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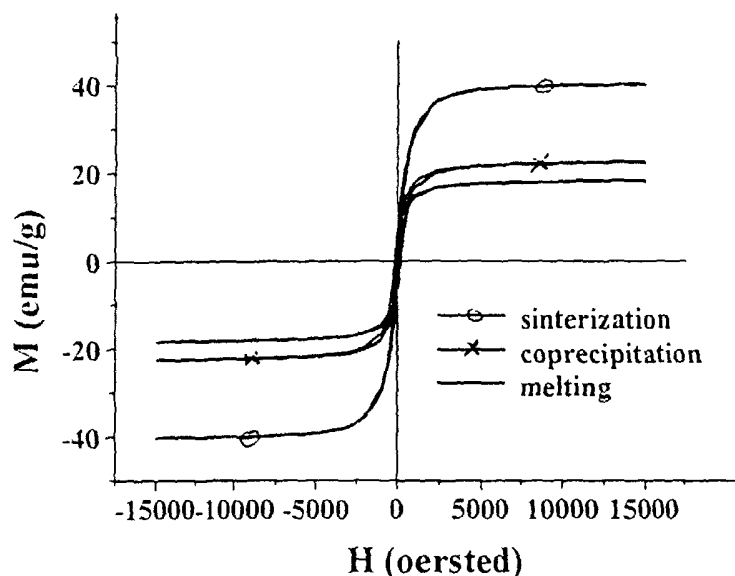
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(54) Title: BIOCOMPATIBLE MAGNETIC MATERIALS FOR THE TREATMENT OF CANCER BY MEANS OF HYPER-
THERMIA, AND PROCESSES FOR THEIR PRODUCTION



(57) Abstract: The present invention relates to the production of biocompatible magnetic materials for cancer therapy by means of hyperthermia. These materials are constituted by a biocompatible vitreous matrix in which there is dispersed a magnetic crystalline phase. The magnetic materials of the invention may be obtained with three different methodologies: coprecipitation, melting, and sintering.



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Biocompatible magnetic materials for the treatment of cancer by means of hyperthermia, and processes for their production

DESCRIPTION

The present invention relates to the development of biocompatible magnetic materials suitable for the treatment of tumoural forms by means of hyperthermia, as well as to the corresponding methods of preparation.

Notoriously, cancer cells are particularly sensitive to heat. It has in fact been verified that when they are heated to a temperature higher than 42.5°C their structure is seriously damaged or destroyed.

This phenomenon is exploited in modern therapeutic techniques to obtain a localized hypothermia on diseased organs of the human body and to bring about selective destruction of cancer cells and neoplastic tissues.

Notoriously, the heating of biological tissues can be obtained using different modalities of generation and transmission of heat.

In techniques of hyperthermia therapy, recourse is had to three types of localized heating: the first

envisages indirect heating of the tissues by setting them in contact with a liquid brought up to an appropriate temperature, the second envisages direct heating of the tissues as a result of electrical currents, whilst the third type exploits indirect heating of the tissues using implantable magnetic elements and applying a variable magnetic field.

The therapeutic methodologies that have gained most ground in the medical sector envisage the implantation or localized application of ferromagnetic materials or devices in the form of rods, needles, granules, or powders, and their heating by means of magnetic fields. It is in fact found that, with the introduction of small magnetic bodies at the level of the tissues affected by neoplastic forms, it is possible to obtain a localized heating of the diseased tissues by application of appropriate magnetic fields. Generally, for these therapeutic applications metals, (Fe-Co-Ni-based) metal alloys, metal oxides, such as Fe_2O_3 and Fe_3O_4 , and ferrites are used.

There is likewise known a therapeutic technique that envisages the implantation of filaments of ferromagnetic alloys and their exposure to an external oscillating magnetic field of pre-set frequency and intensity so as to induce heating thereof.

The ferromagnetic alloys used in these applications are Fe-Co-Ni-based, Ni-Pd-based, and Fe-Pd-based ones.

It is, however, found that these metal materials, once implanted directly in the tissues of the human body, have an undesirable high thermal conductivity that damages the healthy tissues surrounding the implantation area. Furthermore, the reactivity of these magnetic materials leads to the release in biological fluids of metal ions that are toxic for the organism.

In order to attempt to overcome the above drawbacks, materials susceptible to magnetic fields have been developed, in which the ferromagnetic phases have been incorporated in inert matrices, such as glasses and pyroceram.

However, it is found that the aforesaid inert matrices do not have an adequate affinity and biocompatibility with the tissues of the human organism and are thus perceived as foreign bodies.

In addition, it is found that the use of inert matrices with reduced biocompatibility frequently determines the onset of phenomena of local sensitization and the possible development of serious side effects that can occur also immediately after

their implantation in the organism.

There are moreover known materials that contain a magnetic phase inserted in components compatible with the human organism, such as proteins, certain polymers, and biocompatible pyroceram materials. The latter contain, in addition to the ferromagnetic phase, other non-magnetic crystalline phases.

It is, however, found that these materials of more recent production require the use of very intense variable magnetic fields, which are difficult to obtain within hospital structures.

At the current state of the art, there is hence felt the need to have available new biologically compatible magnetic materials that will be readily usable within hospital structures.

One of the general purposes of the present invention consists then in providing a magnetic material for cancer therapy by means of hyperthermia that has a high biocompatibility with the tissues of the human organism and an adequate susceptibility to magnetic fields.

A further purpose of the invention consists in providing methods for making magnetic materials, suitable for thermal treatment of tumoural forms, which are also readily obtainable and do not entail

high production costs.

Yet another purpose of the present invention consists in providing a biocompatible magnetic material suitable for the treatment of cancer by means of hyperthermia that is obtainable by three modes of production.

In the light of these purposes and of still others, which will emerge more evidently hereinafter, there is provided, according to a first aspect of the present invention, a biocompatible magnetic material for the treatment of cancer by means of hyperthermia consisting of a magnetic crystalline phase and a biocompatible matrix in which said biocompatible matrix is a bioactive glass.

Conveniently, in the material of the invention the magnetic crystalline phase is incorporated in the biologically compatible vitreous matrix so that, when the material is implanted and subjected to the action of magnetic fields toxic ions are not released into the organism.

The ferromagnetic phase used in the context of the invention comprises all the materials that undergo heating when they are subjected to the action of a magnetic field, such as, for example, ferromagnetic, ferrimagnetic and/or superparamagnetic materials.

Magnetic materials that are particularly suitable for the purpose according to the present invention are chosen from among ferrites. A typical example of a particularly suitable ferrite is magnetite ($\text{FeO} \cdot \text{Fe}_2\text{O}_3$).

The crystalline ferromagnetic phase, responsible for heating of the material of the invention when subjected to the influence of a magnetic field, is to advantage present in an amount of not less than 30 wt% with respect to the overall weight of the material of the invention.

The ferromagnetic phase incorporated within a biologically compatible vitreous matrix, when inserted in the human body, is not perceived as a foreign body and does not substantially have any side effects.

As biologically compatible vitreous matrix bioactive glasses are used. The term "glass" defines a material obtained through thermal treatment at high temperature of mixtures of oxides up to melting. The molten material, during its subsequent cooling, passes to the solid state without crystallizing, maintaining an amorphous (i.e., disorderly, non-crystalline) structure typical of a liquid. Through subsequent thermal treatments of nucleation and growth, or else by observing appropriate conditions of cooling of the liquid, it is possible to obtain a pyroceram material,

i.e., one in which the formation of crystals of appropriate composition and dimensions, incorporated in the residual amorphous matrix, is induced.

By "biocompatibility" is meant the capacity of a material to stimulate, once implanted, a specific response on the part of the organism that hosts it, without triggering any adverse reactions. In the case of a bioactive glass this response consists in favouring the growth of healthy tissue on its surface.

The biocompatible magnetic material that forms the subject of the present invention may be obtained in different forms: massive objects, granules and/or powders with dimensions comprised between a few micron up to a few centimetres, according to the applications envisaged.

The biocompatible magnetic material that forms the subject of this invention can be applied in a living organism by means of implantation techniques or by means of local application. The high affinity of the vitreous matrix with the tissues of the human organism prevents the onset of side effects and allergic reactions.

The biocompatible magnetic material of the invention is suitable in localized treatment by means of hyperthermia and in particular in the selective

treatment of tumoural forms, including ones located in internal organs or tissues of the human body.

The biocompatible magnetic material of the invention is obtainable by alternative methods of production, which comprise coprecipitation, melting, and sintering of the starting compounds.

According to one of the embodiments, there is described a method for obtaining the biocompatible magnetic materials of the invention that comprises the coprecipitation of the precursor reagents of the oxides that form pyroceram. The reagents in question are water-soluble salts. Preferably, soluble salts of inorganic acids are used, such as, for example, sulphates, chlorides, nitrates, carbonates, and phosphates that precipitate in a basic medium. According to this embodiment, the components are mixed at a colloidal or molecular level.

Coprecipitation occurs in a basic medium, i.e., a solution of a base suitable for converting the metal salt into an oxide. Appropriate bases are preferably inorganic hydroxides, such as sodium hydroxide, lithium hydroxide, ammonium hydroxide, and mixtures thereof. The salts are solubilized in cold or hot water.

Conveniently, in the initial step the aqueous

solutions of the reagent salts are mixed, after which the base is added so as to obtain a precipitate, which is washed with distilled water, filtered, and preferably dried in a stove at a temperature of 150-200°C. The dry powder obtained is preferably ground and treated thermally at a temperature at which it decomposes, typically in the range between 600°C and 900°C.

In the final step, the decomposed powder is subjected to thermal treatment at the melting point of the material obtained.

Typically, a temperature higher than 1400°C is used, conveniently in the range between 1400°C and 1600°C, so that the pyroceram material obtained will contain basically only the magnetic phase. The magnetic phase is formed during cooling.

According to another embodiment, the biocompatible magnetic material of the invention is obtained by means of melting of the reagents constituted by a mixture of insoluble powders of metal salts or oxides. The temperature required for melting of the reagents is higher than the temperature required in the process of coprecipitation since the precursors, being in a solid form, have a lower chemical homogeneity. Generally the melting

temperatures required are higher than 1500°C, and typically are in the range between 1550°C and 1600°C.

According to another embodiment, the biocompatible magnetic material of the invention is obtained by means of sintering of the matrix in bioactive glass with the magnetic crystalline phase.

The bioactive vitreous matrix and the magnetic crystalline phase can be prepared separately. The vitreous matrix can be obtained with the methods for obtaining glasses, or alternatively a commercially available glass is used. The magnetic crystalline phase may be obtained by conventional chemical reactions, or alternatively a commercially available product is used.

Conveniently, the bioactive vitreous phase and the magnetic crystalline phase are first mixed, pressed, and then treated thermally at a sintering temperature, preferably in the range between 900°C and 1000°C. Finally, a sintered composite material is obtained, which incorporates the magnetic phase in the bioactive vitreous matrix.

The following examples are provided purely by way of illustration of the present invention and are not to be understood as in any sense limiting the sphere of protection thereof, as defined in the annexed

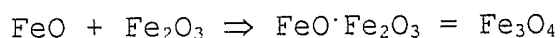
claims.

Example 1

This example illustrates the preparation of a pyroceram material containing magnetite, according to the invention, by means of a process of coprecipitation.

The oxide composition used for making the pyroceram was the following: 13.5 wt% Na₂O, 13.5 wt% CaO, 24.5 wt% SiO₂, 3.3 wt% P₂O₅, 14 wt% FeO, 31 wt% Fe₂O₃.

The amount of FeO and Fe₂O₃ was calculated to form 45 wt% of magnetite, in accordance with the chemical reaction (molar ratio between FeO and Fe₂O₃ = 1):



The reagents used were water-soluble salts: NaNO₃, Ca(NO₃)₂·4H₂O, colloidal SiO₂, (NH₄)₂HPO₄, FeSO₄·7H₂O, Fe(NH₄)(SO₄)₂·12H₂O.

The stoichiometric amounts for forming the oxides of these salts were solubilized separately in water (with the exception of the colloidal SiO₂, which is already an aqueous solution) using a magnetic stirrer on a hot plate.

The various aqueous solutions were then mixed under magnetic stirring. Finally, ammonium hydroxide was

added, until an abundant precipitate was formed. The precipitate was washed repeatedly with distilled water, filtered, and dried in a stove at a temperature of 200°C. The dried powder was ground, after which it underwent thermal treatment at 900°C for 3 hours. During thermal treatment, the mixed salts were decomposed with the development of NO_x-based, SO_x-based, CO₂-based, and NH₃-based vapours. The powder obtained after the thermal treatment was melted in a platinum crucible at 1500°C for 30 minutes, and the product was poured onto a copper plate at room temperature.

In this way a pyroceram was obtained which contained only the magnetite crystals in a biocompatible and bioactive vitreous matrix; there was hence no need for any subsequent thermal treatment of nucleation and growth.

Example 2

This example illustrates the preparation of a pyroceram material containing magnetite, according to the invention, by means of a process of melting.

The oxide composition of the pyroceram used was the one given in Example 1.

The reagents used were Na₂CO₃, CaCO₃, SiO₂, CaHPO₄·2H₂O, Fe₂O₃, FeSO₄·7H₂O.

These reagents were mixed in stoichiometric amounts corresponding to the oxide composition and were melted in a platinum crucible at 1550°C. After 30 minutes of maintenance at the melting temperature, the liquid (molten glass) was poured onto a copper plate at room temperature. There was thus obtained a pyroceram that contained only the magnetite crystals in a biocompatible and bioactive vitreous matrix.

The method of the invention renders superfluous any subsequent thermal treatment of nucleation and growth.

Example 3

This example illustrates the preparation of a pyroceram material containing magnetite, according to the invention, by means of the sintering process.

The sintered material contained a vitreous matrix and the dispersed magnetite phase (45 wt%). The oxide composition of the commercial glass used was the following: 24.5 wt% Na₂O, 24.5 wt% CaO, 45 wt% SiO₂, 6 wt% P₂O₅.

The bioactive and biocompatible glass was obtained using the melting method.

The reagents Na₂CO₃, CaCO₃, SiO₂, and Ca₃(PO₄)₂ were mixed and melted at a temperature of 1500°C for 30 minutes. The liquid was poured at room temperature onto a copper plate to obtain a glass. The glass thus

obtained was ground and sieved to obtain powders with different grain size: one part below 38 μm and a second part between 38 μm and 106 μm . There were mixed together the fraction with a grain size between 38 μm and 106 μm in a proportion of 45 wt%, the fraction with a grain size below 38 μm in a proportion of 10 wt%, and the magnetite with a grain size of 5 μm (Aldrich) in a proportion of 45 wt%.

After mixing, the powders were pressed into the form of disks (30 mm in diameter) using a uniaxial cold press and applying a force of 8 tonnes for 5 seconds. The disks were sintered at a temperature of 900°C for 1 hour in an inert atmosphere (argon). The resulting material was a pyroceram containing magnetite crystals englobed in a vitreous phase.

Example 4

Hysteresis cycles were performed for the materials obtained in the foregoing examples (1-3) using a vibration magnetometer. The magnetic field used was 15 koersted.

The attached Figure 1 is a graphic representation of the results obtained. The magnetic characteristics of the pyrocerams illustrated in Figure 1 are given in Table 1:

Table 1

Technique of preparation	Coercive field H_c (oersted)	Resonance magnetization M_r (emu/g)
Coprecipitation	165	3100
Melting	150	1800
Sintering	80	2000

Illustrated in the attached Figure 2 is a graph that gives on the abscissa the time and on the ordinate the temperature values for a specimen prepared as described in Example 1 by a process of coprecipitation and after application of a very strong variable magnetic field (450 kHz, 1 kW). The power supplied was 40-50 W/g.

By adjusting the frequency and the intensity of the magnetic field applied it is possible to adjust the temperature of heating of the material of the invention so as to reach the optimal temperature for destruction of cancer tissues, which may conveniently be set approximately in the 41-46°C range or higher according to the applications.

Example 5

Given in this example are the general properties of

magnetite.

Thermal conductivity	$1.5 \times 10^{-2} \text{ cal} \cdot \text{sec}^{-1} \cdot \text{cm}^{-1} \cdot \text{deg}^{-1}$
Specific heat	$0.2 \text{ cal} \cdot \text{g}^{-1} \cdot \text{deg}^{-1}$
Electrical conductivity	$250 \text{ } \Omega^{-1} \cdot \text{cm}^{-1}$
Young's modulus	$10^{12} \text{ dyne/cm}^2$
Curie temperature	$585 \text{ } ^\circ\text{C}$
Saturation of magnetization	471 Gauss
Initial permeability (single crystal)	100
Magnetostriction at saturation (polycrystalline)	35×10^{-6}
Anisotropic constant (first order)	$(-1.1 \pm 0.08) \times 10^5 \text{ erg/cm}^3$

CLAIMS

1. A biocompatible magnetic material for the thermal treatment of neoplasms comprising a magnetic crystalline phase and a biocompatible matrix in which said biocompatible matrix is a bioactive glass.

2. The biocompatible magnetic material according to Claim 1, in which said magnetic crystalline phase is dispersed in said biocompatible matrix.

3. The biocompatible magnetic material according to Claim 1 or Claim 2, in which said magnetic crystalline phase is a magnetic material chosen from among ferrites.

4. The biocompatible magnetic material according to any one of Claims 1-3, in which said magnetic crystalline phase is magnetite.

5. The biocompatible magnetic material according to any one of Claims 1-4, in which said magnetic crystalline phase is present in an amount of not less than 30 wt%.

6. A process for producing a biocompatible magnetic material according to Claim 1, comprising melting of a mixture of Na_2CO_3 , CaCO_3 , SiO_2 , $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$, Fe_2O_3 , and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, and subsequent cooling thereof.

7. The process according to Claim 6, in which melting of the reagents occurs at a temperature of between 1500°C and 1600°C.

8. The process according to Claim 7, in which said reagents are kept at the melting temperature for a period of at least 30 minutes.

9. The process for making a biocompatible magnetic material according to Claim 1, comprising the mixing of a vitreous phase and a magnetic crystalline phase, and the sintering of the mixture in an inert or reducing atmosphere.

10. The process according to Claim 9, in which the step of sintering occurs at a temperature of between 900°C and 1000°C.

11. The process according to Claim 9 or 10, in which said crystalline and vitreous phases are pressed prior to being subjected to sintering.

12. The process for the production of a biocompatible magnetic material according to Claim 1, comprising the coprecipitation of water-soluble salts of Na, Ca, P, Fe and of colloidal SiO₂ in a basic solution and the thermal treatment of the powder thus obtained.

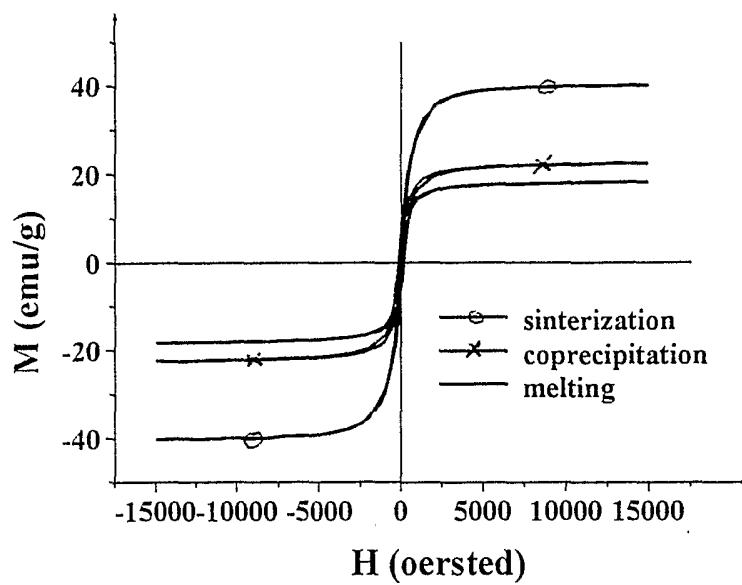
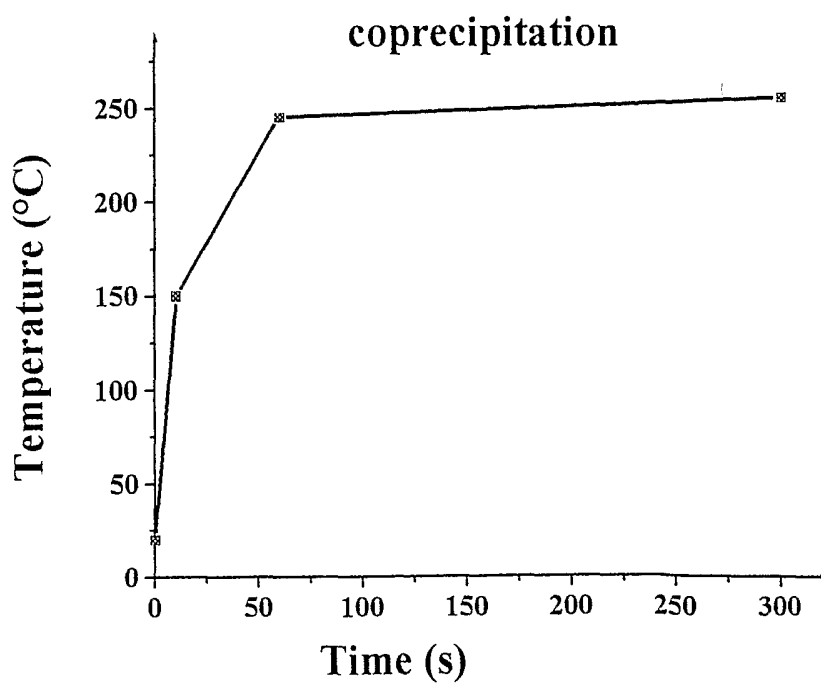
13. The process according to Claim 12, in which the water-soluble salts are NaNO₃, Ca(NO₃)₂ · 4H₂O,

$(\text{NH}_4)_2\text{HPO}_4$, $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, and $\text{Fe}(\text{NH}_4)(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$.

14. The process according to Claim 12 or Claim 13, in which said basic solution is an aqueous solution chosen from among sodium hydroxide, lithium hydroxide, ammonium hydroxide, and mixtures thereof.

15. The process according to any one of Claims 12 to 14, in which subsequently the dry precipitate obtained from the coprecipitation step is ground and subjected to a thermal treatment to decompose the components of the precipitate and then to subsequent melting.

16. The process according to any one of Claims 12 to 15, in which the melting temperature is in the range between 1400°C and 1600°C .

**Fig. 1****Fig. 2**