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(54) Benævnelse: **IMPLANTERBARE PRODUKTER INDEHOLDENDE NANOPARTIKLER**

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Description

The present invention concerns implantable products containing nanoparticles and their use in medicine - in particular, for thermotherapeutic after-treatment following surgical removal of tumors and cancers.

After a surgical removal of tumor tissue, the problem nearly always arises that tumor cells still remain in the body (incomplete resection). After closing the wound, these tumor cells may again grow into a larger tumor and/or metastasise. The chemotherapeutic after-treatments (which are very stressful to the patient) take place for this reason. However, since as little healthy tissue as possible should be removed, the surgeon must achieve a compromise between as complete a tumor removal as possible and the least possible removal of healthy tissue.

It is the object of the present invention to provide products and methods for a more effective after-treatment following cancer surgeries.

The object is achieved via the independent patent claims. Additional advantageous embodiments result from the dependent claims, the examples, and the description.

Surprisingly, it has been found that medical products that are implantable and contain nanoparticles that can be heated in an alternating magnetic field enable an after-treatment to cancer operations that is markedly improved in comparison to chemotherapy, if these medical products are implanted or introduced into the surgical site.

The present invention thus concerns a solid or gel-like medical product that can be heated via an alternating magnetic field, for use in the after-treatment of the surgical site in cancer operations, wherein the medical product is present in the form of a physiologically compatible tissue, sponge, or film, and wherein magnetic particles are contained in the medical product, which magnetic particles generate heat when excited by an alternating magnetic field and thereby heat the medical product.

In the medical product according to the invention, it is decisive that the particles (i.e., the particles that can be excited in an alternating magnetic field) are embedded in or attached to the medical product so as to be stationary.

Conventionally, aqueous solutions of magnetic particles are produced in order to either [sic] conduct the particles laden with pharmacologically active substances to a specific active site via a static magnetic field, or aqueous solutions of particles that can be excited in an alternating magnetic field are injected directly into a tumor, so that the particles accumulate in the tumor cells and destroy said tumor cells via generation of heat. The heat is primarily created via hysteresis heat losses of the particles.

The medical products according to the invention are not aqueous solutions or physiological aqueous solutions or suspensions of the magnetic particles, but rather solid or gel-like carriers (for example, a tissue or a film) in which the particles are firmly embedded. Insofar as they are not biodegradable medical products,

the particles permanently remain in the medical product and, after implantation, the medical product remains permanently at the implanted position - similar to a dental implant or artificial knee joint.

Because the particles remain permanently in the medical product, are not released via diffusion, and are released via the degradation process only in the case of biodegradable medical products, the site where the implanted medical product is located may still be heated even after arbitrary time periods, i.e., after one week post-implantation, after one month post-implantation, after one year post-implantation, and even after 10 years post-implantation.

Preferred embodiments of the present invention pertain to biodegradable medical products which, depending upon the indication, can degrade at different rates in the human and animal body. However, the particles are also not released from these medical products via diffusion, but rather only within the scope of the biodegradation. A breakdown process thus occurs with these bioresorbable medical products, wherein the remainder of the medical product that is still undergoing breakdown may continue to be heated by an alternating magnetic field.

However, with the medical products according to the invention, it is decisive that these are flexible or deformable and are able to follow the surface contour of a tissue or organ, or of the operating space after a surgical tumor removal. The medical products are thus in the form of tissues, which can be placed on tissue or organs or the surgical site and follow the uneven surfaces without any problems, or in the form of a film-

forming composition, which naturally can be applied to any uneven surface.

In this context, what is to be understood as the surgical site is that area that is delimited by the outer edges of a surgical wound. Described in a different way, the surgical site is the transition region or the boundary surface from tumor tissue to healthy tissue. Treatment or after-treatment of this site is very important in order to prevent recidivation.

The medical products described here are deposited upon, applied to, and (in the case of a spray) sprayed upon the surgical site, and thus are intended for after-treatment of the surgical wound after a tumor operation.

The medical products according to the invention are thus primarily intended, not for systemic application, but rather for implantation in the surgical site. Since the medical products according to the invention should normally preferably remain in the surgical site for the duration of the subsequent chemotherapy, depending upon the time interval of planned therapy sessions, the medical products according to the invention are biodegradable, are bioresorbable over a longer time period, or are non-degradable.

It is important that the medical products according to the invention (preferably biodegradable or slowly biodegradable medical products) have no rigid form, but, rather, may flexibly adapt to the surface of the surgical site that is to be covered. In particular, medical products, or carriers for the heatable or warmable particles, that are flexible, easily deformable,

easily adaptable to other shapes, or shapeless are thus preferred.

The medical products according to the invention are thus all non-rigid and non-metallic carriers which adapt to a predetermined surface and cover this to the greatest possible extent, and are additionally suitable for accommodating magnetic particles - in particular, superparamagnetic nanoparticles. The (preferably biodegradable) medical products according to the invention are medical cellulose, bandage materials, wound inserts, surgical thread material, compresses, sponges, or medical textiles.

Medical cellulose and medical textiles preferably represent two-dimensional structures of small thickness, which are impregnated with the particles. The magnetic particles are taken up by the fibre structures of this medical product, which, in dry or pre-moistened form, is then placed in the wound, around the surgical site, after the operation.

Other forms of medical products according to the invention are sponges or generally biodegradable, porous, three-dimensional structures which are able to contain the magnetic particles both on the surface of and inside the porous structure, in the voids as well as the sponge material itself. After an operation, these sponges are placed in the wound and largely, or also, only partially, fill the operating space. The magnetic particles may be released from these sponge-like structures, wherein the particles may also be present in a strongly bound form, however. The release may take place both via diffusion of only loosely bound particles from the voids of the porous

structures and via biodegradation of the sponge structure, if the particles are integrated or embedded in the material of the sponge structure itself.

The medical products according to the invention are intended for implantation in the human and animal body and therefore must be physiologically compatible. It is important that the medical products according to the invention are present, not in aqueous form as a solution or suspension, but rather in a formulation which is viscous or semi-liquid or film-forming or solid, so that the medical product also remains at the desired location after the implantation.

It is also important that the medical product adapt to arbitrary surfaces, i.e., follow the surface contour.

Designated herein as a "medical product" is a carrier with the magnetic particles, and serving as "carriers" are the textiles, celluloses, film-forming compositions, etc. (described here in detail), which may be biodegradable or bio-stable and are non-magnetic, and therefore also may not be heated in an alternating magnetic field without the magnetic particles. The carriers are made up of non-living material, might include x-ray markers or contrast agents, and preferably bind the particles adhesively and/or covalently. By contrast, the particles are for the most part not biodegradable, release heat when excited by an alternating magnetic field, and thereby heat up not only themselves, but also the carrier (and thus the entire medical product) and thereby also the surrounding tissue. As described further below, pharmacological substances (such as cytostatics, for example) can also be

introduced into the medical product, which pharmacological substances may be released via diffusion and/or biodegradation of the carrier and/or the development of heat and/or the alternating magnetic field, primarily in order to fight tumor cells.

What is designated herein as a "tissue" is any medically used textile or cellulose from which bandage materials, wound dressings, bandages, or other medical cloths or fabrics are produced.

The term "biodegradable medical product" refers explicitly only to the matrix for the magnetic particles, but not to the magnetic particles themselves, which are normally not biodegradable. The medical cellulose, bandage materials, wound inserts, surgical thread material, compresses, sponges, or medical textiles wherein or whereupon the magnetic particles are applied or introduced are therefore biodegradable. With the degradable medical products according to the invention with the magnetic particles, the matrix for the magnetic particles (i.e., the medical product without the magnetic particles) thus biodegrades, and the magnetic particles normally remain behind or accumulate in tumor tissue or in the cancer cells, and for the most part do not biodegrade (or only a portion of their coating biodegrades), wherein the magnetic core is normally not biodegradable.

What is understood as an operating space is the area where the removed tumor or the removed cancer was located.

Additional preferred variants of medical products are liquid or gelatinous formulations in the form of

salves, creams, gels, and sprays - in particular, film-forming sprays. These formulations include the magnetic particles and are applied to or sprayed on the surgical site after removal of the tumor.

Apart from the magnetic particles, the medical products according the invention are preferably biodegradable and therefore preferably completely degrade within 1 to 12 months - more preferably, 1 to 6 months - wherein the contained magnetic particles are also released.

The mode of operation of the medical products according to the invention therefore consists in that these should cover the surgical site as completely as possible, so that the magnetic particles optimally remain near the cancer cells or cancer tissue that still remain. The magnetic particles (and preferably, superparamagnetic particles) may be heated in an alternating magnetic field, whereby the cancer cells that still remain can be killed via a thermotherapy. The magnetic particles contained in the medical product according to the invention thereby heat the medical product as a whole, and the magnetic particles diffused out of the medical product heat the cancer cells in which they have been taken up or into which they have penetrated.

This thermotherapeutic treatment may additionally support a conventional chemotherapy or radiation therapy, because the thermotherapeutic treatment causes comparatively few side effects and may be implemented simultaneously with a chemotherapeutic treatment. Since the medical products according to the invention cover the surgical site as completely as possible, or should fill

the operating space as completely as possible, the medical products according to the invention have an optimally direct contact with the still remaining cancer cells and cancer tissue, which can be particularly effectively killed due to the immediate proximity of the magnetic particles. The thermotherapeutic treatment by means of the medical product according to the invention is therefore distinctly more selective and gentle than chemotherapy and radiation therapy.

In a preferred embodiment of the present invention, at least one pharmacologically active substance (preferably, an anti-cancer agent) is bound to the mentioned magnetic particles. Examples of suitable anti-cancer agents are: actinomycines, aminoglutethimide, amsacrine, anastrozole, antagonists of purine and pyrimidine bases, anthracyclines, aromatase inhibitors, asparaginase, antiestrogens, bexaroten, bleomycin, buselerin, busulfan, camptothecin derivatives, capecitabin, carboplatin, carmustin, chlorambucil, cisplatin, cladribin, cyclophosphamide, cytarabin (cytosinarabinoside), alkylated cytostatics, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin (adriamycin), epirubicin, estramustine, etoposide, exemestane, fludarabine, fluorouracil, folic acid antagonists, formestane, gemcitabine, glucocorticoids, goselerin, hormones and hormone antagonists, hycamtin, hydroxyurea, idarubicin, ifosfamide, imatinib, irinotecan, letrozole, leuprorelin, lomustin, melphalan, mercaptopurine, methotrexate, miltefosine, mitomycines, mitosis inhibitors, mitoxantrone, nimustines, oxaliplatin, paclitaxel, pentostatin, procarbazine, tamoxifen, temozolomide, teniposide, testolactone, thiotepum, tioguanine, topoisomerase inhibitors, topotecane, treosulfane, tretinoine, triptorelin, trofosfamides, vinblastine,

vincristine, vindesine, vinorelbine, and cytostatically active antibiotics.

The separation of at least one therapeutically active substance from the particles may also be produced or initiated via an alternating magnetic field. It may thereby be achieved that the thermotherapeutic treatment is further supported via an antiproliferative substance directly in the surgical site, which, again, increases the efficacy. Naturally, a simultaneous or delayed additional chemotherapy or radiation therapy is also possible here.

However, the at least one pharmacological substance does not necessarily need to be bound to the particles (preferably, nanoparticles). It may, without bonding to the particles, additionally be included in the medical product according to the invention or be applied on its surface.

However, the bonding of the active substance to the particles has the advantage that a more goal-oriented release takes place, since the active substance may, together with the particles, penetrate into the cancer cells, or be taken up in cancer cells, and there, initiated via a magnetic field, released.

In this context, "produced or initiated via an alternating magnetic field" means that, on the one hand, the alternating magnetic field or the pulses directly produce the release or separation, or a separation of the active substance takes place indirectly - for example, via the activation of enzymes or the generation of heat.

The medical products containing nanoparticles (in the form of medical cellulose, bandage materials, wound inserts, surgical thread material, compresses, medical sponges, or medical textiles) may thus additionally contain at least one pharmacological substance - preferably, at least one anti-cancer agent. Suitable substances, as well as their bonding to the particles, are described in detail further below.

After application of the medical products or the biodegradable medical products to the surgical site, via application of an external alternating magnetic field, the mentioned implants and implantable medical products are heated in said alternating magnetic field.

The heating of the particles takes place in an alternating magnetic field, wherein the strength of the alternating magnetic field is preferably between 1 and 25 kA/m (more preferably, between 2 and 18 kA/m), and the frequency is preferably between 5 and 5,000 kHz (more preferably, between 10 and 1000 kHz).

Assisted by the heating, the magnetic particles (preferably, superparamagnetic nanoparticles) release nanoparticles, as well as the optionally present active substances, which are taken up at cancer cells and kill these. This gentle therapy form of thermotherapy just described can, in particular, be used in combination with other treatment methods such as radiation therapy and/or chemotherapy.

Magnetic particles

According to the invention, any magnetic particles may be used, as long as these may be heated by an alternating magnetic field.

Accordingly, microparticles - and, in particular, nanoparticles, especially superparamagnetic nanoparticles - are preferred.

The nanoparticles mentioned preferably have a magnetic (particularly preferably, a superparamagnetic) core. Materials such as maghemite, magnetite, iron-nickel alloys, nickel-copper alloys, or cobalt-nickel alloys (for example, FeNi or CoNi) are preferred.

In order to improve the magnetic properties, a second magnetic core layer may also be applied. The result is a higher total coercivity field in comparison to nanoparticles having a single layer core. The first core layer may be comprised of superparamagnetic material, and the second core layer may be comprised of a material differing from the first core layer. Additional layers (which also carry active substances, for example) may be applied around this core. Multi-shell particles for introducing particle-active substance conjugated compounds into tumor cells are described in the application WO 98/58673 A.

The core or cores themselves are comprised of a magnetic material - preferably, a ferromagnetic, antiferromagnetic, ferrimagnetic, antiferrimagnetic, or superparamagnetic material - further preferably, of iron oxides - in particular, superparamagnetic iron oxides or of pure iron which is provided with an oxide layer. Such

nanoparticles may be heated via an alternating magnetic field with a preferred magnetic field strength between 2 and 25 kA/m and a frequency that is preferably between 5 and 5000 kHz. A heating of the tissue containing the nanoparticles to above 50 °C is possible with this technique. Such high temperatures may be achieved because up to 800 pg or more iron in the form of nanoparticles may be taken up per tumor cell, and, thus, the nanoparticles cannot leave the target region over a longer time period, and, in this way, heat may be deposited in the tumor very precisely and without external contact, as well as repeatedly. The heating is based upon the release of translation and rotation heat as a consequence of magnetic relaxation processes, as well as hysteresis heat losses.

The nanoparticles are preferably comprised of iron oxides, and, in particular, of magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3), or mixtures of these two oxides. In general, the preferred nanoparticles may be represented by the forms FeO_x, where X indicates a rational number from 1 to 2. The nanoparticles preferably have a diameter of less than 500 nm. The nanoparticles preferably have an average diameter of 15 nm, or are preferably in a size range from 1 - 200 nm, and, in particular, preferably in a range from 5 - 30 nm.

The production of nanoparticles without active substance and also without coating is described in detail in DE 4428851 A.

In addition to the magnetic materials of the formula FeO_x, where X is a rational number in a range from 1.0 to 2.0, according to the invention, materials of the

general formula MFe_2O_4 can also be used, where M = Co, Ni, Mn, Zn, Cd, Ba, or other ferrites.

It is also possible to furnish nanoparticles with something other than an iron oxide metal core. Especially the metals gold, silver, platinum, copper, cobalt, nickel, iron, manganese, samarium, neodymium, iridium, osmium, ruthenium, rhodium, palladium, or alloys of the aforementioned metals are hereby to be cited.

However, the possibility also exists of producing the nanoparticles from a non-magnetic material - for example, silicon dioxide (SiO_2). Also suitable are silica or polymer particles in which magnetic materials (for example, the aforementioned magnetic materials) are embedded and/or bound.

The magnetic particles may also be derivatised to the effect that chemical structures (for example, antibodies, nucleic acids, peptides, aptamers, or other molecules with pathfinding properties) which increase the affinity of the particles to abnormal cells are located on the surface of the particles. Such surface modifications improve the affinity to cancer cells, due to the recognition of specific surface structures on the abnormal cells. Preferred chemical structures which impart pathfinding properties to the magnetic particles are, for example, polyclonal antibodies, monoclonal antibodies, humanised antibodies, human antibodies, chimeric antibodies, recombinant antibodies, bi-specific antibodies, antibody fragments, aptamers, Fab fragments, Fc fragments, peptides, peptidomimetics, gap-mers, ribozymes, CpG oligomers, DNA-zymes, riboswitches, and lipids.

In a preferred embodiment of the present invention, therapeutically active substances may optionally be bound to the nanoparticles. The bonding of the active substance may take place covalently or via a predominantly covalent bond, and/or via a sufficiently strong ionic bond, interstitial compound, or complex bond, such that an uncontrolled release of the active substance is largely prevented. What is understood as an uncontrolled release is the separation of the active substance without the action of an alternating magnetic field.

Anti-proliferative, anti-migrative, anti-angiogenic, anti-thrombotic, anti-inflammatory, anti-phlogistic, cytostatic, cytotoxic, anti-coagulative, anti-bacterial, anti-viral, and/or anti-mycotic substances may be selected as therapeutically active substances, wherein anti-proliferative, anti-migrative, anti-angiogenic, cytostatic, and/or cytotoxic substances, as well as nucleic acids, amino acids, peptides, proteins, carbohydrates, lipids, glycoproteins, glycanes, or lipoproteins having anti-proliferative, anti-migrative, anti-angiogenic, anti-thrombotic, anti-inflammatory, anti-phlogistic, cytostatic, cytotoxic, anti-coagulative, anti-bacterial, anti-viral, and/or anti-mycotic properties, are preferred. Moreover, these substances may also be radio-sensitizers or sensitizers or intensifiers of other (also combined) conventional cancer treatment methods, or include such sensitizers.

Among other things, alkylation agents, antibiotics having cytostatic properties, antimetabolites, microtubuli inhibitors and topoisomerase inhibitors, platinum-containing compounds and other cytostatics, e.g., asparaginase,

tretinoin, alkaloids, podophyllotoxins, taxanes, and Miltefosin®, hormones, immune modulators, monoclonal antibodies, signal transductors (signal transduction molecules), and cytokines may be used as cytotoxic and/or cytostatic compounds, i.e., chemical compounds having cytotoxic and/or cytostatic properties.

Among other things, chlorethamine, cyclophosphamide, trofosfamides, ifosfamide, melphalan, chlorambucil, busulfan, thiotepa, carmustine, lomustine, dacarbazine, procarbazine, temozolomide, treosulfan, estramustine, and nimustine may be cited as examples of alkylation agents.

Examples of antibiotics having cytostatic properties are daunorubicin, doxorubicin (adriamycin), dactinomycin, mitomycin C, bleomycin, epirubicin (4-epi-adriamycin), idarubicin, mitoxantrone, and amsacrine.

Methotrexate, 5-fluorouracil, 6-thioguanine, 6-mercaptopurine, fludarabine, cladribine, pentostatin, gemcitabine, azathioprine, raltitrexed, capecitabine, cytosinarabinoside, thioguanine, and mercaptopurine may be listed as examples of antimetabolites (antimetabolic substances).

Belonging to the class of alkaloids and podophyllotoxins are, among others, vincristine, vinblastine, vindesine, etoposide, and teniposide. Furthermore, platinum-containing compounds may be used according to the invention. For example, cisplatin, carboplatin, and oxaliplatin are cited as platinum-containing compounds. Numbering among the microtubuli inhibitors are, for example, alkaloids such as vinca-

alkaloids (vincristine, vinblastine, vindesine, venorelbine) and taxanes (Paclitaxel/Taxol®, paclitaxel, and docetaxel), as well as derivatives of paclitaxel. For example, podophyllotoxins (etoposide, teniposide) and camptotheca alkaloids (camptothecine, topotecan, and irinotecan) may be cited as topoisomerase inhibitors.

Numbering among the other cytostatic substances (other cytostatics) are, for example, hydroxycarbamides (hydroxyurea), imatinib, Miltefosin®, amsacrine, pentostatin, bexaroten, tretinoin, and asparaginase. Representatives of the monoclonal antibodies compound class are, among others, trastuzumab (also known as Herceptin®), alemtuzumab (also known as MabCampath®), and rituximab (also known as MabThera®).

According to the invention, hormones such as glucocorticoids (prednisone), estrogens (fosfestrol, estramustine), LHRH (buserelin, goserelin, leuprorelin, triptorelin), flutamide, cyproteronacetate, tamoxifen, toremifen, aminoglutethimide, formestane, exemestane, letrozole, and anastrozole may also be used. Numbering among the classes of immunmodulators, cytokines, antibodies, and signal transductors are interleukin-2, interferon-α, interferon-γ, erythropoietin, G-CSF, trastuzumab (Herceptin®), rituximab (MabThera®), efitinib (Iressa®), ibritumomab (Zevalin®), levamisol, and retinoids.

The aforementioned active substances may be contained together with the magnetic particles in the medical product according to the invention, or may be applied to its surface. In the event that the active substance is covalently or ionically bound to the magnetic

particles or to the medical product or the biodegradable medical product, the bonding of the active substance occurs via, for example, hydroxy groups, amino groups, carbonyl groups, thiol groups, or carboxyl groups, depending upon which functional groups the respective active substance bears.

Hydroxy groups are preferably bound as esters, acetals, or ketals; thio groups are preferably bound as thioesters, thioacetals, or thioketals; amino groups are preferably bound as amides and, in part, also as imines (Schiff's bases); carboxyl groups are preferably bound as esters or amides; and carbonyl groups are preferably bound as ketals.

In addition to this, it is preferred not to bond the active substance or substances directly to a nanoparticle or the medical product or biodegradable medical products, but rather to immobilise them via a linker molecule. The functionalisation of the surface of the nanoparticles is also known, such that amino groups, hydroxy groups, carboxyl groups, or carbonyl groups may be generated on the surface of the nanoparticles according to known methods.

The therapeutically active substances are bonded to the nanoparticles and/or the medical product or the biodegradable medical product directly or via a linker molecule - preferably, by means of an amide bond or ester bond.

Linkers are preferred which include pH-cleavable acetal, ester, hydrazone, or imine groups and may be split via acid or by means of enzymatic reaction.

The amide group is to be cited, as an enzymatically cleavable group in or on the linker molecule. Groups that can be split thermally or by means of acid include, for example, phosphate groups, thiophosphate groups, sulfate groups, phosphamide groups, carbamate groups, or imino groups.

The active substance does not necessarily need to be covalently bound to the linker or the bioresorbable medical product, but rather may also be bound ionically or via hydrogen bridges, or be present in intercalated or complexed form.

As has already been stated, arbitrary magnetic particles may be used in the medical products according to the invention. Examples of such magnetic particles are described in WO 2005070471 A2, WO 0243708 A2, US 5,411,730 A1, WO 2005042142 A2, WO 03026618 A1, WO 2005065282 A2, WO 2006108405 A2, and WO 2007019845 A2.

Biodegradable medical products

The biodegradable medical products according to the invention, in the form of implants, fabric, textiles, wound dressings, or film-forming compositions, remain in the body of the patient after the wound is closed by the surgeon after a cancer operation.

The biodegradable medical products according to the invention serve, in particular, for after-treatment of the surgical site with heat, generated by means of thermotherapy, to kill remaining tumor cells and to prevent recidivation.

The biodegradable medical products according to the invention are thus comprised of physiologically compatible materials and/or are split into physiologically compatible degradation products and components.

The materials for the medical products according to the invention are selected from the group comprising or consisting of: polyacrylic acid, polyacrylates, polymethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyacrylamide, polyacrylnitrile, polyamide, polyetheramide, polyethylene amine, polyimide, polycarbonate, polycarbourethane, polyvinyl ketone, polyvinyl halogenide, polyvinylidene halogenide, polyvinyl ether, polyvinyl aromatics, polyvinyl ester, polyvinyl pyrollidone, polyoxymethylene, polyethylene, polypropylene, polytetrafluorethylene, polyurethane, polyolefin elastomer, polyisobutylene, EPDM rubbers, fluorosilicone, carboxymethylchitosan, polyethylene terephtalate, polyvalerate, carboxymethylcellulose, cellulose, rayon, rayon triacetate, cellulose nitrate, cellulose acetate, hydroxyethylcellulose, cellulose butyrate, cellulose acetate-butyrate, ethylvinyl acetate copolymer, polysulfone, polyethersulfone, epoxy resin, ABS resin, EPDM rubbers, silicone prepolymer, silicone, polysiloxane, polyvinyl halogen, cellulose ether, cellulose triacetate, chitosan, chitosan derivatives, polymerisable oils, polyvalerolactones, poly-ε-decalactone, polylactide, polyglycolide, copolymers of polylactides and polyglycolides, poly-ε-caprolactone, polyhydroxy butyric acid, polyhydroxybutyrate, polyhydroxyvalerate, polyhydroxybutyrate-co-valerate, poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one),

poly-para-dioxanone, polyanhydride, polymaleic acid anhydride, polyhydroxymethacrylate, polycyanoacrylate, polycaprolactone dimethylacrylate, poly-β-maleic acid, polycaprolactone butylacrylate, multiblock polymers made of oligocaprolactone diol and oligodioxanone diol, polyetherester multiblock polymers made of PEG and poly(butylene terephtalate), polypivotolactone, polyglycolic acid trimethylcarbonate, polycaprolactone-glycolides, poly(γ-ethylglutamate), poIy(DTH-iminocarbonate), poly(DTE-co-DT-carbonate), poly(bisphenol A-iminocarbonate), polyorthoester, polyglycol acid trimethylcarbonate, polytrimethylcarbonate, polyiminocarbonate, polyvinyl alcohols, polyester amides, glycolated polyesters, polyphosphoesters, polyphosphazenes, poly[p-carboxy-phenoxy)propane], polyhydroxypentanoic acid, polyethylene oxide-propylene oxide, weak polyurethanes, polyurethanes with amino acid groups in the backbone, polyether ester, polyethylene oxide, polyalkene oxalates, polyorthoesters, carrageenans, starches, collagens, protein-based polymers, polyamino acids, synthetic polyamino acids, zein, modified zein, polyhydroxyalkanoates, pectic acid, actinic acid, fibrin, modified fibrin, casein, modified casein, carboxymethylsulfate, albumin, hyaluronic acid, heparan sulfate, heparin, chondroitin sulfate, dextran, cyclodextrins, copolymers of PEG and polypropylene glycol, gum arabic, guar, or other gum resins, gelatins, collagen, collagen-N-hydroxysuccinimide, lipids, lipoids, polymerisable oils and their modifications, copolymers, and mixtures of the aforementioned substances.

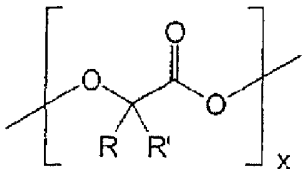
The aforementioned polymers are biodegradable, or may be produced with degrees of polymerisation and cross-linking which are biodegradable.

What is understood by the term "biodegradable" or "bioresorbable" is that these materials are more than 90 wt% broken down or degraded under physiological conditions within a time period of 1 month to 12 months - preferably, up to 6 months.

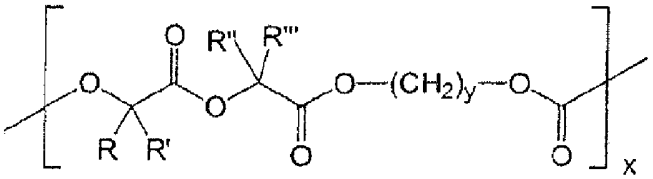
Preferred biodegradable polymers are polylactides, poIygIycoIides, copolymers of polylactides and polyglycolides, polyhydroxybutyrates, polyhydroxymethacrylates, polyorthoester, glycolated polyester, polyvinyl alcohols, polyvinyl pyrrolidone, acrylamide-acrylic acid-copolymers, hyaluronic acid, heparan sulfate, heparin, chondroitin sulfate, dextran, β-cyclodextrins, hydrophilically cross-linked dextrins, alginates, phospholipids, carbomers, cross-linked peptides and proteins, silicones, polyethylene glycol (PEG), polypropylene glycol (PPG), copolymers of PEG and PPG, collagen, polymerisable oils and waxes, as well as their mixtures and copolymers.

Furthermore, polyesters, polylactides, and copolymers of diols and esters or diols and lactides are preferred. For example, ethane-1,2-diol, propane-1,3-diol, or butane-1,4-diol are used as diols.

According to the invention, polyesters in particular are used for the polymer layer. From the group of polyesters, those polymers are in turn preferred which have the following repeat unit:

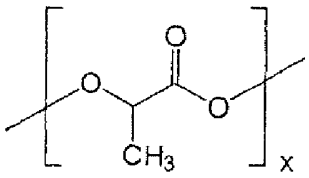


Structure A

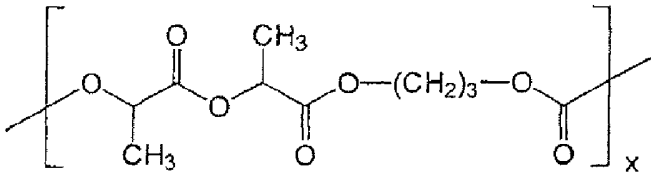


Structure B

In the shown repeat units, R, R', R", and R'" indicate an alkyl substituent having 1 to 5 carbon atoms - in particular, methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, t-butyl, iso-butyl, n-pentyl, or cyclopentyl, and preferably methyl or ethyl. Y stands for a whole number from 1 to 9, and X stands for the degree of polymerisation. Preferred in particular are the following polymers having the repeat units shown:



Structure A1



Structure B1

Cited as additional representatives of the resorbable Resomer® polymers are poly(L-lactide)s having the general formula $-(C_6H_8O_4)_n-$, such as L 210, L 210 S, L 207 S, L 209 S; poly(L-lactide-co-D,L-lactide)s having the general formula $-(C_6H_8O_4)_n-$, such as LR 706, LR 708, L 214 S, LR 704; poly(L-lactide-co-trimethylcarbonate)s having the general formula $-[(C_6H_8O_4)_x-(C_4H_6O_3)_y]_n-$, such as LT 706; poly(L-lactide-co-glycolide)s having the general formula $-[(C_6H_8O_4)_x-(C_4H_4O_4)_y]_n-$, such as LG 824, LG 857; poly(L-lactide-co-ε-caprolactone)s having the general formula $-[(C_6H_8O_4)_x-(C_6H_{10}O_2)_y]_n-$, such as LC 703; poly(D,L-lactide-co-glycolide)s having the general formula $-[(C_6H_8O_4)_x-(C_4H_4O_4)_y]_n-$, such as RG 509 S, RG 502 H, RG 503 H, RG 504

H, RG 502, RG 503, RG 504; poly(D,L- lactide)s having the general formula -[($C_6H_8O_4$)$_n$-, such as R 202 S, R 202 H, R 203 S, and R 203 H. Resomer® 203 S hereby represents the successor to the particularly preferred Resomer® R 203 polymer. The name Resomer® represents a high technology product of the company Boehringer Ingelheim.

In principle, the use of resorbable polymers in the present invention is particularly preferred. Also preferred are homopolymers of lactic acid (polylactides) and polymers that are produced from lactic and glycolic acid.

Biologically stable medical products

The biostable or non-biodegradable medical products according to the invention in the form of sponges, and, in particular, film-forming compositions, or textiles, tissue, cellulose, wound dressings, and the like, are produced from materials that are not or are barely biodegradable.

The materials for the biostable medical products according to the invention are selected from the group comprising or consisting of: polyacrylic acid and polyacrylates such as polymethyl methacrylate, polybutyl methacrylate, polyacrylamide, polyacrylonitriles, polyamides, polyetheramides, polyethyl ertamine, polyimides, polycarbonates, polycarbourethanes, polyvinyl ketones, polyvinyl halogenides, polyvinylidene halogenides, polyvinyl ether, polyvinyl aromatics, polyvinyl ester, polyvinyl pyrollidones, polyoxymethylenes, polyethylene, polypropylene, polytetrafluorethylene, polyurethanes, polyolefin elastomers, polyisobutylene, EPDM rubbers,

fluorosilicones, carboxymethyl chitosan, polyethylene terephtalate, polyvalerates, carboxymethyl cellulose, cellulose, rayon, rayon triacetates, cellulose nitrates, cellulose acetates, hydroxyethyl cellulose, cellulose butyrates, cellulose acetate-butyrates, ethyl vinyl acetate copolymers, polysulfones, epoxy resins, ABS resins, EPDM rubbers, silicones such as polysiloxanes, polyvinyl halogens and copolymers, cellulose ether, cellulose triacetates, chitosan, and copolymers and/or mixtures of the same.

Preferred biostable polymers which are used in medical engineering and for biostable implants are polyether sulfone, substituted polyether sulfone, polyphenyl sulfone, substituted polyphenyl sulfone, polysulfone block copolymers, perfluorinated polysulfone block copolymers, semifluorinated polysulfone block copolymers, substituted polysulfone block copolymers, and/or mixtures of the aforementioned polymers.

Gels

The nanoparticles may also be introduced into gels or hydrogels, or may be components of film-forming sprays which are preferably also biodegradable. For better stabilisation of the gels or film-forming sprays, the nanoparticles described herein may be combined with gel or film formers.

Suitable gel formers or film formers are preferably substances based upon cellulose, such as cellulose nitrate or ethyl cellulose or physiologically harmless addition polymers of these, polyvinyl acetate, partially saponified polyvinyl acetate, mixed addition polymers made up of vinyl acetate and acrylic acid or crotonic acid or maleic acid

monoalkyl ester, ternary mixed addition polymers made up of vinyl acetate and crotonic acid and vinyl neodecanoate, or crotonic acid and vinyl propionate, mixed addition polymers made up of methylvinyl ether and maleic acid monoalkyl ester - in particular, as maleic acid monobutyl ester - mixed addition polymers made up of fatty acid vinyl ester and acrylic acid or methacrylic acid, mixed addition polymers made up of N-vinyl pyrrolidone, methacrylic acid and methacrylic acid alkyl ester, mixed addition polymers made up of acrylic acid and methacrylic acid or acrylic acid alkyl ester or methacrylic acid alkyl ester - in particular, having a content of quaternary ammonium groups - or polymers, copolymers, or mixtures containing ethyl acrylate, methyl methacrylate, or trimethyl ammonioethyl methacrylate chloride, or polyvinyl acetals and polyvinyl butyrals, alkyl-substituted poly-N-vinyl pyrrolidones, alkyl esters made up of mixed addition polymers of olefins and maleic acid anhydride, conversion products of colophonium with acrylic acid, as well as benzoic resin, chitosan, Luvimer 100®, aluminium stearate, carbomers, cocamide MEA, carboxymethyl dextran, carboxymethyl hydroxypropyl guar, or red algae carrageenans.

In the aforementioned esters, the alkyl radicals are customarily short-chained and for the most part do not have more than four C-atoms. Such substances are also designated herein as polymer-forming or gel-forming substances.

Additionally counting among the gel formers or film formers are also water-soluble polymers, e.g., ionic polyamides, polyurethanes, and polyesters, as well as homo- and co-polymers of ethylenically unsaturated monomers. Such substances are under, for example, the trade names Acronal©, Acudyne®, Amerhold®, Amphome®,

Eastman AQ®, Ladival®, Lovocryl®, Luviflex VBM®, Luvimer®, Luviset P. U. R.®, Luviskol®, Luviskol Plus®, Stepanhold®, Ultrahold®, Ultrahold Strong®, or Versatyl®. Luvimer® is a polyacrylate.

Additional components of the gels may primarily be natural polymers. Counting among these are albumin, collagen, hyaluronan, chitosan, and chitin. An especially preferred non-natural polymer is copolymer or block copolymer of polyethylene oxide having terminal α-hydroxy acids or poly-α-hydroxy acids.

Furthermore, glycosaminoglycanes - for example, aggrecan, decorin, biglycan, and fibromodulin - are common components of bioresorbable gels or film-forming solutions or sprays.

Saline solutions - for example, physiological (0.9 percent) table salt solution, PBS (phosphate-buffered saline, i.e., phosphate-buffered physiological table salt solution), DMEM (Dulbecco's Modified Eagle Medium) - may be used in the gels, solutions, and sprays.

Given a use of superparamagnetic nanoparticles having an iron oxide core, a proportion of 3-30 wt% iron oxide in 200 mg gel is preferred; more preferable is a proportion of 5-25 wt% iron oxide in 200 mg gel, and especially preferred is a proportion of 10-20 wt% iron oxide in 200 mg gel.

Polymer carriers

The magnetic particles may already be added during the production of polymers, and are then integrated into the bioresorbable polymers.

Examples of biodegradable medical products according to the invention are polymer beads containing the magnetic particles. The polymer beads are preferably comprised of polyhydroxybutyrate, polylactide, polyglycolide, or copolymers of polylactide-co-glycolide. An additional, particularly preferred material is alginate, as well as Eudragit®. These polymer beads contain up to 20 wt% magnetic particles.

The polymer beads may be used as such or integrated into pastes, or may be immobilised on medical cellulose.

The polymer beads may be heated in an alternating magnetic field, up to temperatures of 50 °C.

Medical cellulose

The coated medical implantable products on which the nanoparticles are applied are preferably bioresorbable. This means that they may dissolve completely in the body, or are at least physiologically well-tolerated.

The medical products containing nanoparticles are, among other things, medical cellulose, bandage materials, wound inserts, surgical thread material, compresses, and medical textiles.

Polyhydroxybutyrates and cellulose derivatives, chitosan derivatives and collagen, polyethylene glycol, polyethylene oxide, and polylactides are preferred materials for medical celluloses and textiles. If alginates are used as wound dressing, products of calcium alginate interwoven with sodium carboxymethyl cellulose

are preferably used. SeaSorb Soft from the company Coloplast is hereby to be cited as an example.

In the event that the nanoparticles are applied to wound bandages and/or wound inserts, the products Tabotamp® and Spongostan® from the company Johnson and Johnson are to be cited in particular. These products are produced via controlled oxidation from regenerated cellulose.

In the event that surgical thread materials are to be impregnated with the nanoparticles, thread materials are used that are preferably comprised of polyglycolic acid, polycaprolactone-coglycolide, or poly-p-dioxanone. Here, the products Marlin®, PCL, and Marisorb® from the company Catgut GmbH are cited as examples.

In the event that compresses are to be impregnated with the nanoparticles, sterile gauze compresses made of 100 % cotton, in particular, are to be used. Here, the Stericomp® and Askina® product lines are to be cited as examples.

In the event that medical pulp is used, a pulp that has a proportion of more than 90 % cellulose is preferred.

In the event that medical textiles are used, Trevira® products are preferred.

The medical textiles and celluloses are sprayed with a solution of the magnetic particles in water, ethanol, or water-ethanol mixtures, or are submerged therein, wherein the submersion or spraying process may

be repeated multiple times after the drying of the medical product.

10 µg to 100 mg of magnetic particles are applied per cm^2 of the surface of the medical product.

100 µg to 2 g of magnetic particles are applied per g of the medical product.

Sponges

The medical sponges are bioresorbable implants with spongy, porous structure.

Preferred materials for medical sponges are collagen, oxidized cellulose, chitosan, thrombin, fibrin, chitin, alginates, hyaluronic acid, PLGA, PGA, PLA, polysaccharides, and globin.

In the event that medical sponges are used, those that have a proportion of more than 90 % collagen are preferred.

100 µg to 2 g of magnetic particles are applied per g of the medical product.

Salves and pastes

In the event that the nanoparticles are incorporated into salves, a salve base is used that is comprised of purified water in a quantity of preferably 5 - 50 wt%, particularly preferably of 10 - 40 wt%, and most preferably of 20 - 30 wt%. The salve additionally includes Vaseline, preferably in a quantity of 40 - 90 wt%, particularly preferably of 50 - 80 wt%, and most preferably of 20 - 60 wt%. The salve may additionally

contain viscous paraffin in a quantity of 5 - 50 wt%, particularly preferably of 10 - 40 wt%, and most preferably of 20 - 30 wt%.

The gel formers and/or film formers that are mentioned here may additionally be added in a quantity of up to 30 wt%. In addition, polymers may be used, e.g., cellulose, chitosan, thrombin, fibrinogen, chitin, alginate, albumin, hyaluronic acid, hyaluronan, polysaccharides, globin, polylactide, polyglycolide, polylactide-co-glycolide, polyhydroxybutyrates, cellulose derivatives, chitosan derivatives, polyethylene glycol, and polyethylene oxide in quantities of up to 30 wt%.

Film-forming sprays

The nanoparticles according to the invention may also be introduced into spray solutions or be components of film-forming sprays. For better stabilisation of the film-forming sprays, the magnetic particles or active substance-containing nanoparticles described herein may be combined with film formers. Film-forming sprays contain at least one or more film formers.

Suitable film formers are preferably substances based upon cellulose, such as cellulose nitrate or ethyl cellulose or physiologically harmless addition polymers of these, polyvinyl acetate, partially saponified polyvinyl acetate, mixed addition polymers made up of vinyl acetate and acrylic acid or crotonic acid or maleic acid monoalkyl ester, ternary mixed addition polymers made up of vinyl acetate and crotonic acid and vinyl neodecanoate, or crotonic acid and vinyl propionate, mixed addition polymers made up of methylvinyl ether and maleic acid monoalkyl ester - in particular, as maleic

acid monobutyl ester - mixed addition polymers made up of fatty acid vinyl ester and acrylic acid or methacrylic acid, mixed addition polymers made up of N-vinyl pyrrolidone, methacrylic acid and methacrylic acid alkyl ester, mixed addition polymers made up of acrylic acid and methacrylic acid or acrylic acid alkyl ester or methacrylic acid alkyl ester - in particular, having a content of quaternary ammonium groups - or polymers, copolymers, or mixtures containing ethyl acrylate, methyl methacrylate, or trimethyl ammonioethyl methacrylate chloride, or polyvinyl acetals and polyvinyl butyrals, alkyl-substituted poly-N-vinyl pyrrolidones, alkyl esters made up of mixed addition polymers of olefins and maleic acid anhydride, conversion products of colophonium with acrylic acid, as well as benzoic resin, chitosan, Luvimer 100®, aluminium stearate, carbomers, cocamide MEA, carboxymethyl dextran, carboxymethyl hydroxypropyl guar, or red algae carrageenans.

In the aforementioned esters, the alkyl radicals are customarily short-chained and for the most part do not have more than four C-atoms.

Counting among the film formers are also water-soluble polymers, e.g., ionic polyamides, polyurethanes, and polyesters, as well as homo- and co-polymers of ethylenically unsaturated monomers. Such substances are under, for example, the trade names Acronal®, Acudyne®, Amerhold®, Amphome®, Eastman AQ®, Ladival®, Lovocryl®, Luviflex VBM®, Luvimer®, Luviset P. U. R.®, Luviskol®, Luviskol Plus©, Stepanhold®, Ultrahold®, Ultrahold Strang®, or Versatyl®. Luvimer® is a polyacrylate developed as a flair styling polymer by the company BASF AG.

Water, ethanol, or water-ethanol mixtures are preferred as solvents.

Given a use of superparamagnetic nanoparticles having an iron oxide core, a proportion of 3-30 wt% iron oxide in 200 mg gel is preferred; particularly preferred is a proportion of 5-25 wt% iron oxide in 200 mg gel, and most preferred is a proportion of 10-20 wt% iron oxide in 200 mg gel.

100 µg to 2 g of magnetic particles are applied per g of the medical product.

The production of the nanoparticle-containing implants takes place by means of dipping or spraying methods. The products to be implanted are thereby immersed in a nanoparticle-containing solution or suspension, or are sprayed with a nanoparticle-containing solution. The products are subsequently dried and packaged in a sterile manner. The gels, salves, solutions, and sprays are obtained by producing the desired pharmaceutical preparation according to standard methods, and the desired quantity of magnetic particles is preferably added in a last step.

The obtained biodegradable medical products are used for treatment and prophylaxis of tumors, carcinomas, and cancer, and, in particular, serve for the after-treatment of the surgical site after a cancer operation, and in particular after removal of a solid tumor.

Examples of cancer and tumor types where the medical products according to the invention may be used are: adenocarcinomas, choroidal melanoma, acute leukemia, acoustic neurinoma, ampulla carcinoma, anal carcinoma,

astrocytomas, basal cell carcinoma, pancreatic cancer, connective tissue tumors, bladder cancer, bronchial carcinoma, non-small cell bronchial carcinoma, breast cancer, Burkitt lymphoma, corpus carcinoma, CUP syndrome, colon cancer, small intestine cancer, small intestine tumors, ovarian cancer, endometrium carcinoma, ependymoma, epithelial cancer types, Ewing tumors, gastrointestinal tumors, gall bladder cancer, gall carcinomas, uterine cancer, cervical cancer, glioblastomas, gynecological tumors, ear, nose, and throat tumors, hemotological neoplasias, urethral cancer, skin cancer, brain tumors (gliomas), brain metastases, testicular cancer, pituitary tumor, carcinoids, Kaposi sarcoma, laryngeal cancer, germ cell tumor, bone cancer, colorectal carcinoma, head-throat tumors (tumors of the ear, nose, and throat region), colon carcinoma, craniopharyngeomas, cancer in the oral region and on the lips, liver cancer, liver metastases, eyelid tumor, lung cancer, lymph node cancer (Hodgkin's/Non-Hodgkin's), lymphomas, stomach cancer, malignant melanoma, malignant neoplasmas, malignancies of the gastrointestinal tract, mammary carcinoma, rectal cancer, medulloblastomas, melanoma, meningeomas, Hodgkin's disease, mycosis fungoides, nose cancer, neurinoma, neuroblastoma, kidney cancer, kidney cell cancer, Non-Hodgkin's lymphoma, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas, u. [sic] osteoplastic carcinomas, osteosarcoma, ovarian carcinoma, pancreatic carcinoma, penile cancer, squamous epithelial carcinoma of the head and throat, prostate cancer, throat cancer, rectal carcinoma, retinal blastoma, vaginal cancer, thyroid carcinoma, Schneeberg disease, esophageal cancer, spinalioma, T-cell lymphoma (mycosis fungoides), thymoma, tubal carcinoma, tumors of the eye, urethral cancer, urological tumors, urothelial carcinoma, vulval cancer,

wart involvement, soft tissue tumors, soft tissue sarcoma, Wilms' tumor, cervical carcinoma, and tongue cancer.

Solid tumors are preferred in particular. Also preferred are prostate carcinomas, brain tumors, sarcomas, cervical carcinomas, ovarian carcinomas, mammary carcinomas, bronchial carcinomas, melanomas, head-throat tumors, esophageal carcinomas, rectal carcinomas, pancreatic, bladder, and kidney carcinomas, and metastases of the liver, brain, and in the lymph nodes.

Also preferred in particular are the application and use of the bioresorbable medical products according to the invention in medicine, preferably together with radiation therapy and/or together with conventional chemotherapy.

This gentle method of thermotherapy includes a spatially limited use of cancer medications, and thus reduces the medication load and the side effects for the patient. In addition to this, the probability of a new metastasis is drastically reduced, since, locally, a cancer treatment of the tumor cells remaining after an incomplete resection occurs selectively. The medications that are possibly located on the implant according to the invention or on the medical product according to the invention may additionally be released from the nanoparticle via an externally applied alternating magnetic field and deploy their effect selectively, directly at the active location. This also allows more precise medication dosing, since, due to the local therapy form, no medication is lost during a transport through the body. The method described above can also be implemented effectively against cancer cells with

nanoparticles lacking linked active substance. The nanoparticles thereby accumulate at the cancer cells or penetrate into the cancer cells, and destroy said cancer cells due to an externally applied magnetic field which heats the magnetic particles.

To further increase affinity with regard to specific cell types, molecules with pathfinding properties - for example, monoclonal antibodies and/or aptamers - may be additionally coupled to the surface of the nanoparticles or to the outer layer or shell of the nanoparticles.

In a preferred embodiment of the present invention, the cores of the magnetic nanoparticles are comprised of magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3), or mixtures of these two oxides, and are preferably superparamagnetic. The cores are, moreover, stabilised via colloidal protective shells that enable a bonding of the therapeutically active substances.

Examples

Example 1A:

General specification for the production of a nanoparticle suspension / solution for the impregnation or spraying or dipping of the carrier

A solution of 0.23 mol $FeCl_2$ and 0.46 mol $FeCl_3$ in 1 L water is degassed with nitrogen. Within 20 minutes, so much 5 M NaOH is added that a pH value of 11.5 is achieved. The resulting precipitate is heated for 10 minutes to 65 °C and is subsequently cooled to room temperature within 5 minutes. The precipitate is

thereupon suspended with deionised and degassed water until the pH value of the wash solution has reached 9. The precipitate is suspended in water, and the suspension is set to pH 6 with glacial acetic acid. 10 vol% of a 30 percent by weight aqueous H_2O solution is added to the resulting suspension and is stirred until the end of the gas development, whereupon the suspension is diluted with water to a solid content of 5 wt% iron oxide.

Example 1B (without oxidation / with air gas treatment):

To produce iron oxide nanoparticles in ethylene glycol, 0.1 mol $FeCl_3*6H_2O$ and 0.2 mol $FeCl_3$ (anhydrous), 50 g sodium acetate, and 195 g diaminohexane were dissolved in 900 mL ethylene glycol and heated for 1 hour to 60 °C. The solution was then heated to boiling point within 30 minutes. The boiling temperature was maintained for 6 hours. The created dispersion was slowly cooled to room temperature.

The particles were washed 3 times with a mixture of ethanol/water. The particles were subsequently suspended again in 900 mL ethylene glycol and gas-treated with atmospheric oxygen. The suspension was heated to the boiling point of ethylene glycol and maintained at this temperature for 24 hours. After cooling, the particles were washed with water/ethanol and suspended in water.

These particles were coated analogously to Example 1G.

Example 1C (with oxidation / with air gas treatment):

To produce iron oxide nanoparticles in ethylene glycol, 0.1 mol $FeCl_3*6H_20$ and 0.2 mol $FeCl_3$ (anhydrous), 50 g sodium acetate, and 195 g diaminohexane were dissolved in 900 mL ethylene glycol and heated for 1 hour to 60 °C. The solution was then heated to boiling point within 30 minutes. The boiling temperature was maintained for 6 hours. The created dispersion was slowly cooled to room temperature.

The particles were washed 3 times with a mixture of ethanol/water. The particles were subsequently suspended again in 900 mL ethylene glycol and gas-treated with atmospheric oxygen. The suspension was heated to the boiling point of ethylene glycol and maintained at this temperature for 24 hours.

After cooling, the particles were washed with water/ethanol and suspended in 900 mL 1 M HNO_3. 450 mL of a 0.7 M iron nitrate solution ($Fe(NO_3)_3$ * 9 H_2O) was added and boiled for one hour under reflux (100 °C). The particles were washed 3 x with respectively 500 mL water.

These particles were coated analogously to Example 1G.

Example 1D (without oxidation / without air gas treatment):

To produce iron oxide nanoparticles in ethylene glycol, 0.1 mol $FeCl_3*6H_2O$ and 0.2 mol $FeCl_3$ (anhydrous), 50 g sodium acetate, and 195 g diaminohexane were dissolved in 900 mL ethylene

glycol and heated for 1 hour to 60 °C. The solution was then heated to boiling point within 30 minutes. The boiling temperature was maintained for 6 hours. The created dispersion was slowly cooled to room temperature.

The particles were washed 3 times with a mixture of ethanol/water. The particles were subsequently suspended again in 900 mL ethylene glycol. The suspension was heated to the boiling point of ethylene glycol and maintained at this temperature for 24 hours.

After cooling, the particles were washed with water/ethanol and suspended in water.

These particles were coated analogously to Example 1G.

Example 1E (with oxidation / without air gas treatment):

To produce iron oxide nanoparticles in ethylene glycol, 0.1 mol $FeCl_3*6H_2O$ and 0.2 mol $FeCl_3$ (anhydrous), 50 g sodium acetate, and 195 g diaminohexane were dissolved in 900 mL ethylene glycol and heated for 1 hour to 60 °C. The solution was then heated to boiling point within 30 minutes. The boiling temperature was maintained for 6 hours. The created dispersion was slowly cooled to room temperature.

The particles were washed 3 times with a mixture of ethanol/water.

The particles were subsequently suspended again in 900 mL ethylene glycol. The suspension was heated to the boiling point of ethylene glycol and maintained at this temperature for 24 hours.

After cooling, the particles were washed with water/ethanol and suspended in 900 ml 1 M HNO_3. 450 mL of a 0.7 M iron nitrate solution ($Fe(NO_3)_3$ * 9 H_2O) was then added and boiled for one hour under reflux (100 °C). The particles were washed 3 x with respectively 500 mL water. These particles were coated analogously to Example 1G.

Example 1F:

To produce iron oxide nanoparticles, a solution of 96 g sodium hydroxide and 680 mL oleic acid in 2000 mL methanol was added to a solution of 216 g iron (III) chloride hexahydrate in 500 mL methanol. The solid that was created was washed with methanol and dissolved in diethyl ether. Extraction was then performed repeatedly with water. The solid was precipitated with acetone, washed, and dried in vacuum.

75 g of this solid was dissolved in 250 mL trioctylamine and heated for 1 hour to 120 °C.

The solution was then heated in an autoclave to 380 °C within 30 minutes. This temperature was maintained for 4 hours. The created dispersion was slowly cooled to room temperature. The particles were washed 3 times with a mixture of ethanol/water.

The particles were subsequently suspended in 300 mL diethylene glycol-dibutyl ether and gas-treated with atmospheric oxygen. The suspension was heated in an autoclave to 300 °C [sic] maintained at this temperature for 24 hours.

These particles were oxidized as in Example 1C and then coated analogously to Example 1G.

Example 1G:

The particles from Examples 1B through 1F were centrifuged out at high g forces and washed with ethanol. 500 mg of the washed product were weighed in an extraction sleeve (603 g, Whatman company) and inserted into a Soxhlet apparatus. 200 mL ethanol as an extraction agent were filled into the feed envelope of the Soxhlet apparatus. The extraction agent was heated to boiling. The continuous extraction was conducted over 8 h and included approximately 16 extraction cycles. The ethanol solution thereby turned yellowish in colour. After the end, the extraction sleeve was removed and the powder transferred into a Schlenk vessel and dried for 1 h in vacuum. To disperse the particles after extraction, 0.5 g of the nanoparticle powder from Example 4 were suspended in 20 mL 0.01 HCl. The nanoparticles were then treated with ultrasound for 30 minutes. 0.5 g of solid sodium oleate was then added.

3.3 mL of a particle dispersion according to Example 5 (0.97 mol/L Fe) and 2.14 mL tetraethoxysilane were added to 120 mL of a mixture of water / ethanol (3:1) and 1.5 wt% ammonia. The dispersion was

stirred during the addition and subsequently treated with ultrasound for 6 hours. The dispersion was purified via centrifugation and redispersion in water.

Example 2: Sponge

Wound insert impregnated with nanoparticles

A commercially available Tabotamp® sponge was immersed for 6 minutes in the nanoparticle suspension produced under Example 1. After drying, the dipping process was repeated an additional two times. Alternatively, the suspension may be applied with a syringe. This process may be repeated multiple times until the desired loading of the sponge is achieved.

Example 3: Medical cellulose

Medical cellulose coated with nanoparticles

A 3-cm-wide and 6-cm-long piece of a wound dressing (for example, SeaSorb Soft from the company Coloplast) comprising calcium alginate and sodium carboxymethylcellulose was sprayed 5 times with approximately 1 mL of the nanoparticle suspension according to Example 1, and was dried for approximately 20 minutes in air after every spraying process. Alternatively, the suspension may be applied with a syringe. This process may be repeated multiple times until the desired loading of the sponge is achieved.

Example 4: Medical cellulose with active substance

Medical cellulose impregnated with nanoparticles and cytostatic agent

A commercially available medical cellulose made of sodium carboxymethyl cellulose, poly-N-vinyl pyrrolidones, and polyethylene oxide (5 cm^2) was immersed for 5 minutes in a nanoparticle suspension produced according to Example 1, which suspension contained 0.3 mg Paclitaxel per ml solution. After drying and sterilisation, the medical product is ready for use.

Example 5: Gel

Production of a gel according to the invention:

4 g of a mixture of collagen type I and collagen type Il are dissolved in one liter of a 50 mM acetic acid solution. The collagen solution is centrifuged for 45 minutes at 4 °C and 9500 revolutions per minute. The supernatant is decanted, filled into a dialysis hose and dialysised for two days with 25 liters of a 1 M acetic acid solution, and subsequently dialysised for 4 days with water.

The collagen solution was subsequently concentrated in the dialysis hose up to a concentration of 20 mg/mL (2 % w/v).

To produce the gel, 10 mL of the collagen solution were incubated with 0.1 mL of a 1 N NaOH solution and 1 mL DMEM (Dulbecco's Modified Eagle Medium 10 X) for one hour at 37 °C.

1.5 g of lyophilised nanoparticles of a size distribution from 1-100 nm was subsequently added.

After a surgical removal of a solid small intestine tumor, the gel was applied as completely as possible to the surgical site.

A subsequent treatment by means of thermotherapy in an alternating magnetic field showed a heating of the surgical sites to 53 °C.

Example 6: Gel with active substance

0.1 g of the cytostatic temozolomide is added to 10 g of the gel produced according to Example 5 and subsequently mixed well.

The administration of the gel took place as described in Example 5.

Example 7: Sponge

2 g globin powder are produced as described in US 2007031474 A.

A sponge-like implant is produced by lyophilising a 1% aqueous suspension of oxidized cellulose at pH 7.2 with 1.5 wt% globin powder. The oxidized cellulose may also be used in the form of fibres or two- or three-dimensional structures.

The obtained sponge-like structure is comprised of approximately 100 mg oxidized cellulose and between 40 and 200 mg globin, and has a volume of approximately 10 cm^3 and a thickness of approximately 3 mm.

The sponge-like structure is sterilised with ethylene oxide and packaged.

Example 8A: Particles with active substance

Production of nanoparticles with attached mitomycin

To attach the cytostatic mitomycin to aminosilane-stabilised iron oxide nanoparticles, a conjugate of mitomycin and an aldehyde-functionalised alkoxysilane (for example, triethoxysilylbutyraldehyde) is first synthesised. In this way, the active substance is attached via an imine bond. This conjugate is added while stirring to an aqueous dispersion of aminosilane-stabilised particles, such as, for example, those from WO 97/38058 A. Ethylene glycol is added to the mixture, and the water is removed via distillation. The conjugate of the active substance and silane is thereby joined to the already present envelope based on aminosilane (condensed). The purification takes place via dialysis with ultra-pure water. A detailed reaction description is included in WO 2006108405 A2.

Example 8B:

The production of nanoparticles with doxorubicin joined to the particle via an avidine bridge is implemented as described in WO 2006108405 A2.

Example 8C:

The production of nanoparticles with doxorubicin connected via a nucleotide sequence is implemented as described in WO 2006108405 A2.

Example 9: Sponge

A sponge-like structure is produced as described in Example 7, wherein, instead of oxidized cellulose, a mixture of collagen type I, collagen type Il, and chitosan (25 wt% : 25 wt% : 50 wt%) is used. The obtained sponge is subsequently impregnated with an aqueous suspension of nanoparticles with linked doxorubicin according to Examples 8B or 8C, and dried. Instead of the subsequent impregnation, the nanoparticle suspension according to Examples 8A, 8B, or 8C may also be added [sic] suspension corresponding to Example 7 and be lyophilised together with the other components.

Example 10: Medical cellulose

Medical cellulose based upon chitosan, uronic acid, and carboxymethyl dextran (4 cm^2, approximately 20 mg) is spread out flat in a petri dish, and an aqueous suspension containing the nanoparticles with joined mitomycin according to Example 8A is applied by drops until the cellulose is loaded with 50 mg of nanoparticles.

Example 11: Gel with nanoparticles

23.5 wt% of unhydrogenated lecithin, 20.0 wt% propylene glycol, 10.0 wt% ethanol, 2.5 wt% sorbitol, 0.05 M phosphate buffer (to 100.0 %) were stirred at room temperature for 16 h.

In order to obtain a nanoparticle gel, the gel that is thus obtained is stirred with nanoparticle suspension from Example 1 for 4 h.

Example 12: Film-forming spray with nanoparticles

172 g maleic acid diethyl ester (supply 1), 98 g maleic acid anhydride (supply 2, in a heatable dropping funnel), 200 g vinyl isobutyl ether (supply 3), and 12 g tert-butyl perneodecanoate (supply 4) are put into corresponding dosing vessels. 111 mL from supply 1, 10 mL from supply 3, and 3 mL from supply 4 are placed in a 2 L agitator vessel (equipped with agitator, heater, return condenser, and the prepared dosing devices, as well as with gas intake and outlet) and heated to 60 °C. At this temperature, the remaining supply 1, the remaining supply 3, and the supply 2 are additionally dosed over 3 hours, and the remaining supply 4 is additionally dosed over 4 hours. Stirring subsequently takes place for an additional 1 hour at 80 °C. A colourless, highly viscous melt is obtained that is mixed at this temperature with 18 g water and stirred for 1 h. After cooling to 75 °C, 480 g ethanol are additionally dosed within 15 minutes, and stirring takes place for 1 h at this temperature. After cooling to 25 °C, a clear, viscous polymer solution having a solid content of 48.1 wt% is obtained.

In order to obtain a film-forming nanoparticle spray, the viscous polymer solution that is thus obtained is stirred with nanoparticle suspension from Example 1 for 2 h.

Example 13: Film-forming spray with nanoparticles and active substance

10 mL of the polymer solution obtained according to Example 12 is mixed with 100 mg carboplatin and 1000 mg lyophilised nanoparticles according to Example 1.

Example 14: Treatment of cervical, thoracic wall, and ENT tumors

A carrier material impregnated with a nanoparticle solution according to Example 1A (2 molar & 3 molar) is applied to a bone. The bone is positioned in a therapy device and exposed to an alternating magnetic field. The temperature increase to be measured at the bone is determined at as constant an ambient temperature as possible. This test setup shows that cervical, thoracic wall, and ENT tumors may be treated in an alternating magnetic field by means of nanoparticle-coated carriers which are applied onto or in a region of a bone.

Materials

- Devices:
  - MFH-12TS therapy device
  - recirculating chiller (Julabo; FC600S) with hose connections,
  - Fixator (rats [sic]) with hose terminals,
  - Polytec Luxtron (model: LAB. KIT) with 2 temperature measurement probes,
  - measurement device for field strength (with probe),
  - water baths (37 °C),
  - calibration probe (calibrated through 11/09)

- Material:

  - 2M or 3M nanoparticle suspension according to Example 1A: respectively treated with ultrasound for 15 minutes
  - carrier material:

    ■ 1: SPONGOSTAN powder

(1 g, resorbable gelatin powder, hemostatic; Johnson+Johnson)

■ 2: SPONGOSTAN Special

(7x5x0.1 cm, resorbable hemostatic gelatin sponge; Johnson+Johnson)

■ 3: Gelita tampon

(1x1x1 cm, sponge-like, made from cured gelatin of porcine origin, hemostyptic, that is completely biodegradable; B. Braun Melsungen AG)

■ 4: Lyostypt

(3x5 cm, wet-stable compress made from native collagen of bovine origin, for local hemostasis, resorbable; B. Braun Melsungen AG)

- bone ("pork loin ribs"),
- forceps,
- modeling clay,
- medical plaster, (Durapore™; 3M; 2.5 cm x 9.14 m)
- cold / warm compress (Pharma-Depot GmbH; 13x14 cm)
- tuberculin syringe (Omnifix®-F; Braun; 0.01 mL/1 mL),
- one-time injection cannula (Sterican®; Braun; 27Gx11/2", 0.40x40 mm),
- Vernier caliper (DialMax. calibrated through 08/09; MS150-4/Atl),
- scalpel (No. 11 blade),
- beakers,
- camera,

• Chemicals:

- hydrogen peroxide (H_2O_2; 30 %),

- algenate (alginic acid sodium salt),

Test setup

A suitable fixator was tempered at 55 °C by means of a circulation cooler, and density tests were implemented.

1. The fixator was positioned in the column of the therapy device.

2. A pre-warmed (37 °C) cold / warm compress was placed at the "head" of the fixator (reduced the air space in the vessel and "buffered" the temperature fluctuations somewhat).

3. Bone:

■ A bone was detached from the loin ribs and the flesh roughly removed.

■ H_2O_2 was placed in a beaker.

■ The bone was subsequently "cleaned" with a scalpel.

■ The bone was divided with a saw into pieces suitable for testing.

4. Field strength:

■ The measurement head for the field strength measurement is positioned at the position in the fixator at which the measurements are later conducted; modeling clay hereby serves as a marking aid.

■ 3 field strengths (that are relevant to the clinical application) are measured: 3.0 kA/m, 3.5 kA/m, 4.0 kA/m.

■ These measurements yielded the following values:

kA/m	% field strength
3.03	14.5
3.49	17.0
4.07	20.5

% field strength is the device setting which corresponds to the associated field strength in kA/m.

5. In the fixator, temperature of the air space and the applicator floor are determined.

Example 14A: Lyostypt

Particle: Nanoparticle suspension according to Example 1A (0.5 mL, 2 molar)

Carrier: Lyostypt®, size: (19.95 x 14.9 x 3.4) mm

Bone: Size: (44.4 x 13.2 x 10.9) mm

A bone piece was measured [dimensions: (44.4 x 13.2 x 10.9) mm], and a piece of carrier [dimensions: (19.95 x 14.9 x 3.4) mm] was cut to size. The carrier is placed on the bone and impregnated with the particles (0.5 mL, 2 molar according to Example 1A). The loaded bone is positioned in the applicator [probe 1 (red): perpendicular from above to the impregnated carrier; probe 2 (blue): base value ("blank" bone)], and the measurement values are determined for the carrier:

nominal field strength: 3.0 kA/m → 14 %	
0:00:00	probe 1: approximately 33 °C, MF↑, blower↑
2:00	probe 1: approximately 36.5 °C
5:15	probe 1: approximately 36.0 °C, carrier substance slides slowly downward, away from the probe

8:40	probe 1: approximately 35.9 °C
9:40	probe 1 ↓ since it "pulled out"
10:00	probe 1: approximately 35.8 °C, MF↓
11:48	probe 1: 32.8 °C, probe realigned
12:30	probe 1: 32.5 °C, MF↑ (14 %)
17:26	probe 1: 35.4 °C, MF↓
20:44	New position: probe situated between carrier substance and bone
21:45	probe 1: 31.8 °C, MF↑ (14 %), blower↑
26:47	probe 1: 33.7 °C, MF↓
28:30	blower↓

nominal field strength: 3.5 kA/m → 17 % (new piece of carrier substance with identical dimensions and volumes of nanotherm, probe between carrier substance and bone)	
0:00:00	probe 1: 26.0 °C, MF↑, blower↑
2:00	probe 1: 30.3 °C
2:35	probe 1: 31.0 °C
2:58	probe 1: 31.3 °C
3:26	probe 1: 31.6 °C
3:46	probe 1: 31.9 °C
4:00	probe 1: 32.0 °C
5:00	probe 1: 32.5 °C
5:44	probe 1: 32.8 °C
6:51	probe 1: 33.0 °C
8:00	probe 1: 33.4 °C
9:00	probe 1: 33.5 °C
10:00	probe 1: 33.6 °C, MF↓
approximately 12:30	probe 1: 29.0 °C
approximately 14:00	probe 1: 29.2 °C

nominal field strength: 4.0 kA/m → 20.5 % (setup unchanged)	
0:00:00	probe 1: 29.3 °C, MF↑, blower↑
1:00	probe 1: 33.0 °C
2:00	probe 1: 34.7 °C (ambient air draft! Cause?)
3:15	probe 1: 35.4 °C
4:00	probe 1: 35.7 °C
5:15	probe 1: 35.9 °C
6:30	probe 1: 36.0 °C
8:00	probe 1: 36.0 °C
9:00	probe 1: 36.1 °C
9:15	probe 1: 36.0 °C; probe 2: 34.5 °C; MF↓
approximately 12:00	probe 1: 30.5 °C; probe 2: 34.6 °C; blower↓

The measurement probe is always positioned between the carrier and the bone.

MF↑:	alternating magnetic field on
MF↓:	alternating magnetic field off
blower↑:	blower on
blower↓:	blower off
probe 1↓:	probe not functioning

Example 14B: Spongostan

Particle:	Nanoparticle suspension according to Example 1A (1.5 mL, 2 molar)
Carrier:	Spongostan powder, mass: 0.3 g
Bone:	Size: (44.4 x 13.2 x 10.9) mm

1.08 g powder (carrier) is impregnated with 1.5 mL particles (2 molar according to Example 1A) and mixed well, and a sub-quantity of m = 0.46 g impregnated carrier is modeled on the bone.

The measurement head for the field strength measurement is positioned at the position in the fixator at which the measurements are later conducted; modeling clay hereby serves as a marking aid. 3 field strengths (that are relevant to the clinical application) are measured: 3.0 kA/m, 3.5 kA/m, 4.0 kA/m.

nominal field strength: 3.0 kA/m → 14 %	
0:00:00	probe 1: 33.6 °C, MF↑, blower↑
2:00	probe 1: 34.8 °C
10:00	probe 1: 35.7 °C, MF↓
after 2′	probe 1: 35.3 °C

nominal field strength: 3.5 kA/m → 17 %	
0:00:00	probe 1: 35.8 °C, MF↑ (blower on)
2:00	probe 1: 36.0 °C
4:00	probe 1: 36.1 °C
5:00	probe 1: 36.3 °C, MF↓

nominal field strength: 4.0 kA/m → 20.05 %	
0:00:00	probe 1: 36.8 °C, MF↑, blower↑
7:50	probe 1: 39.0 °C
9:00	probe 1: 39.2 °C
10:00	probe 1: 39.3 °C, MF↓
after 2′	probe 1: 38.8 °C

Example 14C: Spongostan

Particle: Nanoparticle suspension according to Example 1A (1.6 mL, 2 molar)

Carrier: impregnated carrier from Example 14B, mass: approximately 0.8 g

Bone: Size: (44.4 x 13.2 x 10.9) mm

The quantity of approximately 0.8 g of impregnated carrier remaining in Example 14B is mixed with 1.6 mL particles (2 molar according to Example 1A) and applied to the bone cleaned according to Example 14. The probe is again placed between bone and carrier. The 3 field strengths (3.0 kA/m, 3.5 kA/m, 4.0 kA/m) were measured again.

nominal field strength: 3.0 kA/m → 14 %	
0:00:00	probe 1: 24.1 °C, MF↑, blower↑
7:00	probe 1: 32.0 °C
10:00	probe 1: 33.2 °C
12:02	probe 1: 33.5 °C. MF↓
after 4′	probe 1: 30.8 °C

nominal field strength: 3.5 kA/m → 17 %	
0:00:00	probe 1: 30.7 °C, MF↑ (blower on)
1:00	probe 1: 33.1 °C
5:30	probe 1: 35.6 °C
8:00	probe 1: 35.7 °C
10:00	probe 1: 36.1 °C, MF↓
after 1′	probe 1: 33.3 °C
after 2′	probe 1: 32.2 °C
after 3′	probe 1: 31.8 °C

nominal field strength: 4.0 kA/m → 20.05 %

0:00:00	probe 1: 31.6.8 [sic] °C, MF↑, blower↑
1:00	probe 1: 34.7 °C
4:00	probe 1: 37.0 °C
5:00	probe 1: 37.4 °C
6:00	probe 1: 37.7 °C
7:00	probe 1: 37.6 °C
9:00	probe 1: 37.9 °C
10:00	probe 1: 38.2 °C, MF↓
after 30"	probe 1: 35.4 °C

Example 14D: Spongostan Special

Particle: Nanoparticle suspension according to Example 1A (1.0 mL, 2 molar)

Carrier: impregnated carrier from Example 14B, size: (10.0 x 10.0 x 2.0) mm

Bone: Size: (44.4 x 13.2 x 10.9) mm

In order for the carrier to take up the particles (1.0 mL, 2 molar according to Example 1A), the carrier must be impregnated with the particle suspension (15 minutes). In one packaging, 1 mL particle suspension is injected into the carrier [m = 0.00]; the cuboid takes up the maximum and is placed on the bone.

The measurement takes place as described in Example 14A.

nominal field strength: 3.0 kA/m → 14 %	
0:00:00	probe 1: 25.5 °C, MF↑, blower↑
6:30	probe 1: 30.6 °C
8:00	probe 1: 31.1 °C
9:00	probe 1: 31.4 °C
10:00	probe 1: 31.7 °C

11:00	probe 1: 32.0 °C
12:00	probe 1: 32.0 °C
12:30	probe 1: 32.0 °C, MF↓
after 1'30"	probe 1: 29.8 °C, blower↓
after 3'	probe 1: 29.6 °C

nominal field strength: 3.5 kA/m → 17 %	
0:00:00	probe 1: 29.6 °C, MF↑, blower↑
1:00	probe 1: 32.0 °C
5:00	probe 1: 34.1 °C
10:00	probe 1: 34.6 °C, MF↓
after 1'	probe 1: 31.8 °C

nominal field strength: 4.0 kA/m → 20.05 %	
0:00:00	probe 1: 30.5 °C, MF↑, blower↑
2:30	probe 1: 35.5 °C
4:00	probe 1: 36.2 °C
5:00	probe 1: 36.6 °C
10:00	probe 1: 36.8 °C, MF↓

Example 14E: GeIita tampon

Particle: Nanoparticle suspension according to Example 1A (1.0 mL, 2 molar)

Carrier: Gelita tampon, size: (1 x 1 x 1) cm

Bone: Size: (44.4 x 13.2 x 10.9) mm

In order for the carrier to take up the nanoparticle suspension (1.0 mL, 2 molar according to Example 1A), the carrier must be impregnated with the particle suspension (15 minutes). In the packaging, 1 mL of particle suspension is injected into the Gelita tampon carrier; the cube takes up the maximum (Gelita Tampon [m = 0.00] with nanoparticle suspension: m = 0.45 g) and is placed on the bone.

nominal field strength: 3.0 kA/m → 14 %	
0:00:00	probe 1: 29.1 °C, MF↑, blower↑
5:00	probe 1: 34.7 °C
7:00	probe 1: 35.3 °C
10:00	probe 1: 35.8 °C

nominal field strength: 3.5 kA/m → 17 %	
0:00:00	probe 1: 33.7 °C, MF↑, (blower on)
1:00	probe 1: 35.2 °C
5:00	probe 1: 36.7 °C
10:00	probe 1: 37.1 °C, MF↑

nominal field strength: 4.0 kA/m → 20.05 %	
0:00:00	probe 1: 34.9 °C, MF↑, (blower on)
2:00	probe 1: 37.8 °C
3:00	probe 1: 38.3 °C
5:00	probe 1: 38.8 °C
7:00	probe 1: 39.0 °C
10:00	probe 1: 39.2 °C, MF↓

PATENTKRAV

1. Et fast eller geleagtigt medicinprodukt, som kan opvarmes ved hjælp af et magnetisk vekselstrømsfelt, til anvendelse ved efterbehandling af det opererede område ved kræftoperationer, hvor medicinproduktet foreligger i form af fysiologisk forligeligt væv, svamp eller film, og hvor magnetiske partikler er indeholdt i medicinproduktet, som stimuleret af et magnetisk vekselstrømsfelt genererer varme og dermed opvarmer medicinproduktet.

2. Medicinprodukt til anvendelse ifølge krav 1, hvor

i) partiklerne er indlagt eller hæftet fast i medicinproduktet; og/eller
hvor ii) partiklerne forbliver vedvarende i medicinproduktet, ikke frigives ved diffusion og produkter kun frigives i tilfælde af biologisk nedbrydelig medicin på grund af nedbrydningsprocessen; og/eller
hvor iii) medicinproduktet kan deformeres og kan følge overfladeforløbet i vævet eller organet eller operationsområdet efter en kirurgisk tumorfjernelse.

3. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor medicinproduktet er biologisk nedbrydeligt.

4. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor der ved partiklerne er tale om mikropartikler eller nanopartikler, og/eller hvor

partiklerne er paramagnetiske eller superparamagnetiske.

5. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor

i) medicinproduktet imprægneres, belægges eller indblødes med de magnetiske partikler, og/eller

ii) medicinproduktet kan resorberes biologisk inden for 1 til 12 måneder, og/eller

iii) medicinproduktet er fysiologisk forligeligt og nedbrydes i fysiologisk forligelige bestanddele, og/eller

iv) medicinproduktet er fleksibelt og ikke består af metal eller en metallegering, og hvor medicinproduktet ikke foreligger som vandig opløsning af partiklerne.

6. Medicinprodukt til anvendelse ifølge ethvert af kravene 3-5, hvor det biologisk nedbrydelige medicinprodukt frigiver de magnetiske partikler og/eller afgiver dem til omgivende tumorvæv eller tumorceller.

7. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor de magnetiske partikler er indeholdt i en koncentration på 10 µg til 100 mg pro cm^2 overflade af medicinproduktet, og/eller hvor de magnetiske partikler er indeholdt i en koncentration på 100 µg til 2 g pr. g af medicinproduktet.

8. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor der ved medicinproduktet er

tale om medicinsk cellestof, forbindsmateriale, sårindlæg, kirurgisk symateriale, kompresser, svampe, medicinske tekstiler eller filmdannende sammensætninger.

9. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor medicinproduktet derudover mindst indeholder en terapeutisk effektiv substans udvalgt blandt gruppen omfattende anti-proliferative, antimigrative, anti-angiogene, anti-trombotiske, anti-inflammatoriske, anti-flogistiske, cytostatiske, cytotoksiske, antikoagulative, anti-bakterielle, anti-virale og/eller anti-mykotiske lægemiddelstoffer, især hvor mindst en terapeutisk substans udvælges blandt gruppen omfattende actinomycin D, aminoglutetimid, amsacrin, anastrozol, antagonister af purin- og pyrimidin-baser, antracycliner, aromatasehæmmer, asparaginase, antiøstrogener, bexarotene, bleomycin, buselerin, busulfan, camptotecin-derivater, capecitabin, carboplatin, carmustin, klorambucil, cisplatin, cladribin, cyclofosfamid, cytarabin, cytosinarabinosid, alkylierende cytostatika, dacarbazin, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, estramustin, etoposid, exemestan, fludarabin, fluorouracil, folsyrearitagonister, formestan, gemcitabin, glucocorticoider, goselerin, hormoner og hormonantagonister, hycamtin, hydroxyharnstof, idarubicin, ifosfamid, imatinib, irinotecan, letrozol, leuprorelin, lomustin, melfalan, mercaptopurin, metotrexat, miltefosin, mitomycine, mitosehæmstoffer, mitoxantron, nimustine, oxaliplatin, paclitaxel, pentostatin, procarbazin,

tamoxifer, temozolomid, teniposid, testolacton, tiotepa, tioguanin, topoisomerase-inhibitorer, topotecan, treosulfan, tretinoin, triptorelin, trofosfamider, vinblastin, vincristin, vindesin, vinorelbin, cytostatisk effektive antibiotika.

10. Medicinprodukt til anvendelse ifølge krav 9, hvor mindst et lægemiddelstof er adhæsivt, ionisk, kovalent eller bundet til partiklen via en linker.

11. Medicinprodukt til anvendelse ifølge ethvert af kravene 9 eller 10, hvor afløsningen af mindst et lægemiddelstof initieres af bæreren over et magnetisk vekselstrømsfelt.

12. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor medicinproduktet består af følgende materiale: Polyakrylsyre, polyakrylater, polymetylmethakrylat, polybutylmetakrylat, polyisobutylmethakrylat, polyakrylamid, polyakrylnitril, polyamid, polyeteramid, polyetylenamin, polyimid, polykarbonat, polycarbouretan, polyvinylketon, polyvinylhalogenid, polyvinylidenhalogenid, polyvinylæter, polyvinylaromater, polyvinylester, polyvinylpyrrolidon, polyoxymetylen, polyætylen, polypropylen, polytetrafluorætylen, polyuretan, polyolefin-elastomer, polyisobutylen, EPDM-gummi, fluorosilikone, carboxymetylchitosan, polyætylentereftalat, polyvalerat, carboxymetylcellulose, cellulose, rayon, rayontriacetat, cellulosenitrat, celluloseacetat, hydroxyætylcellulose, cellulosebutyrat, celluloseacetatbutyrat, ætylvinylacetatcopolymer,

polysulfon, polyætersulfon, epoxyharpiks, ABS-harpiks, EPDM-gummi, silikonepræpolymer, silikone, polysiloxan, polyvinylhalogen, celluloseæter, cellulosetriacetat, chitosan, chitosanderivater, polymeriserbare olier, polyvalerolactone, poly-ε-decalacton, polylactid, polyglycolid, copolymerer af polylactider og polyglycolider, poly-ε-caprolacton, polyhydroxysmørsyre, polyhydroxybutyrat, polyhydroxyvalerat, polyhydroxybutyrat-co-valerat, poly(1,4-dioxan-2,3-dion), poly(1,3-dioxan-2-on), polyparadioxanon, polyanhydrid, polymaleinsyreanhydrid, polyhydroxymetakrylat, polycyanoakrylat, polycaprolactondimetylakrylat, poly-β-mateinsyre, polycaprolactonbutylakrylat, multiblokpolymerer af oligocaprolactondiol og oligodioxanondiol, polyæterester-multiblokpolymerer af PEG og poly(butylentereftalat), polypivotolacton, polyglycolsyretrimetylkarbonat, polycaprolactonglycolid, poly(γ-ethylglutamat), poIy(DTH-Iminokarbonat), poly(DTE-co-DT-karbonat), poly(bisfenol A-iminokarbonat), polyortoester, polyglycolsyretrimetylkarbonat, polytrimetylkarbonat, polyiminokarbonat, polyvinylalkohol, polyesteramider, glycoIerede polyestere, polyfosfoestere, polyfosfacener, poly [p-carboxyphenoxy)propan], polyhydroxypentansyre, polyætylenoxidpropylenoxid, bløde polyuretaner, polyuretaner med aminosyrerester i backbone, polyæterester, polyætylenoxid, polyalkenoxalater, polyortoestere, carrageenaner, stivelse, kollagen, proteinbaserede polymerer, polyaminosyrer, syntetiske polyaminosyrer, zein, modificeret zein, polyhydroxyalkanoater, pektinsyre, aktinsyre, fibrin, modificeret fibrin, kasein, modificeret kasein, carboxymetylsulfat, albumin,

hyaluronsyre, heparansulfat, heparin, chondroitinsulfat, dextran, cyclodextriner, copolymerer af PEG og polypropylenglycol, gummi arabicum, guar eller anden gummiharpiks, gelatine, kollagen, kollagen-N-hydroxysuccinimid, lipider, lipoider, polymerserbare olier og deres modifikationer, copolymerer og blandinger af ovennævnte substanser.

13. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor kræften, tumoren eller den proliferative sygdom er udvalgt blandt gruppen omfattende: Adenokarcinomer, årehudmelanom, akut leukæmi, akustikusneurinom, ampulkarcinom, analkarcinom, astrozytomer, basaliom, pancreacancer, bindevævstumor, blærekræft, bronkialkarcinom, bronkialkarcinom ikke med små celler, brystkræft, burkitt-lymfom, korpuskarcinom, CUP-syndrom, tyktarmskræft, tyndtarmskræft, tyndtarmstumorer, æggestokkræft, endometriumkarcinom, ependymom, epitel-kræfttyper, Ewing-tumorer, gastrointestinale tumorer, galdeblærekræft, galdekarcinomer, livmoderkræft, livmoderhalskræft, glioblastomer, gynækologiske tumorer, hals-, næse- og øretumorer, hæmatologiske neoplasier, urinrørskræft, hudkræft, hjernetumorer (gliomer), hjernemetastaser, testikelkræft, hypofysetumor, karcinoider, kaposi-sarkom, strubehovedkræft, kimcelletumor, knoglekræft, kolorektalt karcinom, hoved-hals-tumorer (tumorer i hals-, næse- og øreområdet), kolonkarcinom, kraniofaryngeomer, kræft i mundområdet og på læben, leverkræft, levermetastaser, øjetumor, lungekræft, lymfekirtelkræft (Hodgkin/Non-Hodgkin), lymfomer,

mavekræft, malign melanom, malign neoplasma, malignomer i mave-tarm-regionen, mammakancinom, endetarmskræft, medulloblastomer, melanom, meningeomer, Morbus Hodgkin, mycosis fungoides, næsekræft, neurinom, neuroblastom, nyrekræft, nyrecellekarcinomer, Non-Hodgkin-lymfomer, oligodendrogliom, øsophaguskarcinom, osteolytiske karcinomer, osteoplastiske karcinomer, osteosarkom, ovarial-karcinom, pankreaskarcinom, peniskræft, pladeepitelkarcinomer i hoved og hals, prostatakræft, ganekræft, rektumkarcinom, retinoblastom, skedekræft, skjoldbruskkirtelkarcinom, Schneeberger-sygdom, spiserørskræft, spinaliom, T-celle-lymfom (mycosis fungoides), tymom, tubekarcinom, tumorer i øjet, uretrakræft, urologiske tumorer, urotelkarcinom, vulvakræft, vortedeltagelse, bløddeletumorer, bløddelearkom, Wilms-tumor, cervixkarcinom og tungekræft.

14. Medicinprodukt til anvendelse ifølge ethvert af foregående krav, hvor efterbehandling af det operative område tjener til forhindring af recidivdannelse.

15. Anvendelse af fast eller geleagtigt fysiologisk væv, svamp eller film, som kan opvarmes ved hjælp af et magnetisk vekselstrømsfelt, til fremstilling af et medicinprodukt til efterbehandling af det opererede område ved kræftoperationer, hvor magnetiske partikler er indeholdt i medicinproduktet, som stimuleret af et magnetisk vekselstrømsfelt genererer varme og dermed opvarmer medicinproduktet.