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(54) **Title:** METHOD FOR OBTAINING ULTRAFINE SUPERPARAMAGNETIC MAGNESIUM-DOPED GAMMA IRON(III) OXIDE NANOPARTICLES WITH IMPROVED MAGNETIC PROPERTIES AND NANOPARTICLES OBTAINED BY THIS METHOD

(57) **Abstract:** The object of the invention is a method for obtaining ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium, characterized in that it involves the following steps: a) mixing iron(III) acetylacetonate, magnesium acetate tetrahydrate, dibenzyl ether and oleic acid at room temperature; b) bringing the mixture obtained by step a) to 190-200 °C for 25-30 min.; c) heating the mixture for 50 min. at 190-200 °C; d) heating the mixture for 80 min. at 230-235 °C; e) cooling the mixture to room temperature and washing it; f) separating the nanoparticles with a magnet; g) stabilizing the purified nanoparticles with a stabilizer, which is mPEG-silane; whereby, steps a-g) are carried out in an atmosphere, which is air. Another object of the invention is ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium obtained by the method according to the invention and characterized by the fact that their average size is 27-28 nm, the maximum magnetization based on hysteresis loop registration is 65 emu/g.

Method for obtaining ultrafine superparamagnetic magnesium-doped gamma iron(III) oxide nanoparticles with improved magnetic properties and nanoparticles obtained by this method

The subject of the invention is a method for obtaining ultrafine superparamagnetic gamma iron(III) oxide nanoparticles doped with magnesium and nanoparticles produced by this method.

Ultrafine superparamagnetic iron oxide nanoparticles (USPIO nanoparticles) are a nanomaterial with potential applications in nanomedicine, particularly in oncology treatment using magnetic hyperthermia (*X. Liu, et al. Theranostics 2020, 10(8), 3793-3815; A. F. Sumser, et al. Int. J. Hyperthermia 2020, 37(1), 15-27; Y. Lu, et al. Int. J. Hyperthemia 2020, 37(3), 141-154; I. Raouf, et al. J. Therm. Biol. 2020, 91, 102644; S. Nardecchia, et al. Nanomaterials 2019, 9(2), 191; C.S.S.R. Kumar, F. Mohammad. Adv. Drug Deliv. Rev. 2011, 63(9), 789-808; B. Thiesen, A. Jordan, Int. J. Hyperthermia 2008, 24(6), 467–474*).

Another application of USPIO nanoparticles is known from application description US2014249413 A1 as a treatment for a disease or condition associated with activated macrophages. However, the USPIO nanoparticles used are superparamagnetic iron oxide nanoparticles with diameters ranging from 1 to 50 nm, more commonly 5 to 40 nm, which are typically made of maghemite (Fe_2O_3) or magnetite (Fe_3O_4) with regions containing crystals with unpaired spins. These magnetic domains are disordered in the absence of a magnetic field, but when a field is applied (i.e., during an MRI), the magnetic domains align, creating a magnetic moment much greater than the sum of the individual unpaired electrons without causing residual particle magnetization. When injected into the blood, USPIO nanoparticles are captured by macrophages and accumulate in inflamed tissues.

In the state of the art, many ways of obtaining USPIO nanoparticles are known. USPIO nanoparticles obtained by co-precipitation method starting from precursors of iron(II) and iron(III) salts are considered, resulting in nanoparticles of Fe_3O_4 type (*C. M. Cheng, et al. J. Magn. Magn. Mater. 2009, 321, 2663–2669; A. Mukhopadhyay, et al. ACS Appl. Mater. Interfaces 2012, 4, 142−149; J. Muro-Cruces, et al. ACS Nano 2019, 13, 7716−7728*). On the other hand, other methods of synthesizing USPIO nanoparticles are known, in which the most common is the use of an iron(II) precursor, resulting in nanoparticles of the Fe_2O_3 type (*W. Wu, et al. Sci. Technol. Adv. Mater. 2015, 16, 023501; Q. Liu, et al. J Nanobiotechnol 2021, 19, 171*). Reactions are carried out in air, in an inert gas atmosphere or in an oxygen/inert gas atmosphere. Significant differences can be identified between all methods of obtaining USPIO

nanoparticles in the time and temperature of the various stages of the synthesis reaction, such as nanoparticle growth or aging. The synthesis and application in magnetic hyperthermia of USPIO nanoparticles containing also other metals, such as, for example, copper, is also considered (*S. M. Fotukian, et al. J. Alloys Compd. 2020, 816, 152548*), manganese and zinc (*A. Bhardwaj, et al. Sci Rep. 2020, 10, 15249*), cobalt (*C. Pereira, et al. Chem. Mater. 2012, 24, 1496−1504*) or gold (*M. R. Abedin, et al. J Nanobiotechnol 2018, 16, 80*). The goal behind this research is to improve the hyperthermal properties of the nanomaterial, which would enable more efficient destruction of tumors. Numerous literature reviews on USPIO magnetic nanoparticles indicate that the magnetic properties of the nanomaterial depend not only on the atomic composition (Fe_3O_4, Fe_2O_4, α-Fe_2O_3, γ-Fe_2O_3, etc.), but also, among others, on the size and shape of the nanoparticles (*A. Rajan, N. K. Sahu, J. Nanopart. Res. 2020, 22, 319; S. Laurent, et al. Chem. Rev. 2008, 108, 2064–2110; S. Khizar, et al. ACS Appl. Nano Mater. 2021, 4, 4284−4306; Y. Wang, et al. Mat. Today. Adv. 2020, 8, 100119; H. Etemadi, P. G. Plieger, Advances. Adv. Therap. 2020, 3, 2000061*).

A method of preparing a biologically active dispersed system (nano-liquid) based on iron(II, III) oxide nanoparticles is known from the application description RU2493857 C1. The method includes the preparation of a 3-6% solution of low molecular weight polyvinylpyrrolidone 8000 ± 2000 (MW), in which the solvent is a liquid containing 2.75-5.5 g of sodium chloride, 0.21-0.42 g of potassium chloride, 0.25-0.5 g of calcium chloride, 0.00025-0.005 g of magnesium chloride, 0.115-0.23 g of sodium bicarbonate and water. The resulting solution is added to a powder mixture of USPIO-grade iron(II, III) oxide nanoparticles with sizes of 5-8 nm, deposited on sodium chloride crystals. The whole mixture is stirred and kept at +60 °C for 2 hours. The resulting liquid is gradually cooled to room temperature (+20 °C) with subsequent separation from the precipitate.

From the application description KR20130097882 A, a method for producing a cluster of ferrite nanoparticles is known. According to the disclosed method, 2.0 g of sodium carbonate in 30 ml of acetic acid anhydride was dissolved in ethylene glycol and the solution was stirred vigorously at room temperature. Then 1.5 mmol of cobalt ferrite precursor or nickel chloride and 3.0 mmol ($COCl_2$-$6H_2O$ or $NiCl_2$-$6H_2O$) and $FeCl_3$-$6H_2O$ were slowly added to the solution. The mixture was reacted by stirring at 50 °C for at least 2 hours to produce a homogeneous suspension. The reaction was further carried out in a high-temperature/high-pressure reactor for 6 hours at 200 °C, then the particles were cooled to room temperature. The resulting particles were collected in an external magnetic field. The particles were washed two or three times with water and ethanol, then heated to 500 °C (at 1 °C/min) and sintered for 3 hours.

From patent description KR101280808 B1, ferritic superparamagnetic nanoparticles exhibiting high magnetic induction heating capability and specific loss force in low magnetic field and frequency range, harmless to the human body, and a method of producing them are known. In the disclosed method, iron(III) acetylacetonate and a raw material solution at room temperature containing at least one material selected from the group consisting of Mg, Mn, Ni, Zn and Co is heated to 195 °C and then maintained at the same temperature, after which it was heated to 200-204 °C and then to 203-210 °C. In another variant of the method, Fe(III) acetylacetonate and a raw material solution at room temperature containing at least one material selected from the group consisting of Mg, Mn, Ni, Zn and Co is heated to 120-140 °C for 25 min, and then maintained at the same temperature for 55 to 65 min. Next, heating of the solution of the raw material obtained in the preliminary stage is carried out to 200 to 210 °C for 18 to 23 minutes, and then maintained at the same temperature for 55 to 62 minutes. The next stage is heating for 6 to 12 minutes to the boiling point of the solvent, and then maintaining the raw material solution at the same temperature for 45 to 55 minutes.

The application description US20160176722 presents a method for producing magnetite and ferrite nanoparticles in a single vessel in situ synthesis involving the following steps: mixing iron(III) nitrate [$Fe(NO_3)_3$] with fatty acid to form a mixture; mixing a solvent with the mixture; heating the solvent mixture and maintaining the solvent mixture at a temperature between 300 °C and 320 °C; and precipitating magnetite and ferrite nanoparticles; wherein the nanoparticles have a relative standard deviation of diameter less than or equal to 10%.

From the application description CN104445437A, a method for producing magnetic iron oxide nanoparticles is known, which includes the following steps of adding Fe^{2+} and Fe^{3+} salts at a molar ratio of Fe^{2+} salt to Fe^{3+} salt (1.2-1.4) : 2 in distilled water, to which polyethylene glycol is added. The reaction is then carried out for 5-10 minutes under ultrasonic conditions at 30-50 °C to obtain the reaction liquid, carry out magnetic separation of the obtained reaction liquid with a magnet, and then wash the reaction liquid 3-5 times with ethanol to obtain iron oxide nanoparticles. The disclosed method does not require a nitrogen atmosphere, high pressure or high temperature, and has the advantages of simplicity, the use of readily available raw materials and the possibility of large-scale industrial production.

The state of the art knows how to obtain magnesium-containing USPIO nanoparticles (*J.-t. Jang et al. Adv. Mater. 2018, 30, 1704362; J.-t. Jang and S. Bae, Appl. Phys. Lett. 2017, 111, 183703*). The authors found improved magnetic properties of this nanomaterial compared to magnesium-free USPIO. However, the mentioned synthesis method has some disadvantages. First, the reaction must be carried out at the boiling point of dibenzyl ether (296 °C). This not

only requires the use of a suitable apparatus to achieve and maintain this temperature of the reaction mixture over time (50 min), but also carries the dangers of the possibility of forming explosive mixtures of dibenzyl ether with air during prolonged heating at the boiling point. Second, the reaction should be carried out with a device that allows the reaction mixture to be subjected to barbotage with an Ar/O_2 mixture (volume ratio of 1 : 4). This activity requires the use of a suitable specialized apparatus, also bearing in mind the required flow rate of these gases indicated by the authors (100 $mL \cdot min^{-1}$).

Similarly, application description EP2377811 A2 discloses a method for producing processed superparamagnetic ferrite nanoparticles doped with magnesium with a particle size of 10 nm. The disclosed method includes mixing a raw material containing iron(III) acetylacetonate, magnesium and a solvent; performing a primary heat treatment to produce nanoparticle embryos; and performing a secondary heat treatment to produce nanoparticles, followed by washing, centrifugation, drying and grinding of the nanoparticles. During the first heat treatment, the temperature of the mixture was gradually raised to 200 °C over 30 minutes and maintained at that level for another 30 minutes. During the second heat treatment, the temperature of the mixture was gradually raised to the melting point of benzyl ether, that is, 296 °C, over about 30 minutes.

Thus, the state of the art does not directly indicate what process conditions should be used to improve the magnetic properties of USPIO nanoparticles. This is the subject of research being carried out around the world. This also applies to the synthesis of USPIO magnetic nanoparticles containing other metals. Thus, there is a need to develop a new way of synthesizing magnetic iron oxide (USPIO) nanoparticles toward further improving their magnetic properties and, consequently, their hyperthermic properties in an alternating magnetic field, particularly with a view to the application of the obtained nanomaterials, among others, in oncological treatment using magnetic hyperthermia.

The purpose of the invention is to develop a new method for obtaining ultrafine superparamagnetic gamma iron(III) oxide (USPIO) doped with magnesium nanoparticles with improved magnetic properties.

Unexpectedly, the inventors of the invention have developed a method in which ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium with improved magnetic properties can be easily obtained using milder process conditions in air, commercially available reactants, and without the need to carry out the reaction in an atmosphere of argon or Ar/O_2.

The object of the invention is a method for obtaining ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium with improved magnetic properties, characterized in that it includes the following steps:

a) mixing iron(III) acetylacetonate, magnesium acetate tetrahydrate, dibenzyl ether and oleic acid at room temperature;

b) bringing the mixture obtained by step a) to a temperature of 190-200 °C in 25-30 min;

c) heating the mixture for 50 min at 190-200 °C;

d) heating the mixture for 80 min at 230-235 °C;

e) cooling the mixture to room temperature and washing it out;

f) separation of nanoparticles with a magnet;

g) stabilization of purified nanoparticles with a stabilizer that is mPEG-silane;

whereby, stages (a-g) are conducted in an atmosphere that is air.

Another object of the invention are ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium obtained by the method according to the invention characterized by the fact that their average size is 27-28 nm, the maximum magnetization based on hysteresis loop registration is 65 emu/g.

The invention provides the following benefits:

- Conducting reactions under milder conditions than indicated by the literature: reducing costs and energy intensity;
- The synthesis method according to the invention is carried out in air, so there is no need for a complex apparatus for generating Ar/O_2;
- No need for synthesis under inert gas conditions;
- Simplicity of the research equipment used - no requirement for specialized equipment, which reduces the cost of the process;
- Improving the functional properties of nanomaterial, including the magnetic properties of nanoparticles obtained by the method according to the invention;
- Favorable functional properties of the obtained nanoparticles (e.g., improved magnetic and hyperthermal properties in an alternating magnetic field);
- Nanoparticles produced by the method according to the invention may find application in nanomedicine, particularly in oncology treatment using magnetic hyperthermia.

Detailed description of the invention:

The descriptions of the implementations of the invention in this application are given by way of example and are not intended to limit the scope of the invention. The described

implementations include various features, not all of which are required in all implementations of the invention. Some implementations use only some of the features or possible combinations of features. The described variants of the implementations of the invention and the implementations of the invention that include various combinations of the features listed in the described implementations will come to the mind of an expert in the field. In contrast, the scope of the invention is limited only by the claims.

In addition, as used in this description, the phrase "in an implementation" and "in certain implementations" should be understood as in one or more implementations. In addition, the features present in the various implementations may be combined with each other.

In the first aspect, the invention relates to a method of obtaining ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium characterized by improved magnetic and hyperthermal properties in an alternating magnetic field.

In one implementation of the method according to the invention, the reaction is carried out in air. Iron(III) acetylacetonate and magnesium acetate tetrahydrate are placed in a flask. After adding dibenzyl ether and oleic acid, the mixture is stirred at room temperature for 15 minutes. In 30 minutes, the mixture is brought to 200 °C and heated at 200 °C for 50 minutes. Then, the temperature of the reaction mixture is quickly (i.e., within about 5 minutes) raised to 230 °C and the process is continued at this temperature for 80 minutes. After the mixture has cooled to room temperature, rinsing is carried out.

In another implementation, the mixture is brought to 190 °C in 25 minutes and then heated at this temperature for 50 minutes. In the next step, the temperature of the reaction mixture is quickly (i.e., within about 5 minutes) raised to 235 °C and the process is continued at this temperature for 80 minutes. After the mixture has cooled to room temperature, rinsing is carried out.

In one implementation, several washes with ethanol are carried out, and the obtained precipitate is centrifuged. After removing the supernatant after the last wash, the obtained precipitate is poured over a mixture of ethanol, oleic acid and ammonia and shaken at room temperature for 2 hours. The precipitate is separated from the supernatant with a magnet and washed with acetone. Toluene is added to the resulting precipitate, shaken for 10 minutes and then triethylamine and mPEG-silane (methoxy-poly(ethylene glycol)-silane) are added. The mixture is stirred with a magnetic stirrer at 80 °C for 24 hours. The precipitate is separated from the supernatant with a magnet, then washed with toluene, ethanol and water to obtain ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium with improved magnetic properties.

In a further aspect, the invention relates to ultrafine superparamagnetic magnesium-doped gamma iron(III) oxide (USPIO) nanoparticles, which were produced by the method according to the invention, whose average size is 27-28 nm, the maximum magnetization based on hysteresis loop registration is 65 emu/g.

In one implementation, the ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles obtained by the method according to the invention doped with magnesium according to the invention have the following properties:

FT-IR (KBr): υ = 570 (s), 940 (w), 1105 (m), 1250 (w), 1350 (w), 1410 (w), 1525 (w), 1620 (w) cm^{-1}

FT-Raman: Raman shift = 618, 740 cm^{-1}

Average particle size (based on TEM): 28 nm

Average particle size (based on XRD): 27 nm

Powder diffractogram (XRD): 2θ = 220, 311, 400, 422, 511, 440 deg

The elemental composition (based on EDS) is shown in Table 1:

Component	% mass content	% atomic content
C	11.32	22.23
N	0.72	1.08
O	37.20	54.93
Mg	0.09	0.08
Si	0.53	0.45
Cl	0.09	0.06
Fe	50.05	21.17

Maximum magnetization (based on hysteresis loop registration):65 emu/g

Magnetic hyperthermia: C = 3 mg/ml, T_{max} = 92 °C, H = 23 mT, f = 109.96 kHz, t_{max} = 15.8 min.

In one implementation, ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium and subjected to an alternating magnetic field of 23 mT and a frequency of 109.96 kHz in an aqueous suspension (3 mg/ml) reach a maximum magnetic hyperthermia of 92 °C within 15.8 minutes. The ablative temperature (43.5 °C) is reached in the first minute of magnetization.

The invention is shown in the following non-limiting implementation examples.

Example 1.

The reaction is carried out in air. Iron(III) acetylacetonate (2.0 mmol) and magnesium acetate tetrahydrate (0.13 mmol) are placed in a flask. After adding dibenzyl ether (20 mL) and oleic acid (1.2 mmol), the mixture is stirred at room temperature for 15 minutes. In 30 minutes, the mixture is brought to 200 °C and heated at 200 °C for 50 minutes. Then, the temperature of the reaction mixture is quickly raised to 230 °C and the process continues at this temperature for 80 minutes. After the mixture has cooled to room temperature, ethanol (70 mL) is added. The resulting precipitate is centrifuged (5000 rpm, 25 min) and washed several times with ethanol. After removing the supernatant after the last washing, the resulting precipitate is poured over a mixture of ethanol (20 mL), oleic acid (6 mL) and ammonia (1.5 mL) and shaken (500 rpm) at room temperature for 2 hours. The precipitate is separated from the supernatant with a magnet and washed with acetone. Toluene (15 mL) is added to the resulting precipitate, shaken for 10 minutes and then triethylamine (8 mL) and mPEG-silane (550 Da; 1 mL) are added. The mixture is stirred with a magnetic stirrer at 80 °C for 24 hours. The precipitate is separated from the supernatant using a magnet, washed with toluene, ethanol and water to obtain ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium with improved magnetic properties.

Example 2.

The reaction is carried out in air. Iron(III) acetylacetonate (2.0 mmol) and magnesium acetate tetrahydrate (0.13 mmol) are placed in a flask. After adding dibenzyl ether (20 mL) and oleic acid (1.2 mmol), the mixture is stirred at room temperature for 15 minutes. In 25 minutes, the mixture is brought to 190 °C and heated at 190 °C for 50 minutes. Then, the temperature of the reaction mixture is quickly raised to 235 °C and the process continues at this temperature for 80 minutes. After the mixture has cooled to room temperature, ethanol (70 mL) is added. The resulting precipitate is centrifuged (5000 rpm, 25 min) and washed several times with ethanol. After removing the supernatant after the last washing, the resulting precipitate is poured over a mixture of ethanol (20 mL), oleic acid (6 mL) and ammonia (1.5 mL) and shaken (500 rpm) at room temperature for 2 hours. The precipitate is separated from the supernatant with a magnet and washed with acetone. Toluene (15 mL) is added to the resulting precipitate, shaken for 10 minutes and then triethylamine (8 mL) and mPEG-silane (550 Da; 1 mL) are added. The mixture is stirred with a magnetic stirrer at 80 °C for 24 hours. The precipitate is separated from the supernatant using a magnet, washed with toluene, ethanol and water to obtain ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium with improved magnetic properties.

Example 3.

Ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium were produced by the method according to example 1. In this implementation example, superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium have the following properties:

FT-IR (KBr): υ = 570 (s), 940 (w), 1105 (m), 1250 (w), 1350 (w), 1410 (w), 1525 (w), 1620 (w) cm^{-1}

FT-Raman: Raman shift = 618, 740 cm^{-1}

Average particle size (based on TEM): 28 nm

Average particle size (based on XRD): 27 nm

Powder diffractogram (XRD): 2θ = 220, 311, 400, 422, 511, 440 deg

The elemental composition (based on EDS) is shown in Table 1.

Maximum magnetization (based on hysteresis loop registration):65 emu/g

Magnetic hyperthermia: C = 3 mg/ml, T_{max} = 92 °C, H = 23 mT, f = 109.96 kHz, t_{max} = 15.8 min.

Ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium subjected in an aqueous suspension (3 mg/ml) to an alternating magnetic field of 23 mT and a frequency of 109.96 kHz reach a maximum magnetic hyperthermia of 92 °C within 15.8 minutes. The ablative temperature (43.5 °C) is reached in the first minute of magnetization.

Patent claims

1. Method for the preparation of ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium, notable in that it includes the following steps:

a) mixing iron(III) acetylacetonate, magnesium acetate tetrahydrate, dibenzyl ether and oleic acid at room temperature;

b) bringing the mixture obtained by step a) to 190-200 °C for 25-30 min.;

c) heating the mixture for 50 min. at 190-200 °C;

d) heating the mixture for 80 min. at 230-235 °C;

e) cooling the mixture to room temperature and washing it;

f) separating the nanoparticles with a magnet;

g) stabilizing the purified nanoparticles with a stabilizer, which is mPEG-silane;

whereby, steps a-g) are carried out in an atmosphere, which is air.

2. Ultrafine superparamagnetic gamma iron(III) oxide (USPIO) nanoparticles doped with magnesium obtained by the method according to claim 1, characterized by the fact that their average size is 27-28 nm, the maximum magnetization based on hysteresis loop registration is 65 emu/g.

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2023/000021

A. CLASSIFICATION OF SUBJECT MATTER
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ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
H01F B82Y

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JUNG-TAK JANG ET AL: "Giant Magnetic Heat Induction of Magnesium-Doped [gamma]-Fe2O3 Superparamagnetic Nanoparticles for Completely Killing Tumors", ADVANCED MATERIALS, VCH PUBLISHERS, DE, vol. 30, no. 6, 20 December 2017 (2017-12-20), pages 1-26, XP071873995, ISSN: 0935-9648, DOI: 10.1002/ADMA.201704362 page 3, column 1, paragraph 1; figure 2c -/--	1,2

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2023	25/08/2023

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& JANG JUNG-TAK ET AL: "[Supporting Information] Giant Magnetic Heat Induction of Magnesium-Doped [gamma]-Fe 2 O 3 Superparamagnetic Nanoparticles for Completely Killing Tumors", ADVANCED MATERIALS, vol. 30, no. 6, 20 December 2017 (2017-12-20), page 1704362, XP093070451, DE ISSN: 0935-9648, DOI: 10.1002/adma.201704362 Retrieved from the Internet: URL:https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002%2Fadma.201704362> page 2 - page 3, paragraph 1 figures S2,S7,S9	
X	EP 2 377 811 A2 (NURI VISTA CO LTD [KR]) 19 October 2011 (2011-10-19) paragraphs [0015], [0018] - [0026]; claims 1,3-7	1,2
A	JANG JUNG-TAK ET AL: "Mg shallow doping effects on the ac magnetic self-heating characteristics of [gamma]-Fe2O3superparamagnetic nanoparticles for highly efficient hyperthermia", APPLIED PHYSICS LETTERS, AMERICAN INSTITUTE OF PHYSICS, 2 HUNTINGTON QUADRANGLE, MELVILLE, NY 11747, vol. 111, no. 18, 1 November 2017 (2017-11-01), XP012223336, ISSN: 0003-6951, DOI: 10.1063/1.5000841 [retrieved on 2017-11-01] page 2; figures 1,2,4	1,2
A	US 2012/018382 A1 (STEIN ADAM L [US]) 26 January 2012 (2012-01-26) paragraphs [0112], [0120]; example 1	1,2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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