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A MAGNETIC FIELD CONTROLLABLE IMPLANTABLE DEVICE AND A METHOD OF CONTROLLED DRUG RELEASE THEREFROM

Field of the Invention

The invention relates to medicine, pharmacology and biotechnology, specifically, the invention relates to on-demand drug delivery systems which are implantable or deployable in the body of a patient, and more specifically, to magnetic field controllable implantable devices.

Background of the Invention

Implants are medical devices manufactured to replace a missing biological structure, support a damaged biological structure, or enhance an existing biological structure. The surface of implants that contact the body might be made of a biomedical material to provide better compatibility with tissues. In some cases implants contain electronics e.g. artificial pacemaker and cochlear implants. Some implants are bioactive, such as subcutaneous drug delivery devices in the form of implantable pills or drug-eluting stents.

Recent developments in implantation technologies lead to substantial progress in medicine and the number of implants-related surgeries is constantly growing. Implants with magnetic elements start playing an important role. Such implants include magnetic implants functioning as magnetic field concentrators for targeted drug delivery, used in conjunction with magnetic nanoparticles administered intravenously (*Zachary G. Forbes et al, Validation of high gradient magnetic field based drug delivery to magnetizable implants under flow, IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING , v. 55, Issue: 2 P. 643-649*), dental magnetic attachments (Dental Magnetic Attachments http://www.aichi-steel.co.jp/ENGLISH/pro_info/pro_intro/elect_1.html), multifunctional ear implants based on permanent magnets (*Bulletin of the Magnetic Society, Vol.14(3), p. 7 (2014)*), and some others.

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Further examples include a biodegradable device that could provide multi-dose drug delivery, described in *Grayson ACR, Choi IS, Tyler BM, et al. Multi-pulse drug delivery from a resorbable polymeric microchip device. Nat Mater. 2003; 2(11):767–772.* The device comprises biodegradable polymeric microchips having reservoirs that could each be filled with a different drug. In another approach (*Yang R, Gorelov A V, Aldabbagh F, Carroll WM, Rochev Y. An implantable thermoresponsive drug delivery system based on Peltier device. International journal of pharmaceutics. 2013;447(1-2):109–14*) a Peltier electronic element was incorporated with a thermoresponsive thin film based drug delivery system to form a new drug delivery device which can regulate the release of a drug in a water environment. The pulsatile on-demand release profile of the model drug was obtained by turning the current signal on and off. However, implantation of microchips having the size of several centimetres, required in these approaches, is not always possible leading to limited applicability of such drug-delivery systems.

More technologically advanced are implants coated with composites of thermally sensitive hydrogels and optically active nanoparticles that are heated externally, for example, by near-infrared light inducing plasma resonance in the nanoparticles, see *Sershen SR, Westcott SL, Halas NJ, West JL. Temperature-sensitive polymer–nanoshell composites for photothermally modulated drug delivery. Journal of Biomedical Materials Research. 2000; 51(3):293–298.* However, this approach is difficult to implement in practice because biological tissues are not completely transparent even for infrared and microwave radiation.

Patent publications US 2002/0128704, US 2005/0278014 disclose a method for controlling the activity of drugs on or in drug-coated or drug-loaded implantable devices such as stents and other metallic devices. In this method, heating of a device, such as stent, can be used to release drugs applied to the stent in release layers, to activate drugs on the stent that have little or no activity at body temperature and to enhance for defined periods the reaction environment at the stent for drug-adjacent tissue interactions. A drug can be released from a heat sensitive release material within the stent or the surface of the stent. Heat is supplied by exposing the stent having adequate magnetic permeability to an electromagnetic field, preferably below 1MHz. The authors discuss that the inductive heating is supposed to be non-

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invasive and precisely controlled. However, the heat generation during inductive heating is difficult to control, because it depends on many parameters, including the material of the stent and its location within the body. Therefore, there is an inherent danger of overheating the tissue that surrounds the implant or of insufficient heating resulting in ineffective treatment. Because of inductive heating, only materials having adequate magnetic permeability can be used, such as metals. Accordingly, the use of biodegradable or plastic implants is excluded.

According to another approach, US 6,544,163 discloses an apparatus and method for controlling a magnetically controllable embolic in the embolization of an aneurysm. The magnetic embolization apparatus includes a catheter having a distal portion adapted for insertion within an aneurysm of a blood vessel, a permanent magnet carried by the distal portion of the catheter to internally induce a magnetic field from within the aneurysm to control a magnetic field controllable embolic to embolize the aneurysm, and an electromagnet carried by the distal portion of the catheter to internally induce a magnetic field to control delivery of the magnetic field controllable embolic. The method includes delivering a magnetic-field controllable embolic into an aneurysm, inducing a magnetic field in the aneurysm to control the magnetic-field controllable embolic to embolize the aneurysm with the permanent magnet of the catheter, and controlling the delivery of the magnetic-field controllable embolic into the aneurysm with an electromagnet. However, this approach requires delivering a permanent magnet and an electromagnet in the catheter that is extremely inconvenient in many delicate surgery operations.

International publication WO 2005/042142 discloses biocompatible, thermosensitive polymer carriers that can be heated, with the aid of a high-frequency magnetic alternating field, by encapsulating magnetic and/or metallic colloids or magnetic nanoparticles. As a result of the inductive heating of the polymer matrix, physical structure changes are triggered in the polymer matrix that lead to the bioactive substances encapsulated in the matrix being released within a short period of time. The carriers charged with the corresponding active agent that are produced in this way can be applied to the desired physiological or bio-analytical sites of action with the aid of known administration methods such as injection, implantation, infiltration, diffusion, streaming or biopsy. The local application of the magnetic

particles can be further intensified by positioning the particles exactly at the desired spots using electro- or strong permanent magnets that are placed over the target area or site of action from the outside. Once the polymer particles have reached their site of action they can be heated up to above body temperature by applying a high-frequency magnetic alternating field, resulting in a change in the physical structure of the polymer matrix. The change in the physical structure triggers a concentrated and quick release of the encapsulated active agents from the matrix. However, in order to heat the aforementioned magnetic and/or metallic substances up to the relevant temperatures, a special design of the magnetic field is required with respect to the magnetic field strength and frequency. The polymer particles may undesirably diffuse from the application site and application of these particles to some locations, such as blood vessel walls, can be difficult. Additionally, as the typical release time of a drug, according to this method is short, about 5 minutes, it is inappropriate when a prolonged drug release is needed.

Therefore, there is need for improved implantable devices capable of selectively and safely releasing drugs in controlled manner at the site of interest.

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Brief Summary of the Invention

It is the objective of the present invention to provide a magnetic field controllable implantable device capable of incorporating and selectively releasing drugs on demand at the site of interest.

In particular, the object of the invention is to provide an improved magnetic field controllable implantable device that would be capable of retaining active substance during installation of the device such that the active substance is not lost during the installation, whilst, when it is required, providing pulsed and/or pulsatile release of the active substance, at the same time, avoiding and/or preventing overheating or insufficient heating of the device.

The technical objective stated above has been accomplished by providing a magnetic field controllable implantable device comprising a device body having an outer periphery, and a coating covering at least part of the outer periphery of the device body and comprising the following layers in the order from the inside to the outside:

- a first insulating layer;

- a layer of magnetic material having positive or negative magnetocaloric effect of at least 3 K/T;

- a layer of a sensitive material comprising active substance and capable of controlling a retention/release rate of the active substance;

- a second insulating layer permeable for the active substance and/or having a plurality of pores.

In accordance with an embodiment of the present disclosure the first insulating layer is selected from a heat insulating layer, an infrared radiation reflecting layer, or a combination thereof.

Preferably, the first insulating layer is adjacent to the outer periphery of the device body, however, if appropriate, additional layers can be applied on the outer periphery of the device body under the first insulating layer, or over the first insulating layer.

In accordance with an embodiment of the present disclosure the second insulating layer is porous and/or active substance-permeable, i.e. comprises a plurality of pores to provide permeability for releasing the active substance when subjected to certain conditions. The second insulating layer is selected from a porous heat insulating layer, a porous infrared radiation reflecting layer, or a combination thereof.

In accordance with an embodiment of the present disclosure a heat insulating layer is comprised of polystyrene, silica gel, polyurethane, bioceramics, or any combination thereof.

In accordance with an embodiment of the present disclosure an infrared radiation reflecting layer is comprised of a metal or a metallic alloy, preferably nickel-free stainless steel, titanium-based alloys, or tantalum.

In accordance with an embodiment of the present disclosure a magnetic material is selected from the group comprising rare earth metals, such as gadolinium, terbium, dysprosium, holmium, transient metals, such as iron, nickel, cobalt, magnesium, noble metals,

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such as rodium, palladium; their oxides, compositions, combinations, solid dispersions, and alloys, such as Gd_5Si_4, $Gd_5Si_{2,06}Ge_{1,94}$, Gd_7Pd_3, $MnFeP_{0,35}As_{0,65}$, $Fe_{0.5}Rh_{0.5}$, Ni-Mn-Ga, and MnAs.

In some embodiments, a magnetic material has positive or negative magnetocaloric effect of at least 0.5 K/T, at least 1 K/T, at least 1.5 K/T, at least 2 K/T, at least 2.5 K/T, at least 3 K/T, at least 3.5 K/T, at least 4 K/T, at least 4.5 K/T, at least 5 K/T, at least 5.5 K/T, at least 6 K/T, at least 6.5 K/T, at least 7 K/T, at least 7.5 K/T, at least 8 K/T.

In accordance with an embodiment of the present disclosure, a layer of sensitive material comprises at least one material selected from polymers, copolymers, hydrogels, biopolymers, or any combination thereof.

In accordance with an embodiment of the present disclosure, a layer of sensitive material comprises:

- a mixture of two or more different polymers; or/and
- two or more layers of different polymers; or/and
- two or more patches of different polymers.

In accordance with an embodiment of the present disclosure, at least one, preferably two or more, of polymers are heat-sensitive polymers with a phase transition temperature near the body temperature.

In accordance with an embodiment of the present disclosure, different heat-sensitive polymers have different phase transition temperatures.

In accordance with an embodiment of the present disclosure, a heat-sensitive polymer is selected from a group comprising polybutyl methacrylate (pBMA), polyN-isopropylacrylamide (PNIPAM), copolymerized N-isopropyl-acrylamide (NIPAM) with N-isopropylmethacrylamide (NIPMAM) and acrylamide (AAm) and/or any combination thereof.

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Polymer layer with multiple polymers allows multiple triggering of the thermosensitive polymers at different temperatures as well as provides thermal insulation for the device so that the increased or decreased temperature can be maintained longer without heat exchange with the surrounding tissues.

In accordance with an embodiment of the present disclosure, at least one, preferably two or more, of the sensitive polymers are deformation-sensitive polymers with low yield stress, in particular, poly(lactic-co-glycolic) acid.

In accordance with an embodiment of the present disclosure, the layer of sensitive material further comprises contrasting agents that allow controlling the degree of the drug release from the polymer using magnetic resonance imaging.

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In accordance with an embodiment of the present disclosure, a porous/permeable polymer layer has pores allowing interstitial fluid and blood plasma to pass through thereby allowing release of the active substance.

In accordance with an embodiment of the present disclosure, an implantable device is a stent, a catheter, a prosthesis of joints or bones, a pin or a screw for osteosynthesis, a denture, a pacemaker, an insulin pump, a silicone implant, a neural implant, a brain chip, a cochlear implant, or a dental implant.

In accordance with another aspect of the present invention, a method of controlled drug release is provided, the method comprising the steps of: implanting a magnetic field controllable implantable device into a patient body; and subjecting the implanted device to magnetic field in a controlled manner to release the active substance.

In accordance with an embodiment of the present disclosure, the magnetic field is alternating magnetic field created by an external source and having the frequency between about 1 kHz and about 100 kHz.

In accordance with an embodiment of the present disclosure, the magnetic field is constant magnetic field applied periodically and created by an external source.

A magnetic field controllable implantable device disclosed herein provides several technical effects and has surprising advantages over the devices known in the prior art.

In particular, it was surprisingly found by the inventors that the magnetic field controllable implantable device disclosed herein provides retention of the active substance during installation of the device in a patient's body and preserves the active substance therein until the intended release time. The prior art drug-bearing implantable devices usually loose up to 85-90% of the drug due to leakage during installation and only 10-15% of the drug is retained until the intended release time.

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Further, surprisingly, it was found by the inventors when making research that the device according to the invention is capable of providing pulsed and/or pulsatile release of the active substance. Such capability is very important because pulsed delivery of a drug often mimics the functioning of the living systems and minimizes undesired side effects and, therefore, provides optimal therapeutic effect of the drug.

Additionally, in practice, during functioning, a magnetic field controllable device according to the invention, comprising a device body and a coating having insulating layers, which are adjacent to a layer of magnetic material having positive or negative magnetocaloric effect of at least 3 K/T, provides self-regulating the temperature of the disclosed device close to the temperature of a subject or patient body. This is attained by choosing a magnetic material having the phase transition temperature close to the body temperature. As a result, overheating or insufficient heating of the implantable device inherent to known implants is avoided. This result is achieved without using invasive temperature sensors.

Thus, the disclosed device according to the invention has a number of advantages as described above. Therefore, it can advantageously be used in wide variety of applications involving implantable devices. In particular, the implantable device can be used as a stent, a

catheter, prosthesis of joints or bones, a pin or a screw for osteosynthesis, a denture, a pacemaker, an insulin pump, a silicone implant, a neural implant, a brain chip, a cochlear implant, or a dental implant.

Additionally, the disclosed device can be used in applications involving manipulation of complex bio-medical systems and processes by external magnetic field, in particular, the magnetic field controllable implantable device can be used, for example, for controlling hormone discharge and controlling other devices implanted in a body such as microrobots, sensors, etc.

Advantageously, since magnetic field used to control the device described herein does not interfere with body tissues, the inventive device does not have side effects inherent to infrared and microwave radiation controllable devices of the prior art.

An implantable device described herein can also be refilled *in situ* by introducing intravenously magnetic nanoparticles with active substance. Once these magnetic nanoparticles carrying the active substance pass through the blood vessels system and are collected on the device, the device is supplemented with fresh portions of active substance.

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Detailed Description of the Invention

Each interval disclosed in this application is understood as a set of all numbers belonging to this interval. Therefore, each interval includes all and each value belonging to this interval, as well as any of its subintervals. If not indicated otherwise, the boundary points of an interval are assumed to be part of the interval. For example, if the interval [0; 1] is disclosed then it is understood that each number, for example, 0.76 and 0.1, within this interval is also part of the disclosure. Likewise, by disclosing the interval [0; 1] it is assumed that all and each of its subintervals, for example, [0.2; 0.3] and [0.23; 0.7], are also part of the disclosure.

For the purpose of this application the term "magnetic field controllable implantable device" is a device or an apparatus that can be delivered to a patient's body and then activated by applying magnetic field.

The device body has shape and functionality that is appropriate for the intended treatment and location in the patient's body.

In accordance with an embodiment to the present disclosure, the device body can be manufactured in the form of a stent, a catheter, a prosthesis of joints or bones, a pin or a screw for osteosynthesis, a denture, a pacemaker, an insulin pump, a silicone implant, a neural implant, or a brain chip, or another appropriate shape. Further, the device body can be manufactured in the form of a spiral and function as an oscillating circuit.

In accordance with an embodiment to the present disclosure the device body is made of a nonmetallic material, particularly, a biodegradable material. Any suitable biodegradable polymer can be used including, but not limited to polylactic acid, 3-hydroxypropionic acid, or any combination thereof. Suitable biodegradable polymers are known in the art; see, for example, Avérousand L., Pollet E. (eds.), Environmental Silicate Nano-Biocomposites Green Energy and Technology, Springer-Verlag London 2012, Ch. 2. In another embodiment the body of the implantable device is made of a mixture of biodegradable polymers.

In accordance with another embodiment to the present disclosure the device body is made of a metallic material, in particular, a biocompatible metal or metal alloy.

For the purpose of this application the term "magnetocaloric effect" means heat release (positive magnetocaloric effect) or heat absorption (negative magnetocaloric effect) in a magnetic material under action of applied magnetic field. If these changes take place under adiabatic or quasi-adiabatic conditions they result in increasing or decreasing temperature of a sample of the magnetic material. Magnetocaloric effect is based on the ability of any magnetic material to change its temperature and entropy under applied constant magnetic field, as it takes place at gas or steam compression or expansion or, for example, in traditional refrigerators.

Change of magnetic material temperature takes place as a result of redistribution of internal energy of magnetic material between the system of magnetic moments of its atoms and crystal lattice.

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Magnetocaloric effect, in particular, determines magnetocaloric properties of magnetic materials, and the higher the effect is, the more effective is release or absorption of heat in magnetic materials under magnetic field.

In accordance with an embodiment to the present disclosure the magnetic material comprised in the layer of magnetic material has the temperature of magnetic phase transition around the temperature of animal or human body.

In accordance with an embodiment to the present disclosure, the magnetic material is selected from the group including but not limited to, rare earth metals, such as gadolinium, terbium, dysprosium, holmium, transient metals, such as iron, nickel, cobalt, magnesium, noble metals, such as rhodium, palladium; their oxides, compositions, combinations, solid dispersions, and alloys, such as Gd_5Si_4, $Gd_5Si_{2,06}Ge_{1,94}$, Gd_7Pd_3; $MnFeP_{0,35}As_{0,65}$ and MnAs.

Further examples of the materials with high magnetocaloric effect and with phase transition temperature close to the human body temperature (from 36 °C up to about 37°C) that can be used in embodiments according with the present disclosure are reported in details for example in A.M. Tishin, Y.I. Spichkin Magnetocaloric effect and its application, Institute of Physics Publishing, Bristol and Philadelphia, 2003, pp. 410-411. In particular, there are alloys based on precious metals (rhodium, palladium, platinum), rare-earth elements (metals), as, for example, gadolinium Gd (Curie temperature about 295 K and MCE value $\Delta T = 5.8$ K at $H = 2$ T), alloys or their intermetallic compounds, as, for example, iron-rhodium alloy $Fe_{0.49}Rh_{0.51}$ (magnetic phase transition temperature of antiferromagnetism – ferromagnetism is about 310–316 K and MCE value reaches minus 13 K in the field of 2 T); gadolinium-silicon alloy Gd_5Si_4 (with temperature of maximum MCE value $\Delta T = 8.8$ K at $T = 336$ K and $H = 5$ T); gadolinium-silicon-germanium alloy $Gd_5Si_{2.06}Ge_{1.94}$ ($\Delta T = 8$ K in the field of 5 T and at $T = 306$ K); gadolinium-palladium alloy Gd_7Pd_3 ($\Delta T = 8.5$ K at $T = 323$ K and $H = 5$ T); manganese-iron-phosphorus-arsenic alloy $MnFeP_{0.35}As_{0.65}$ (maximum of MCE $T = 332$ K); manganese-arsenic alloy MnAs ($\Delta T = 13$ K at $T = 318$ K and $H = 5$ T) and others.

From magnetic measurements it is known, that temperatures of magnetic phase transitions strongly depend on concentration of alloyed metals and elements in alloys and compounds of rare-earth metals (REM). It is possible to achieve the required magnetocaloric

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effect and to provide required temperature, for example, of magnetic phase transition, close to the human body temperature, by variation of the content of a certain element in the alloy. Generally, for example, magnetic phase transition takes place in a wide range of magnetic fields with magnetic strength from several kOe up to 60kOe (kiloerstad) and more.

In accordance with an embodiment to the present disclosure, magnetic material may be combination of two or more magnetic materials with different values of magnetocaloric effect. Furthermore, different magnetic materials may be arranged in layers, each layer may be comprised of a magnetic material with different value of magnetocaloric effect. In one embodiment the layers of the magnetic material(s) may have the thickness in the range from 1 μm to 100 μm. In another embodiment the thickness is in the range from 10 μm to 50 μm, or from 15 μm to 30 μm.

Layers of magnetic material can be prepared using various known technologies, for example, by the plasma method in inert medium (for example, under argon) from particles of one or another metal (element) with initial size, for example, 50–100 μm, or, for example, similar to the method disclosed in SU 1746162, 7/7/1992, or by deposition of nanoparticle layer on a substrate.

For the purpose of this application "a heat insulating layer" is a layer of material having low thermal conductivity and providing reduction of heat transfer (the transfer of thermal energy between objects of differing temperature) between the coating interior and the surroundings. Materials that can be used in the heat insulating layer are known in the art, and include, in particular, bioceramics, polystyrene, silica gel, and polyurethane. The heat insulating layers prevents losses of thermal energy generated in the magnetic material. The thickness of the heat insulating layer is in the range between 1 μm and 100 μm, particularly in the range between 3 μm and 20 μm, more particularly in the range between 5 μm and 15 μm. The layers of heat insulating material can be prepared using various known technologies, for example by film casting or spin coating.

The heat insulating layer may be part of the first insulating layer, second insulating layer, or both.

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If the device body is made of a nonmetallic material, in particular, a polymer, then the presence of a heat insulating layer in the first insulating layer is optional. In this case the device body provides heat insulation.

A heat insulating layer located in the second insulating layer is made of a mesoporous material and comprises plurality of pores. The pores form a passage for releasing the active substance in the form of molecules or nanoparticles. The pores are large enough for allowing the interstitial fluid and blood plasma to pass through and contact with the polymer layer comprising the active substance. The pores, at the same time, are small enough for preventing direct contact of flowing liquid with the polymer layer as thus preventing convective heat losses. The pores are not penetrable for blood cells and blood corpuscle. In some embodiments the size of the pores are in the range from 1 to 100 nm, particularly, in the range from 2 to 50 nm, more particularly, in the range from 5 to 30 nm.

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For the purpose of this application "an infrared radiation reflecting layer" is a layer of material that is capable of changing the direction of incident infrared radiation at an interface between that material and an adjacent layer from which the radiation originated so that the radiation is returned into the adjacent layer. Materials that can be used in the infrared radiation reflecting layer are known in the art, and include, in particular, biocompatible metals and metallic alloys, more particularly, nickel-free stainless steel, titanium-based alloys, tantalum. The infrared radiation reflecting layer prevents losses of infrared energy generated in the magnetic material. The thickness of the infrared radiation reflecting layer is in the range between 0.1 μm and 1 μm, in particularly in the range between 0.3 μm and 0.7 μm, more partucularly the range between 0.4 μm and 0.6 μm. The infrared radiation reflecting layer can be prepared using various known techniques, in particular by cold gas spraying or chemical metallization.

An infrared radiation reflecting layer may be part of the first insulating layer, second insulating layer, or both.

If the device body is made of a metallic material then the presence of an infrared radiation reflecting layer in the first insulating layer is optional. In this case the device body acts as a reflective surface for infrared radiation.

An infrared radiation reflecting layer located in the second insulating layer has plurality of pores for passage of the active substance. The pores in an infrared radiation reflecting layer are about the same size as that in a heat insulating layer. In some embodiments the size of the pores are in the range from 1 to 100 nm, particularly, in the range from 2 to 50 nm, more particularly, in the range from 5 to 30 nm.

For the purpose of this application "a layer of sensitive material" is a layer of a material that is capable of changing its structure and/or properties in response to the increase or decrease in temperature or in response to applied strain significantly enough to release desired amount of active substance.

In accordance with an embodiment to the present disclosure the layer of sensitive material comprises at least one material selected from polymers, copolymers, hydrogels, biopolymers, or any combination thereof.

In accordance with an embodiment to the present disclosure the layer of sensitive material is a layer of heat-sensitive material.

The heat-sensitive material is capable of controlling a retention/release rate of an active substance meaning that the heat-sensitive material is capable of influencing, in multiple ways, a retention/release rate of the active substance. For example, an active substance may be encapsulated in the heat-sensitive material. Alternatively, the active substance may be dissolved in the heat-sensitive material in which case the release rate of the active substance from the device will depend on the solubility and diffusion rate of this substance in the heat-sensitive material.

In accordance with an embodiment to the present disclosure the layer of heat-sensitive material comprises a mixture of two or more of different polymers at least partially covering the layer of magnetic material. The layer of heat-sensitive material may comprise two or more layers of different polymers, or two or more patches of different polymers. At least one polymer comprised in the layer of heat-sensitive material is a heat-sensitive polymer.

Multiple layers of polymers allow multiple triggering of the heat-sensitive polymers at different temperatures as well as provide thermal insulation for the device so that the increased

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or decreased temperature can be maintained longer without heat exchange with the surrounding tissues.

In accordance with still another embodiment to the present disclosure the polymer material may comprise heat-sensitive polymer or copolymer exhibiting transition from insoluble to soluble form around LCST (low critical solution temperature). The polymer below the LCST (hydrophilic state) is brought in contact with the active substance, in particular, in the form of aqueous solution. The polymer in the solution swells and intakes the active substance. The polymer is then heated above LCST (hydrophobic state) that leads to polymer collapse and capture of the active substance inside the polymer. The active substance is released on site when the temperature of the heat-sensitive polymer falls below the critical point defined by the phase transition temperature in aqueous polymer solutions, because of thermal contact with a magnetic material with lower temperature.

Polymers and copolymers with lower critical solution temperature that may be used in accordance with embodiments to the present disclosure are prepared from the following heat-sensitive monomers: N-ethyl acrylamide, N-*n*-propyl acrylamide, N-*n*-propyl methacrylamide, N-isopropyl acrylamide, N-isopropyl methacrylamide, N-cyclopropyl acrylamide, N-cyclopropyl methacrylamide, N-ethoxyethyl acrylamide, N-ethoxyethyl methacrylamide, N,N-disubstituted (meth)acrylamide, such as N,N-dimethyl (meth)acrylamide and copolymers based on them.

N-substituted acrylamides and methacrylamides, O-substituted acrylamides and methacrylamides, and also other monomers, capable to copolymerize with monomers, which form heat-sensitive polymers, may be used as comonomers for heat-sensitive copolymers.

In particular, copolymers of N-isopropyl acrylamide (NIPAAm) and N-*tert*-butyl acrylamide (tBuAM) may be used as heat-sensitive polymers.

Besides acrylamides and methacrylamides the following compounds with lower critical solution temperature may be used as heat-sensitive polymers: N-vinyl caprolactam and polyoxamers based on them, such as threeblock copolymers formed from polyoxyethylene and polyoxypropylene.

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Besides the said polymers with lower critical solution temperature, biopolymers forming gel at increasing temperature, such as methyl cellulose, may be used. Heat-sensitive medium may be solutions and gels based on gelatin and collagen.

More generally, the layer of heat-sensitive material may be comprised of any temperature-sensitive (heat-sensitive) polymer-comprising medium or compound, in particular, heat-sensitive hydrogels and biopolymers.

In accordance with another embodiment to the present disclosure the layer of sensitive material is a layer of a deformation-sensitive material.

In accordance with an embodiment to the present disclosure the layer of deformation-sensitive material comprises a mixture of two or more of different polymers at least partially covering the layer of magnetic material. The layer of deformation-sensitive material may comprise two or more layers of different polymers, or two or more patches of different polymers. At least one polymer comprised in the layer of deformation-sensitive material is a deformation-sensitive polymer.

A possible mechanism of release of the active substance from the layer of deformation-sensitive material is deformation of the magnetic material under the action of magnetic field. When subjected to magnetic field the layer of magnetic material experiences mechanical strain due to magnetic shape-memory or due to magnetostriction that leads to mechanical deformation of the layer of the deformation-sensitive material followed by its fracture. Then the active substance leaks or is otherwise released from the polymer coating through the formed fractures. Deformation-sensitive material comprises deformation-sensitive polymers with low yield stress, in particular, poly(lactic-co-glycolic) acid. Particular magnetic materials having magnetic shape-memory include Ni-Mn-Ga alloy, having relative deformation up to 10%.

In accordance with another embodiment to the present disclosure, the layer of sensitive material further comprises contrasting agents. The contrasting agents allow controlling the degree of the drug release from the polymer using magnetic resonance imaging.

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For the purpose of this application “active substance” is a substance including but not limited to, a chemical agent, a pharmaceutical, a biologically active substance, biological object, a genetic construct.

In medicine, especially preferable active substances selected from the group including but not limited to anti-inflammatory agents, antibiotics, pain killers, anti-allergic, anti-histamine, anti-tumor, antivirus, anti-diabetic, anti-ulcer, anti-hyperlipidemic, anti-thrombosis agents, beta-blockers, vasodilators, bone resorbtion inhibitors, anti-proliferative agents and others.

The term "pharmaceutical" refers to a product, which includes all compounds, which cause a certain biological response. The term "pharmaceutical" refers to any drug administered to mammals, including, but not limited to, humans, domestic animals, wild animals and animals raised for the use of its meat, or other products such, as agricultural animals and cattle. The term "pharmaceutical" includes, but not limited to, the following classes of pharmaceuticals: therapeutic drugs, preventive drugs and diagnostic drugs. Examples of pharmaceuticals which may be implanted in a polymeric matrix, include but are not limited to: colchicine, narcotic analgesic drugs; salts of gold; corticosteroids; hormones; antimalarial drugs; indole derivatives; pharmaceuticals for arthritis treatment; antibiotics, including Tetracyclines, Penicillin, Streptomycin and Aureomycin; antihelmintic and canine distemper drugs, applied to domestic animals and large cattle, such, as, for example, phenothiazine; drugs based on sulfur, such, as sulfioxazole; anti-proliferative agents (paclitaxel, Sirolimus); antitumor drugs; pharmaceuticals supervising addictions, such as agents controlling alcohol addiction and agents controlling tobacco addiction; antagonists of drug addiction, such, as methadone; weight-controlling drugs; thyroid gland controlling drugs; analgesics; drugs controlling fertilization or contraception hormones; amphetamines; antihypertensive drugs; antiinflammatories agents; antitussives; sedatives; neuromuscular relaxants; antiepileptic drugs; antidepressants; antidisrhythmic drugs; vasodilating drugs; antihypertensive diuretics; antidiabetic agents; anticoagulants; antituberculous agents; antipsyhotic agents; hormones and peptides. It is assumed, that above list is not full and simply represents the wide diversification of pharmaceuticals that may be incorporated into the polymer layer. Preferably, a pharmaceutical refers to a peptide.

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The amount of drug distributed in the layer of heat-sensitive material depends on various factors including, for example, specific pharmaceutical; function which it should carry out; required period of time for release of a pharmaceutical; quantity of administered pharmaceutical and dimensions of an implant. Generally, dosage of a pharmaceutical, i.e. amount of pharmaceutical in the heat-sensitive material, is selected from the range about from 0.5 % (w/w) up to 95 % (w/w), particularly, from about 5 % (w/w) to about 75 % (w/w), and, more particularly, from about 10 % (w/w) to about 60 % (w/w).

In accordance with another embodiment to the present disclosure, the active substance can be bonded to the sensitive material.

The term "bonded" herein includes but is not limited to adsorbed form, absorbed, solvated, dispersed, suspended, encapsulated form, linked by covalent bonds or Van-der-Vaals bonds, via linkers, peptide bonds, is enclosed within semi-permeable membrane, or bonded by mechanical bonds or physical bonds, such as by magnetic forces or electric forces, such as dipole-dipole bonds.

Bioactive compounds in accordance with an embodiment to the present disclosure are antigens, antibodies, nucleotides, gelling agents, enzymes, bacteria, yeast, fungi, viruses, polysaccharides, lipids, proteins, hormones, carbohydrates, cellular material.

The pharmaceutical content may be from about 0.5 to about 95 % (w/w) of the polymeric material. Preferably, the pharmaceutical content is from about 5 to about 75 % (w/w) of microparticles.

In accordance with another embodiment to the present disclosure a method of controlled drug release is provided, the method comprising the steps of: implanting the device disclosed herein into a patient body; and subjecting the implanted device to magnetic field in a controlled manner to release the active substance.

In some embodiments the magnetic field is alternating magnetic field, created by an external source and having the frequency between 1 kHz and 100 kHz.

In some embodiments the magnetic field is a pulsed magnetic field applied periodically, wherein application of a constant magnetic field created by a permanent magnet, a MRI apparatus, or another appropriate device for a first period of time is followed by removing the magnet or otherwise "switching off the magnetic field" for a second period of

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time. The first and the second periods of time are of the order of minutes and in each case can be determined by an experienced practitioner without undue experimentation.

Implantation of the device to required location in the patient body is within the skills of a medical professional. Before implantation the device is charged with an appropriate amount of active substance suitable for treatment of a particular condition or disease.

The magnetic field is applied to a predetermined location and for predetermined amount of time to effect cooling/heating of the magnetic material to a temperature sufficient for release of the active substance in a predetermined location and predetermined time.

In some application regimes, most suitable for one-time release of the active substance, a constant magnetic field is required. Magnetic fields required for one-time release are of the order of 1 T. In particular, permanent magnetic fields are from 0.1 to 10T, more particularly, from 0.5 to 5 T, still more particularly, from 1 to 3T.

Alternatively, a pulsed or periodic magnetic field may be used for continuous release of the active substance.

The present disclosure will be illustrated by the following non-limiting examples.

Example 1. Manufacturing of a magnetic field controllable implantable device.

The magnetic field controlled implantable device disclosed herein was tested to determine its ability to encapsulate and then release active substance upon application of magnetic field. A prototype of the implantable device was manufactured by first depositing a 0.1 mm film of gadolinium on a polystyrene plate. Gadolinium has *positive* magnetocaloric effect of about 3K/T at 294K. Then pNIPAM polymer film having a thickness of 10 μm in the collapsed state was casted on the gadolinium film. The resulting composite structure was immersed into a 1 $\mu g/cm^3$ solution of colchicine at 25°C which is below the low critical solution temperature for pNIPAM (32°C). The film of pNIPAM was impregnated with the colchicine solution and at these conditions had a thickness of 100 μm. The composite structure was then rinsed with hot water (with temperature above the low critical solution temperature for pNIPAM) leading to collapse of the polymer. The surface density of colchicine captured in

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the polymer was 0.1 μg/cm^2. Finally, the polymer layer was sandwiched between the Gd foil and a layer of mesoporous ZrO_2-based bioceramics.

Example 2. Active substance release assessed by cytotoxicity data

The NCTC clone L929 cell line was used to test release of colchicine from the prototype device prepared in Example 1. A solution containing the culture maintained at 37°C was mixed with Syto9 and propidium iodide dyes and then put into a 10 ml test tube. The prototype of Example 1 was immersed in the solution. A permanent magnet was slowly brought in proximity of the test tube thus providing gradual application of a 2T constant magnetic field. The slow approach of the magnet provided quasi-isothermal application of the magnetic field. The heat generated in the gadolinium film was dissipated during the application of the field and thus the temperature of the solution was maintained at around 37°C.

After thermal equilibration the magnet was quickly removed away from the test tube resulting in a temperatures drop to 32°C and colchicine release. The solution then was stored at 37°C for 24 hours.

The number of dead and living sells was then assessed visually in a hemocytometer. Syto 9 dye penetrates membranes of both living and dead cells and colors DNA and RNA into green. Propidium iodide penetrates membranes of only dead cells and colors the nuclei into red. Thus it is possible to visualize the number of dead and living sells in a sample.

In this example only 10% of living cells remained in the solution after 24 hours. This number can be compared to 99% of living cells remained in the solution when 0.1 μg/cm^3 of colchicine was introduced directly into the solution under same conditions.

Such dramatic difference in activity may be explained by higher colchicine and cells concentrations (because of cells adsorption) at the implant prototype surface. This effect is advantageous because in most cases active substance needs to be delivered to an implant surface where detrimental effects take place. Intravenous administration of equivalent amount of active substance (analogous to direct introduction of colchicine into the solution in this experiment) results in a much lower concentration of the active substance at the implant surface and at the same time may cause undesired side effects at other sites of a body.

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Example 3. $Fe_{0.49}Rh_{0.51}$-based magnetic field controllable implantable device.

The same test protocol as in Examples 1 and 2 was used in this example, except that $Fe_{0.49}Rh_{0.51}$ foil was used instead of gadolinium foil. $Fe_{0.49}Rh_{0.51}$ has *negative* magnetocaloric effect of about 6K/T at 294K. Accordingly, the cooling required to initiate colchicine release was accomplished by quickly bringing a permanent magnet in proximity of the test tube thus providing quick application of 2T constant magnetic field.

After thermal equilibration the magnet was slowly removed away from the test tube and the solution was stored at 37°C for 24 hours.

After that period the number of dead and living sells was assessed as described above. In this example 3% of living cells remained in the solution after 24 hours.

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AMENDED CLAIMS

(in Response to the Examination Report under section 18(3) of July 1, 2014)

1. A magnetic field controllable implantable device comprising
   a device body having an outer periphery, and
   a coating covering at least part of the outer periphery of the device body, comprising the following layers in the order from the inside to the outside:
   a first insulating layer;
   a layer of magnetic material having positive or negative magnetocaloric effect of at least 3 K/T;
   a layer of a sensitive material comprising active substance and capable of controlling a retention/release rate of the active substance;
   a second insulating layer permeable for the active substance.
2. The implantable device according to claim 1 wherein the first insulating layer is selected from a heat insulating layer, an infrared radiation reflecting layer, or a combination thereof.
3. The implantable device according to any one of claims 1-2 wherein the second insulating layer permeable for the active substance comprises a plurality of pores and is selected from a porous/permeable heat insulating layer, a porous/permeable infrared radiation reflecting layer, or a combination thereof.
4. The implantable device according to anyone of claims 1-3 wherein the heat insulating layer is comprised of polystyrene, silica gel, polyurethane, bioceramics, or any combination thereof.
5. The implantable device according to anyone of claims 1-4 wherein the infrared radiation reflecting layer is comprised of a metal or a metallic alloy, preferably nickel-free stainless steel, titanium-based alloys, or tantalum.
6. The implantable device according to anyone of claims 1-5 wherein the magnetic material is selected from the group comprising rare earth metals, such as gadolinium,

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terbium, dysprosium, holmium, transient metals, such as iron, nickel, cobalt, magnesium, noble metals, such as rodium, palladium; their oxides, compositions, combinations, solid dispersions, and alloys, such as Gd_5Si_4, $Gd_5Si_{2,06}Ge_{1,94}$, Gd_7Pd_3, $MnFeP_{0,35}As_{0,65}$, $Fe_{0.5}Rh_{0.5}$, Ni-Mn-Ga, and MnAs.

7. The implantable device according to anyone of claims 1-6 wherein the layer of sensitive material comprises at least one material selected from polymers, copolymers, hydrogels, biopolymers, or any combination thereof.

8. The implantable device according to any one of claims 1-7 wherein the layer of sensitive material comprises:
   - a mixture of two or more different polymers; or
   - two or more layers of different polymers; or
   - two or more patches of different polymers.

9. The implantable device according to any one of claims 7-8 wherein at least one, preferably two or more, of the polymers are heat-sensitive polymers with a phase transition temperature near the body temperature.

10. The implantable device according to any one of claims 8-9 wherein the different heat-sensitive polymers have different phase transition temperatures.

11. The implantable device according to any one of claims 9-10 wherein the heat-sensitive polymer is selected from a group comprising polybutyl methacrylate (pBMA), polyN-isopropylacrylamide (PNIPAM), copolymerized N-isopropyl-acrylamide (NIPAM) with N-isopropylmethacrylamide (NIPMAM) and acrylamide (AAm) and/or any combination thereof.

12. The implantable device according to anyone of claims 1-11 wherein at least one, preferably two or more, of the sensitive polymers are deformation-sensitive polymers with low yield stress, in particular, poly(lactic-co-glycolic) acid.

13. The implantable device according to anyone of claims 1-12 wherein the layer of sensitive material further comprises contrasting agents that allow controlling the degree of the drug release from the polymer using magnetic resonance imaging.

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14. The implantable device according to anyone of claims 1-13 wherein the pores allow the interstitial fluid and blood plasma to pass through thereby allowing release of the active substance.

15. The implantable device according to anyone of claims 1-14 wherein it is a stent, a catheter, a prosthesis of joints or bones, a pin or a screw for osteosynthesis, a denture, a pacemaker, an insulin pump, a silicone implant, a neural implant, a brain chip, a cochlear implant, or a dental implant.

16. A method of controlled drug release, comprising the steps of: immersing the device according to any one of claims 1-15 into a solution; and subjecting the immersed device to magnetic field in a controlled manner to release the active substance into the solution.

17. The method according to claim 16 wherein the magnetic field is alternating magnetic field, created by an external source and having the frequency between 1 kHz and 100 kHz.

18. The method according to claim 16 wherein the magnetic field is constant magnetic field applied periodically and created by an external source.

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