(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2018 (25.01.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/015733 A1

(51) International Patent Classification:
A61K 41/00 (2006.01) *B82Y 5/00* (2011.01)
A61K 9/50 (2006.01)

(21) International Application Number:
PCT/GB2017/052105

(22) International Filing Date:
18 July 2017 (18.07.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1612562.7 20 July 2016 (20.07.2016) GB
1618863.3 08 November 2016 (08.11.2016) GB

(71) Applicant: **UBICOAT LTD** [GB/GB]; Keepers, Longfords, Minchinhampton, Stroud Gloucestershire GL6 9AN (GB).

(72) Inventors: **BINNS, Robert Davidson**; Keepers, Longfords, Minchinhampton, Stroud Gloucestershire GL6 9AN (GB). **KINMONT, John William Patrick**; Manor Farmhouse, Rodmarton, Stroud, Cirencester Gloucestershire GL7 6PE (GB).

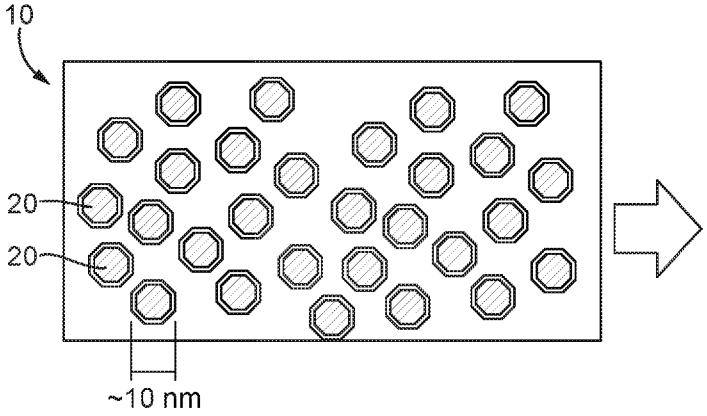
(74) Agent: **KATE BUTLER IP LTD**; Office 2, Eight Bells House Serviced Offices, 14 Church Street, Tetbury, Gloucestershire GL8 8JG (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

(54) Title: PRODUCTION OF NANOSCALE POWDERS OF EMBEDDED NANOPARTICLES

Fig. 1(a)



(57) Abstract: The invention provides a liquid-dispersible powder comprising nanoscale grains of matrix embedded with one or more isolated nanoparticles and a composition for the magnetic nanoparticle hyperthermia (MNH) treatment of tumours comprising nanoscale grains of matrix material containing one or more isolated nanoparticles. The invention also provides a method of production of a liquid-dispersible powder described herein, the method comprising the steps of providing nanoparticles prepared under ultra-high vacuum (UHV) gas phase conditions; co-depositing the nanoparticles within a matrix material under UHV gas phase conditions; and grinding the film to a fine powder comprising grains of groups of matrix material isolated nanoparticles. The invention also provides a method of reducing the agglomeration of nanoparticles in liquid, the method comprising isolating nanoparticles in nanoscale grains of matrix material, and the use of a liquid-dispersible powder comprising nanoscale grains of matrix material containing one or more isolated nanoparticles in the manufacture of a medicament for the MNH treatment of tumours.

WO 2018/015733 A1

[Continued on next page]

TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

Production of Nanoscale Powders of Embedded Nanoparticles

The present invention relates to the use of water-dispersible powder comprising nanoscale grains of a matrix material containing one or more isolated nanoparticles, in particular, magnetic nanoparticles. The powder of the present invention may be further dispersed in liquid, such as water, for use in medical treatments including magnetic nanoparticle hyperthermia (MNH) of tumours.

Background to the invention

It is well known that nanoparticles with sizes less than about 10 nm display special magnetic, optical and chemical properties that provide them with a very high performance in various applications. The most flexible way to synthesise nanoparticles is to use ultra-high vacuum (UHV) gas-phase methods that enable very good size control, flexibility of the constituent elements and the ability to produce complex core-shell and alloy structures. Although the method is costly compared to chemical synthesis, it enables the production of nanoparticles with unparalleled performance in certain high-end applications.

One of these high-end applications is the MNH treatment of tumours. This is a radical nanotechnology-based therapy that uses magnetic nanoparticles to raise the temperature of a tumour by a few degrees thus encouraging apoptosis of the cancer cells without harming surrounding tissue. As all cancers respond in the same way to heat this is a generically useful therapy. However, it has been found that the currently available Fe oxide nanoparticles used do not produce sufficient heat for a general tumour therapy.

One way to combat this is to use UHV gas-phase produced nanoparticles containing a pure Fe core and a biocompatible shell, for example Fe Oxide (Fe@FeO particles). Such particles have been shown to produce an order of magnitude more heat per gram of material. Such particles necessarily have to be produced in UHV conditions to avoid oxidising the Fe core.

However, despite addressing the heat requirement issue using advances in nanoparticle technology, a generic problem with all nanoparticles is their tendency to agglomerate,

which always degrades their performance. This is also true in the case of core/shell nanoparticles. Although a method has been developed to deposit these in water for medical applications, they rapidly agglomerate, which reduces their heating performance.

There is therefore a need for a method to reduce the agglomeration of nanoparticles, and in particular magnetic nanoparticles, in fluid such as water so that the advantageous properties of nanoparticles can be exploited whilst minimising the heating and other property compromises due to agglomeration.

It is an object of the present invention to address the problems of the prior art.

Statements of invention

A first aspect of the present invention provides a liquid-dispersible powder comprising nanoscale grains of a matrix material composed of one or more biocompatible oxides, in which the matrix material contains a plurality of isolated nanoparticles, wherein each nanoparticle comprises a magnetic core selected from one or more of Fe or an alloy of Fe/Co.

The liquid-dispersible powder may for example be a water-dispersible powder.

The term "nanoparticles" used herein is intended to include simple elemental, core/shell, and alloy structures.

The biocompatible oxide is any suitable oxide capable of being sputter coated to form a matrix or shell, preferably a matrix. Sputter coating is a deposition process to cover a substrate with a thin layer of material. Any suitable method of sputter coating may be used. For example, the oxide coatings may for example be provided or deposited, for example co-deposited, using a pulsed or RF power supply at approximately 100W and a gas pressure of approximately 0.1 mbar.

Suitable oxides include, but are not limited to, one or more of: Al_2O_3 and/or alumina. The biocompatible oxide shell is preferably thermally stable. Preferably, the

biocompatible oxide is stable at ambient pressure and at temperatures around the temperature of the human body. In one embodiment, the biocompatible oxide is stable at ambient pressure and at a temperature of at least 37 °C, preferably at least 40 °C, more preferably at least 45 °C, for example at least 50 °C. The term stable is used herein to refer to the biocompatible oxide remaining intact within the powder without any degradation, such as for example thermal degradation, under the conditions described herein.

A second aspect of the present invention provides a composition for the magnetic nanoparticle hyperthermia (MNH) treatment of tumours comprising nanoscale grains of a matrix material composed of one or more biocompatible oxides, in which the matrix material contains a plurality of isolated nanoparticles, wherein each nanoparticle comprises a magnetic core selected from one of more of Fe or an alloy of Fe/Co.

A third aspect of the present invention provides a method of production of a liquid-dispersible powder according to any preceding claim, the method comprising the steps of:

a. providing nanoparticles prepared under ultra-high vacuum (UHV) gas phase conditions, wherein each nanoparticle comprises a magnetic core selected from one of more of Fe or an alloy of Fe/Co;
b. co-depositing the nanoparticles within a matrix composed of one or more biocompatible oxides under UHV gas phase conditions;
c. grinding the film to a fine powder comprising grains of groups of matrix isolated nanoparticles.

The grinding step may comprise ball milling, however, any suitable method may be used to grind the film provided it results in a suitably fine powder. The resultant powder has to be sufficiently fine to pass through the smallest capillary of the body.

A fourth aspect of the present invention provides a method of reducing the agglomeration of nanoparticles in water, the method comprising isolating a plurality of nanoparticles in nanoscale grains of a matrix material composed of one or more biocompatible oxides, wherein each magnetic nanoparticle comprises a magnetic core selected from one of more of Fe or an alloy of Fe/Co.

A fifth aspect of the present invention provides a liquid-dispersible powder comprising nanoscale grains of a matrix material composed of one or more biocompatible oxides, in which the matrix material contains a plurality of isolated nanoparticles, wherein each magnetic nanoparticle comprises a magnetic core selected from one of more of Fe or an alloy of Fe/Co in the magnetic nanoparticle hyperthermia (MNH) treatment of tumours.

MNH is an emerging cancer treatment, based on the fact that magnetic nanoparticles produce heat when exposed to an alternating magnetic field. By targeting the magnetic nanoparticles to the tumours either by the body's natural processes such as EPR, magnetic targeting or biological targeting, then exposing the cells to an alternating magnetic field of predetermined amplitude and frequency, the cell temperature would rise thereby encouraging apoptosis of the cells without harm to surrounding tissues.

However, one drawback to such a treatment is that the magnetic nanoparticles have to be dispersed in a liquid before they can be delivered to the body, for example into the bloodstream. Dispersal of magnetic nanoparticles in liquid leads to agglomeration with consequential altering of the desirable properties of the particles. By embedding the nanoparticles within a matrix material of the powder of the present invention, the nanoparticles are inherently spatially separated from one another and agglomeration is minimised. The nanoscale nature of the grains of matrix material are sufficiently big to contain a plurality of nanoparticles per grain whilst remaining small enough to be liquid-dispersible, for example water-dispersible, and therefore useful in medical applications.

In any aspect of the present invention, the nanoscale grains are preferably provided in the form of a liquid-dispersible powder, for example a water-dispersible powder. Alternatively, the composition may be provided in the form of a liquid-based solution, for example water-based solution, in which the grains of matrix have already been dispersed.

Typically, the nanoparticles are around 15nm in diameter. As a nanoscale grain of matrix material may be as large as 100nm in width, it can therefore be appreciated that each grain of matrix material may retain several embedded nanoparticles therein

thereby allowing the dispersal of nanoparticles, and particularly magnetic nanoparticles, within liquid such as but not limited to water, whilst minimising agglomeration.

As mentioned above, at least a portion of the nanoparticles comprise magnetic nanoparticles. In one embodiment, each magnetic nanoparticle may comprise a magnetic core, such as for example an iron (Fe) core and/or an alloy core comprising iron/cobalt, encased in a biocompatible shell, composed of for example one more of: Fe oxide, gold, or silver, or any combination thereof. For example, the magnetic nanoparticles may be composed of Fe oxide (Fe@FeO), gold (Fe@Au) or silver (Fe@Ag) particles, or any combination thereof. However, it is to be appreciated that the present invention may be carried out using magnetic nanoparticles of alternative composition.

Preferably, the nanoparticles are isolated in the matrix under UHV gas phase conditions.

The matrix material protects the magnetic nanoparticles by preventing oxidation of the nanoparticles. The matrix material thereby helps to ensure that the magnetic properties of the nanoparticles are retained within, and during use of, the powder.

Description of the drawings:

Embodiments of the present invention will now be described by way of example only and with reference to the following figures:

Figure 1 (a) shows a thin film of matrix with embedded nanoparticles prior to milling, in accordance with a first embodiment of the present invention; and

Figure 1(b) shows nanoscale grains of matrix with embedded nanoparticles after milling, in accordance with the embodiment of figure 1.

Specific description

Magnetic nanoparticles with an iron (Fe) core surrounded by a biocompatible shell, for example iron oxide (FeO) which is otherwise referred to as Fe@FeO nanoparticles, were produced using ultra-high vacuum (UHV) gas-phase methods. It is however to be understood that the present invention is not limited to magnetic nanoparticles comprising an iron core. The nanoparticles may comprise other magnetic cores, such as for example alloy cores such as for example iron/cobalt alloy cores. It is also to be understood that the biocompatible shell is not limited to being composed of iron oxide. The biocompatible shell may be composed of one or more of: Fe oxide, gold or silver particles, or any combination thereof. The nanoparticles may for example comprise one or more of an iron core surrounded with iron oxide (Fe@FeO), an iron core surrounded with gold (Fe@Au), or an iron core surrounded with silver (Fe@Ag), or any combination thereof. The use of UHV gas-phase methods facilitates the production of magnetic nanoparticles having a relatively narrow size distribution of around 10 nm in size, whilst minimising nanoparticle agglomeration. Uncontrolled particle agglomeration would adversely affect the desirable properties of the nanoparticles.

The nanoparticles, for example Fe@FeO nanoparticles, are then co-deposited within a matrix under UHV conditions to produce a thin film with embedded isolated magnetic nanoparticles. The matrix material may be any material capable of sputter coating. Suitable oxides include, but are not limited to, one or more of: Al_2O_3 or alumina. Any suitable method of sputter coating of the nanoparticles with the matrix material may be used. For example, the oxide coatings may for example be provided using a pulsed or RF power supply at approximately 100W and a gas pressure of approximately 0.1 mbar. It is however to be understood that the method of depositing nanoparticles within the matrix material is not to be limited to these process parameters.

Figure 1(a) shows such a thin film matrix 10 with embedded nanoparticles 20 isolated within the film 10. As can be seen from figure 1, there is no agglomeration of the nanoparticles 20 within the film 10 and each nanoparticle 20 is spatially isolated from neighbouring nanoparticles 20.

In order to use the magnetic nanoparticles in medical applications, the nanoparticles must be liquid-dispersible, for example water-dispersible. Therefore, the thin film was subjected to grinding by a ball mill to produce a fine powder of nanoscale grains 30 of matrix containing small groups of embedded magnetic nanoparticles 20. Figure 1(b) shows the film 10 of figure 1 after the milling process. Nanoscale grains 30 of matrix 10 are shown, each approximately 100 nm in size, each grain 30 having a group of embedded magnetic nanoparticles 20 clearly spatially isolated from one another.

It should be noted that the nanoscale grains 30 of matrix 10 isolated nanoparticles 20 as shown in figure 1(b) which are each approximately 100 nm in size are still small enough for use in medical applications such as the magnetic nanoparticle hyperthermia (MNH) treatment of tumours or bacterial infections. The size of each nanoscale grain 30 is still at least 100 times smaller than the finest capillaries in the human body.

In order to use the fine powder of nanoscale grains 30 in medical applications, the fine powder must be dispersed in liquid. The nanoscale dimensions of the grains 30 facilitates efficient dispersal of the grains 30 in liquid, such as but not limited to water. The fine powder may be added to water to provide a liquid composition comprising nanoscale grains of matrix embedded with a plurality of isolated nanoparticles which can be used for medical applications such as, but not restricted to MNH treatment of cancer tumours.

This embodiment of the present invention demonstrates how a suspension of magnetic nanoparticles can be produced for medical applications whilst avoiding the typical problems of agglomeration. It should be noted that due to the arrangement of embedded nanomagnetic particles within the thin matrix of each grain 30, even if some agglomeration of grains 30 within a liquid is experienced, the magnetic nanoparticles will remain spatially isolated from one another, thereby retaining their desirable properties.

Finally, it is to be appreciated that the milling process itself will result in some modification of the individual nanoparticles. For example, the strain induced by the milling process would alter the magnetic anisotropy of the nanoparticles. Therefore,

the milling process itself can be used as an additional way of controlling the characteristics of the nanoparticles and the performance of the final fine powder.

Although the example refers to the use of Fe@FeO nanoparticles it is to be understood that the present invention is not limited to magnetic nanoparticles comprising an Fe core coated in a biocompatible shell comprising FeO. The magnetic nanoparticles may comprise a core selected from one or more of Fe or an alloy of Fe/Co. The biocompatible shell may comprise one or more of FeO, gold, or silver, or any combination thereof.

CLAIMS

1. A liquid-dispersible powder comprising nanoscale grains of a matrix material composed of one or more biocompatible oxides, in which the matrix material contains a plurality of isolated nanoparticles, wherein each nanoparticle comprises a magnetic core selected from one or more of Fe or an alloy of Fe/Co.

2. A composition for the magnetic nanoparticle hyperthermia (MNH) treatment of tumours comprising nanoscale grains of a matrix material containing one or more isolated nanoparticles.

3. A composition according to claim 2, wherein the nanoscale grains are provided in the form of a liquid dispersible powder.

4. A liquid-dispersible powder according to claim 1 or a composition according to claim 2 or claim 3, wherein the nanoparticles are around 15nm in size.

5. A liquid-dispersible powder or composition according to any preceding claim, wherein each magnetic nanoparticle comprises a magnetic core selected from one or more of Fe or an alloy of Fe/Co encased in a biocompatible shell.

6. A liquid-dispersible powder of composition according to claim 5, in which the biocompatible shell comprises one or more of: Fe oxide, gold, or silver, or any combination thereof

7. A method of production of a liquid-dispersible powder according to any preceding claim, the method comprising the steps of:

   a. providing nanoparticles prepared under ultra-high vacuum (UHV) gas phase conditions, wherein each magnetic nanoparticle comprises a

magnetic core selected from one of more of Fe or an alloy of Fe/Co;

b. co-depositing a plurality of nanoparticles within a matrix material composed of one or more biocompatible oxides under UHV gas phase conditions;

c. grinding the film to a fine powder comprising grains of groups of matrix isolated nanoparticles.

8. A method according to claim 7, wherein the grinding step comprises ball milling.

9. A method of reducing the agglomeration of nanoparticles in liquid, the method comprising isolating a plurality of nanoparticles in nanoscale grains of a matrix material composed of one or more biocompatible oxides.

10. A method according to claim 9, wherein the nanoparticles are isolated in the matrix material under UHV gas phase conditions.

11. A liquid-dispersible powder comprising nanoscale grains of a matrix material composed of one or more biocompatible oxides, in which the matrix material contains a plurality of isolated nanoparticles, wherein each nanoparticle comprises a magnetic core selected from one of more of Fe or an alloy of Fe/Co for use in the magnetic nanoparticle hyperthermia (MNH) treatment of tumours.

12. A method according to any one of claims 7 to10 or a powder according to claim 11, wherein the nanoparticles are around 15nm in size.

13. A method according to any one of claims 7 to 12 or a powder according to claim 11, wherein each magnetic nanoparticle comprises a magnetic core selected from one of more of Fe or an alloy of Fe/Co encased in a biocompatible shell.

Fig. 1(b)

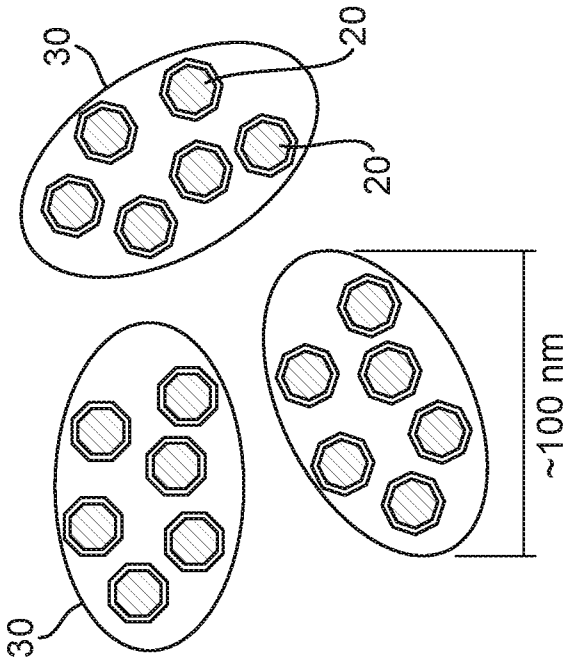
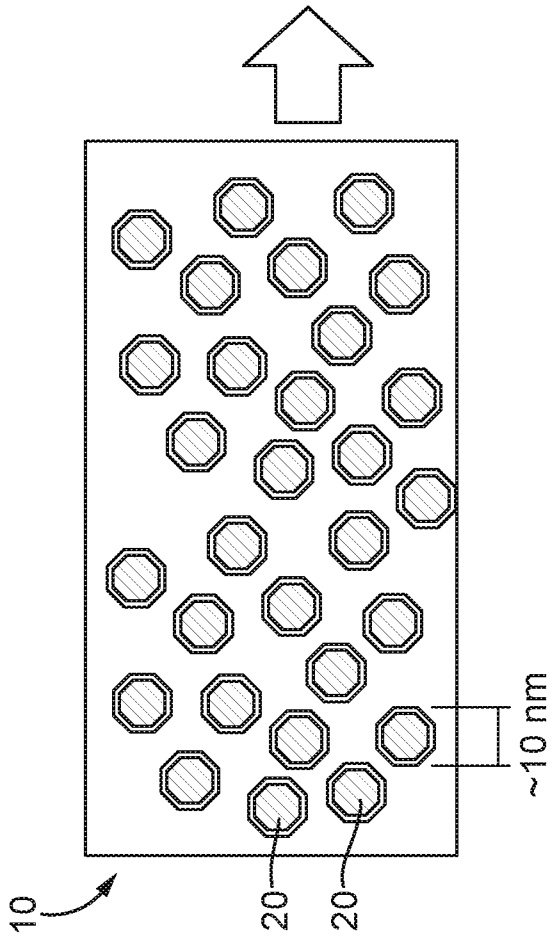


Fig. 1(a)



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/052105

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K41/00 A61K9/50 B82Y5/00
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)
A61K 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, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/064921 A1 (SIRTEX MEDICAL LTD [AU]; JONES STEPHEN KEITH [AU]; RUTHERFORD KATRINA) 5 August 2004 (2004-08-05)	1-6,9, 11-13
Y	page 9, line 24 - line 26; claims 9-11; examples 2,3	7,8,10

X	WO 2015/070036 A1 (UNIV JOHNS HOPKINS [US]) 14 May 2015 (2015-05-14)	1-6,9, 11-13
Y	claims; figures 1,8	7,8,10

X	WO 2015/176025 A1 (METHODIST HOSPITAL [US]) 19 November 2015 (2015-11-19)	1-6,9, 11-13
Y	paragraph [0114] - paragraph [0117]; claims 1,5,16; figures 7A, 7B, 22B-F paragraph [0137] - paragraph [0138] paragraph [0178]	7,8,10

	-/--	

[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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 2017	23/10/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bayrak, Sinasi

2

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.
X	US 2012/003321 A1 (PENG MINGLI [CN] ET AL) 5 January 2012 (2012-01-05) figure 1; examples	1-6
X	EP 0 000 667 A1 (UNIV NORTHWESTERN [US]) 7 February 1979 (1979-02-07) page 18, line 7 - line 10; claims; example 3	1-6,9, 11-13
X	WO 2009/002569 A2 (UNIV CALIFORNIA [US]; GUO ZHANHU [US]; PARK SUNG [US]; HAHN THOMAS H [] 31 December 2008 (2008-12-31)	1-6,9, 11-13
Y	claim 22	7,8,10
X	WO 2004/032155 A1 (NANOMAGNETICS LTD [GB]; MAYES ERIC L [GB]; WARNE BARNABY [GB]; WONG KI) 15 April 2004 (2004-04-15)	1-6,9
Y	paragraph [0004] - paragraph [0007]; claims; examples 3,4	7,8,10
X	B. OPREA ET AL: "Dispersion and Functionalization of Nanoparticles Synthesized by Gas Aggregation Source: Opening New Routes Toward the Fabrication of Nanoparticles for Biomedicine", LANGMUIR, vol. 31, no. 51, 29 December 2015 (2015-12-29), pages 13813-13820, XP055413382, US ISSN: 0743-7463, DOI: 10.1021/acs.langmuir.5b03399	1-10
Y	*see "Experimental Procedure"*; page 13814; figure 1	7,8,10

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2017/052105

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004064921 A1	05-08-2004	AT 535280 T	15-12-2011
		AU 2004206770 A1	05-08-2004
		EP 1594571 A1	16-11-2005
		ES 2378365 T3	11-04-2012
		US 2006147381 A1	06-07-2006
		US 2014249351 A1	04-09-2014
		WO 2004064921 A1	05-08-2004
WO 2015070036 A1	14-05-2015	US 2016271274 A1	22-09-2016
		WO 2015070036 A1	14-05-2015
WO 2015176025 A1	19-11-2015	NONE	
US 2012003321 A1	05-01-2012	CN 101759882 A	30-06-2010
		US 2012003321 A1	05-01-2012
		WO 2010072018 A1	01-07-2010
EP 0000667 A1	07-02-1979	CA 1109792 A	29-09-1981
		DE 2862289 D1	11-08-1983
		EP 0000667 A1	07-02-1979
		IE 47305 B1	22-02-1984
		IT 1097568 B	31-08-1985
		JP S5464626 A	24-05-1979
		JP S5649889 B2	25-11-1981
		US 4357259 A	02-11-1982
WO 2009002569 A2	31-12-2008	NONE	
WO 2004032155 A1	15-04-2004	AU 2003299161 A1	23-04-2004
		BR 0314530 A	26-07-2005
		CA 2499461 A1	15-04-2004
		CN 1703763 A	30-11-2005
		EP 1550141 A1	06-07-2005
		GB 2393728 A	07-04-2004
		JP 2006501662 A	12-01-2006
		KR 20050073470 A	13-07-2005
		MX PA05003523 A	03-06-2005
		US 2006177879 A1	10-08-2006
		WO 2004032155 A1	15-04-2004