCeP_2O_7$ nanomaterials

IV Discussion

There are two main families of contrast agents: positive contrast agents or T_1 agents (longitudinal relaxation) and negative or T_2 contrast agents (transverse relaxation) (4).
The quality of MRI imaging relies on the gray-scale coding of the relaxation time of water protons. Indeed, in T_1 encoding, if the T_1 relaxation time is short, the image is much clearer. However, T_2 encoding implies that if the T_2 relaxation time is short, the image is darker (5).

Moreover, in a study of quantum spin liquids (13), in the presence of a gap, the longitudinal relaxation time T_1 follows an activation law (exponential function in terms of the gap energy):

$$\mathbf{T_1 \propto exp(Eg^{opt}/k_BT)}$$

With T: the temperature; K_B: Boltzmann constant.

In addition, we have demonstrated in the experimental part using UV-visible spectrometry that the gap energy of our $SrCeP_2O_7$ nanomaterial (Eg^{opt} = 1.06 eV) is lower than that of the $SrGdP_2O_7$ nanomaterial (Eg^{opt} = 1.12 eV).

As a result, using the activation law and the gap energy, the $SrCeP_2O_7$ nanomaterial has a reduced T1 relaxation time compared to the $SrGdP_2O_7$ nanomaterial. Therefore, a better speed of magnetic relaxation 1/T1. Indeed, our nanomaterial $SrCeP_2O_7$, which is based on Cerium, will be a good positive contrast agent.
We also noticed, in the X-ray diffraction characterization of the $SrCeP_2O_7$ nanomaterial, that the shape of the spectrum peaks is very small, this indicates that the average grain size of our nanomaterial based on Cerium is very small;
Indeed, the widths of the spectra are directly proportional to the size of the grains (14). So a better ability to trap water molecules in the $SrCeP_2O_7$ structure.

All these elements revealed to us the idea of reinforcing this experimental result of positive contrast agent based on $SrCeP_2O_7$. Indeed, we thought to increase the local proton concentration by introducing a mechanism (figures 10 and 11) to our nanomaterial such that water can easily penetrate in its internal structure. The aim is to amplify the contrast of the observed signal.

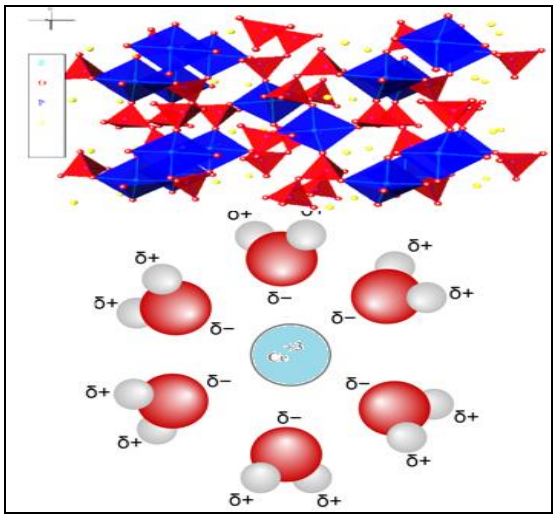

Fig. 10. Mechanism Picture

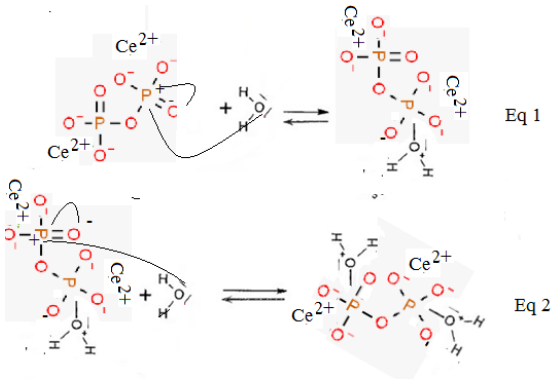

Fig. 11. Reaction mechanism of water molecules with the Cerium complex

V Conclusion

In magnetic resonance imaging, particularly in the use of contrast agents, the American and European notified bodies have issued an alert on the injection of all Gadolinium chelates in patients with severe renal insufficiency, because of the high toxicity of this chemical element Gd^{3+}. Conversely, the relevant catalytic and pharmacological properties of Cerium (Ce^{2+}) have made it the subject of several therapeutic applications.

In our study, we prepared two phosphate nanomaterials: $SrGdP_2O_7$ and $SrCeP_2O_7$ by the solid-state reaction route. The objective is to synthesize an effective nanomaterial that could be a better positive contrast agent based on Cerium. The Gap energies values of two nanomaterials showed that the $SrCeP_2O_7$ has a better magnetic speed 1/T1 in comparison with the $SrGdP_2O_7$, so a better longitudinal relaxation.

Therefore, our nanomaterial based on Cerium $SrCeP_2O_7$ will be a good positive contrast agent.

References

1. Bazhukova IN, Sokovnin SY, Ilves VG, Myshkina AV, Vazirov RA, Pizurova N, et al. Luminescence and optical properties of cerium oxide nanoparticles. Opt Mater (Amst) [Internet]. 2019 Jun;92:136–42. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0925346719302502
2. Nicolas L, Leclerc P, Guilloteau D, Lebtahi R. Médicaments radiopharmaceutiques : du diagnostic au théranostique des tumeurs neuroendocrines. Médecine Nucléaire. 2021 May;45(3):127–34.
3. Noury M, Lafontaine C. De la nanomédecine à la nanosanté : vers un nouveau paradigme biomédical. Socio-anthropologie [Internet]. 2014 Jun 15;(29):13–35. Available from: http://journals.openedition.org/socio-anthropologie/1635
4. Tsapis N. Agents de contraste pour l'imagerie médicale. médecine/sciences [Internet]. 2017 Jan 25;33(1):18–24. Available from: http://www.medecinesciences.org/10.1051/medsci/20173301004
5. Port M. Chapitre 9 : Les agents de contraste dans l'imagerie par résonance magnétique, pour le diagnostic médical. In: La chimie et la santé [Internet]. EDP Sciences; 2020. p. 153–68. Available from: https://www.degruyter.com/document/doi/10.1051/978-2-7598-0934-9.c012/html
6. Hermann P, Kotek J, Kubíček V, Lukeš I. Gadolinium(iii) complexes as MRI contrast agents: ligand design and properties of the complexes. Dalt Trans [Internet]. 2008;(23):3027. Available from: http://xlink.rsc.org/?DOI=b719704g
7. RASSCHAERT M. Capture cérébrale de chélates de gadolinium: imagerie multimodale et analyse des conséquences neurotoxicologiques. Université Paris-Saclay; 2019.
8. ZHANG, Sam et ZHAO D (ed. . Advances in magnetic materials: processing, properties, and performance. Boca Raton, Florida CRC Press. 2017;758.
9. Zambon A, Malavasi G, Pallini A, Fraulini F, Lusvardi G. Cerium Containing Bioactive Glasses: A Review. ACS Biomater Sci Eng [Internet]. 2021 Sep 13;7(9):4388–401. Available from: https://pubs.acs.org/doi/10.1021/acsbiomaterials.1c00414
10. Elayakumar K, Dinesh A, Manikandan A, Palanivelu M, Kavitha G, Prakash S, et al. Structural, morphological, enhanced magnetic properties and antibacterial bio-medical activity of rare earth element (REE) cerium (Ce3+) doped CoFe2O4 nanoparticles. J Magn Magn Mater [Internet]. 2019 Apr;476:157–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0304885318326787
11. Li H, Xia P, Pan S, Qi Z, Fu C, Yu Z, et al. The Advances of Ceria Nanoparticles for Biomedical Applications in Orthopaedics. Int J Nanomedicine [Internet]. 2020 Sep;Volume 15:7199–214. Available from: https://www.dovepress.com/the-advances-of-ceria-nanoparticles-for-biomedical-applications-in-ort-peer-reviewed-article-IJN
12. Khan SA, Gambhir S, Ahmad A. Extracellular biosynthesis of gadolinium oxide (Gd 2 O 3) nanoparticles, their biodistribution and bioconjugation with the chemically modified anticancer drug taxol. Beilstein J Nanotechnol. 2014 Mar;5:249–57.
13. Bert F, Mendels P, Cépas O, Lhuillier C. Quand la frustration rend plus dynamique : les liquides de spins quantiques. Reflets la Phys. 2013 Dec;(37):4–11.
14. Eberhart J-P. Analyse structurale et chimique des matériaux. Paris : Du. Paris : Dunod D 1997, editor. 1997. IV-614 p.