

Drug delivery materials made by sol/gel technology

Field Of The Invention

The present invention is directed to drug delivery materials comprising a
5 biologically or therapeutically active compound encapsulated in a shell and being
incorporated in a matrix prepared by sol/gel technology, particularly for use in
implants. Specifically, the present invention is directed to a drug delivery material
which provides a controlled release of the active agents and which optionally may be
controllably dissolvable or bioerodible. Furthermore, the present invention is
10 directed to a process for manufacturing such delivery materials which comprises the
steps of encapsulating at least one biologically or therapeutically active agent in a
shell and combining the encapsulated active compound with a sol, followed by
converting the resulting combination into the inventive drug delivery material.

Background Of The Invention

15 Materials being implanted into the human or animal body must have certain
bio-chemical properties in order to avoid unwanted side-effects such as inflammatory
tissue responses or immune reactions through chemical and/or physical irritations
resulting in intolerance reactions and the like. Implant materials must be bio-
compatible, non-toxic and should serve for a large variety of different purposes
20 requiring a wide range of different properties. Implant materials used for medical
implants such as surgical and/or orthopaedic screws, plates, joint prostheses, artificial
heart-valves, vascular prostheses, stents as well as subcutaneously or intramuscularly
implantable active agent depots require biocompatible materials having sufficient
mechanical strength if support of tissue is required, for example, in the case of stents
25 or bone implants, and, on the other hand, implant materials in some instances need to
have bio-active properties such that the surrounding tissue may form an interfacial
bond with the implant. For implantable active agent depots it is often preferred that
the materials used are dissolvable in the presence of physiological fluids or being
slowly bioerodible.

30 Among the several approaches to find implant materials providing sufficient
possibilities to vary the material's intrinsic properties, it has been found that, for

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example, bio-active glasses or glass ceramics made by sol/gel process technology are suitable materials for the production of support implants and drug delivery depots as well as synthetic graft materials in load-bearing situations. Bio-active glasses and glass ceramics, depending on their specific composition, may undergo surface corrosion reactions when exposed to body fluids or may even produce materials which are fully bioerodible or dissolvable in the presence of physiological fluids.

For example, international patent application WO 96/03117 describes carriers comprising silica-based glass providing for the controlled release of biologically active molecules and their methods of preparation. The carriers disclosed therein are prepared using a sol/gel derived process, and biologically active molecules such as, i.e., antibiotics or proteins can be incorporated in the matrix of the glass during the production process. The release rate of the bio-active molecules in this prior art is controlled by controlling the micro-porosity of the sol/gel glasses by varying the water content, addition of acids, aging and drying time. Due to the controllable micro-porosity of such bio-active sol/gel derived glasses, subsequent controlled release of the active agent is achieved.

However, the disadvantage of the materials described in WO 96/03117 is that, although the release of the active agent may be delayed, this occurs somehow inspecifically and the actual release rate of the active agent exhibits large fluctuations which may lead to severe side-effects with some agents.

European patent application EP 0 680 753 A2 describes a sol/gel derived silica material, containing a biologically active substance such as therapeutically active agents, where the release rate of the active agent is controlled by the addition of penetration enhancers such as polyethylene glycol or sorbitol or other modifying agents which enhance the release of the active agent by aiding dissolution by swelling processes or by inhibiting diffusion in order to modify the permeability of the matrix. Such modifying agents used for more exactly adjusting the release rate of the active agent are, for example, water soluble substances such as sugars or salts of

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organic acids, which accelerate the release rate from the matrix because due to their solubility in body fluids, these substances are dissolved and thus increase the permeability of the sol/gel produced matrix. Additional modifying agents mentioned in EP 0 680 753 for increasing the permeability of the matrix in the presence of body fluids are polyanionic compounds such as salts of polystyrene sulfonic acid, polyacrylic acids, carboxymethyl celluloses, dextrane sulphate or cellulose sulphate and the like. In all embodiments of EP 0 680 753, the release modifying agents are those which accelerate the release of the active agent. The main disadvantage of the teaching of EP 0 680 753 is that such multi-component systems are rather complex, costly, and it is very difficult to reproducibly adjust the release rate of the active agent with the use of penetration adjuvants and modifiers.

In view of the above, there is a need for bio-compatible drug delivery materials which may be produced as coatings or bulk materials, especially for the production of implants or coated implants, which reliably and reproducibly provide for an individually adjustable controlled release of the active agent incorporated therein.

Summary Of The Invention

Therefore, it is an object of the present invention to provide drug delivery materials which are easily producible at low cost. A further object of the present invention is to provide drug delivery materials allowing for a controlled and reproducible release of the active agent incorporated therein. A further object of the present invention is to provide controlled release delivery materials suitable for the production of medical implants. A further object of the present invention is to provide controlled release drug delivery materials which may be used for coating of medical implants such as aortic valves or stents and the like. A still further object of the present invention is to provide a process which avoids detrimental interactions of the active agents with the sol/gel materials, allowing for the use of sensitive drugs to be incorporated in sol/gel matrix without deactivating the active agent.

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The above objects are solved in accordance with the present invention which provides solid drug delivery materials comprising biologically or therapeutically active agents encapsulated in a shell, which are further incorporated in a sol/gel matrix.

5 In a further aspect, the present invention is directed to a process for the manufacture of drug delivery materials, the process comprising the steps of encapsulating at least one biologically and/or therapeutically active agent in a shell, combining the encapsulated active compound with sol and converting the resulting combination into a solid or semi-solid material.

10 In an other aspect, the present invention is directed to a process for the manufacture of a drug delivery material and the resulting material itself, wherein the biologically or therapeutically active compound is first encapsulated in a polymeric shell before being combined with a sol.

 Preferably, the biologically or therapeutically active compound is a therapeutic
15 agent which is capable of providing a direct or indirect therapeutic, physiologic and/or pharmacologic effect in a human or animal organism.

 Especially preferred are medicaments, drugs, pro-drugs, targeting groups and the like. Especially preferred are active agents comprising one or more targeting groups.

20 The sol used for preparing the inventive materials may be formed in a hydrolytic or non-hydrolytic sol/gel process. For encapsulating the active agents in a polymer shell, bioresorbable and biopolymers are especially preferred.

 In particularly preferred exemplary embodiments of the present invention, the material produced in accordance with the present invention is dissolvable in
25 physiologic fluids or has bioerodible properties in the presence of such fluids. Particularly preferred are inventive materials providing for a sustained or controlled release of the active agent when inserted into the human or animal body.

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The use of the inventive drug delivery material for coating of stents or other medical implants is a particularly preferred aspect of the present invention.

Detailed Description

5 Sol/gel technology allows for the production of highly biocompatible, in some instances even bioerodible, materials at low temperatures. In the present invention, it has been found that sol/gel derived materials form suitable matrices for drug delivery materials or coatings, and a combination of a sol/gel derived matrix with polymer encapsulated drugs incorporated therein provides controlled release materials with optimizable release characteristics for a wide variety of biomedical applications.

10 The sol/gel-process technology is widely applied to build up different types of networks. The linkage of the components under formation of the sol or gel can take place in several ways, e.g. via hydrolytic or non-hydrolytic sol/gel-processing as known in the prior art in principle. The present invention utilizes sol/gel technology to produce drug delivery materials. The production of materials such as aereogels or
15 xerogels by sol/gel-processing were known for many years.

A "sol" is a dispersion of colloidal particles in a liquid, and the term "gel" connotes an interconnected, rigid network of pores of submicrometer dimensions and polymeric chains whose average length is typically greater than a micrometer. For example, the sol/gel-process may involve mixing of the precursors, e.g. a sol/gel
20 forming components into a sol, adding further additives or materials, casting the mixture in a mold or applying the sol onto a substrate in the form of a coating, gelation of the mixture, whereby the colloidal particles are linked together to become a porous three-dimensional network, aging of the gel to increase its strength; converting the gel into a solid material by drying from liquid and/or dehydration or
25 chemical stabilisation of the pore network, and densification of the material to produce structures with ranges of physical properties. Such processes are described, for example, in Henge and West, The Sol/Gel-Process, 90 Chem. Ref. 33 (1990).

The term "sol/gel" as used within this specification may mean either a sol or a gel. The sol can be converted into a gel as mentioned above, e.g. by aging, curing, raising of pH, evaporation of solvent or any other conventional methods.

5 The term semi-solid refers to materials having a gel-like consistency, i.e. being substantially dimensionally stable at room temperature, but have a certain elasticity and flexibility, typically due to a residual solvent content.

The inventive drug delivery materials for example exhibit the advantageous property that they can be easily and reproducibly processed at low temperature from sols and/or gels. Particularly, sols/gels and combinations prepared in accordance
10 with the process of the present invention are suitable for coating of almost any type of substrate with porous or non-porous drug delivery film coatings. According to the process of the invention, coatings as well as shaped bulk drug delivery materials can be obtained.

According to the process of the present invention, in a first step biologically or
15 therapeutically active agents are encapsulated in a polymer material.

Active agents

The active agents which may be used in the present invention are preferably biologically and/or therapeutically active agents, herein generally referred to as "active agents" or "active compounds".

20 The active agents suitable for being encapsulated and incorporated into the drug delivery material may preferably be therapeutically active agents which are capable of providing direct or indirect therapeutic, physiologic and/or pharmacologic effect in a human or animal organism.

In an alternative exemplary embodiment of the present invention, the active
25 agent may also be a compound for agricultural purposes, for example a fertilizer, pesticide, microbicide, herbicide, algicide and the like.

Therapeutically or pharmaceutically active agents for the production of drug delivery materials are, however, preferred. The therapeutically active agent may be

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any conventional medicament, drug, pro-drug or even a targeting group or a drug or pro-drug comprising a targeting group.

The active agents may be in crystalline, polymorphous or amorphous form or any combination thereof in order to be used in the present invention. Suitable therapeutically active agents may be selected from the group comprising enzyme inhibitors, hormones, cytokines, growth factors, receptor ligands, antibodies, antigens, ion binding agents such as crown ethers and chelating compounds, substantially complementary nucleic acids, nucleic acid binding proteins including transcriptions factors, toxins and the like. Examples of active agents are, for example, cytokines such as erythropoietine (EPO), thrombopoietine (TPO), interleukines (including IL-1 to IL-17), insulin, insulin-like growth factors (including IGF-1 and IGF-2), epidermal growth factor (EGF), transforming growth factors (including TGF- α and TGF- β), human growth hormone, transferrin, low density lipoproteins, high density lipoproteins, leptin, VEGF, PDGF, ciliary neurotrophic factor, prolactin, adrenocorticotrophic hormone (ACTH), calcitonin, human chorionic gonadotropin, cortisol, estradiol, follicle stimulating hormone (FSH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), progesterone, testosterone, toxins including ricin and further active agents such as those included in Physician's Desk Reference, 58th Edition, Medical Economics Data Production Company, Montvale, N.J., 2004 and the Merck Index, 13th Edition (particularly pages Ther-1 to Ther-29), all of which are incorporated herein by reference.

In a preferred exemplary embodiment of the present invention, the therapeutically active agent is selected from the group of drugs for the therapy of oncological diseases and cellular or tissue alterations. Suitable therapeutic agents are, e.g., antineoplastic agents, including alkylating agents such as alkyl sulfonates, e.g., busulfan, improsulfan, piposulfan, aziridines such as benzodepa, carboquone, meturedpa, uredepa; ethyleneimine and methylmelamines such as altretamine, triethylene melamine, triethylene phosphoramide, triethylene thiophosphoramide,

trimethylolmelamine; so-called nitrogen mustards such as chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethaminoxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitroso urea-compounds such as

5 carmustine, chlorozotocin, fotenmustine, lomustine, nimustine, ranimustine; dacarbazine, mannomustine, mitobranitol, mitolactol; pipobroman; doxorubicin and cis-platinum and its derivatives, and the like, combinations and/or derivatives of any of the foregoing.

In a further exemplary embodiment of the present invention, the therapeutically

10 active agent may be selected from the group comprising anti-viral and anti-bacterial agents such as aclacinomycin, actinomycin, anthramycin, azaserine, bleomycin, cuctinomycin, carubicin, carzinophilin, chromomycines, ductinomycin, daunorubicin, 6-diazo-5-oxn-1-norieucin, doxorubicin, epirubicin, mitomycins, mycophenolsäure, mogalumycin, olivomycin, peplomycin, plicamycin,

15 porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, aminoglycosides or polyenes or macrolid-antibiotics, and the like, combinations and/or derivatives of any of the foregoing.

In a further exemplary embodiment of the present invention, the therapeutically active agent may be selected from radio-sensitizer drugs, steroidal or non-steroidal

20 anti-inflammatory drugs, or agents referring to angiogenesis, such as e.g. endostatin, angiostatin, interferones, platelet factor 4 (PF4), thrombospondin, transforming growth factor beta, tissue inhibitors of the metalloproteinases -1, -2 and -3 (TIMP-1, -2 and -3), TNP-470, marimastat, neovastat, BMS-275291, COL-3, AG3340, thalidomide, squalamine, combrestastatin, SU5416, SU6668, IFN-[alpha],

25 EMD121974, CAI, IL-12 and IM862 and the like, combinations and/or derivatives of any of the foregoing.

In a further exemplary embodiment of the present invention, the therapeutically-active agent may be selected from the group comprising nucleic

acids, wherein the term nucleic acids also comprises oligonucleotides wherein at least two nucleotides are covalently linked to each other, for example in order to provide gene therapeutic or antisense effects. Nucleic acids preferably comprise phosphodiester bonds, which also comprise those which are analogues having

5 different backbones. Analogues may also contain backbones such as, for example, phosphoramidate (Beaucage et al., *Tetrahedron* 49(10):1925 (1993) and the references cited therein; Letsinger, *J. Org. Chem.* 35:3800 (1970); Sprinzl et al., *Eur. J. Biochem.* 81:579 (1977); Letsinger et al., *Nucl. Acids Res.* 14:3487 (1986); Sawai et al., *Chem. Lett.* 805 (1984), Letsinger et al., *J. Am. Chem. Soc.* 110:4470 (1988); and

10 Pauwels et al., *Chemica Scripta* 26:141 (1986)); phosphorothioate (Mag et al., *Nucleic Acids Res.* 19:1437 (1991); and U.S. Pat. No. 5,644,048), phosphorodithioate (Briu et al., *J. Am. Chem. Soc.* 111:2321 (1989), O-methylphosphoroamidite-compounds (see Eckstein, *Oligonucleotides and Analogues: A Practical Approach*, Oxford University Press), and peptide-nucleic acid-backbones

15 and their compounds (see Egholm, *J. Am. Chem. Soc.* 114:1895 (1992); Meier et al., *Chem. Int. Ed. Engl.* 31:1008 (1992); Nielsen, *Nature*, 365:566 (1993); Carlsson et al., *Nature* 380:207 (1996), wherein these references are incorporated by reference herein. further analogues are those having ionic backbones, see Denpcy et al., *Proc. Natl. Acad. Sci. USA* 92:6097 (1995), or non-ionic backbones, see U.S. Pat. Nos.

20 5,386,023, 5,637,684, 5,602,240, 5,216,141 and 4,469,863; Kiedrowski et al., *Angew. Chem. Intl. Ed. English* 30:423 (1991); Letsinger et al., *J. Am. Chem. Soc.* 110:4470 (1988); Letsinger et al., *Nucleoside & Nucleotide* 13:1597 (1994); chapters 2 and 3, *ASC Symposium Series 580, "Carbohydrate Modifications in Antisense Research"*, Ed. Y. S. Sanghui and P. Dan Cook; Mesmaeker et al., *Bioorganic &*

25 *Medicinal Chem. Lett.* 4:395 (1994); Jeffs et al., *J. Biomolecular NMR* 34:17 (1994); *Tetrahedron Lett.* 37:743 (1996), and non-ribose-backbones, including those which are described in U.S. Pat. Nos. 5,235,033 and 5,034,506, and in chapters 6 and 7 of *ASC Symposium Series 580, "Carbohydrate Modifications in Antisense Research"*,

Ed. Y. S. Sanghui and P. Dan Cook. The nucleic acids having one or more carbocyclic sugars are also suitable as nucleic acids for use in the present invention, see Jenkins et al., Chemical Society Review (1995), pages 169 to 176 as well as others which are described in Rawls, C & E News, 2 June 1997, page 36, herewith incorporated by
5 reference. Besides the selection of the nucleic acids and nucleic acid analogues known in the prior art, also any mixtures of naturally occurring nucleic acids and nucleic acid analogues or mixtures of nucleic acid analogues may be used.

In a further exemplary embodiment of the present invention, the therapeutically active agent may be selected from metal ion complexes, as described in PCT
10 US95/16377, PCT US95/16377, PCT US96/19900, PCT US96/15527 and herewith incorporated by reference, wherein such agents reduce or inactivate the bioactivity of their target molecules, preferably proteins such as enzymes.

Preferred therapeutically active agents may also be anti-migratory, anti-proliferative or immune-suppressive, anti-inflammatory or re-endothelializing agents
15 such as, e.g., everolimus, tacrolimus, sirolimus, mycofenolate-mofetil, rapamycin, paclitaxel, actinomycine D, angiopeptin, batimastate, estradiol, VEGF, statines and others, their derivatives and analogues.

Further preferred are active agents or combinations of active agents selected from heparin, synthetic heparin analogs (e.g., fondaparinux), hirudin, antithrombin
20 III, drotrecogin alpha; fibrinolytics such as alteplase, plasmin, lysokinases, factor XIIa, prourokinase, urokinase, anistreplase, streptokinase; platelet aggregation inhibitors such as acetylsalicylic acid [aspirin], ticlopidine, clopidogrel, abciximab, dextrans; corticosteroids such as alclometasone, amcinonide, augmented betamethasone, beclomethasone, betamethasone, budesonide, cortisone, clobetasol,
25 clocortolone, desonide, desoximetasone, dexamethasone, fluocinolone, fluocinonide, flurandrenolide, flunisolide, fluticasone, halcinonide, halobetasol, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisone, prednisolone, triamcinolone; so-called non-steroidal anti-inflammatory drugs (NSAIDs) such as

- diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin, celecoxib, rofecoxib; cytostatics such as alkaloides and podophyllum toxins such as vinblastine,
- 5 vincristine; alkylating agents such as nitrosoureas, nitrogen lost analogs; cytotoxic antibiotics such as daunorubicin, doxorubicin and other anthracyclines and related substances, bleomycin, mitomycin; antimetabolites such as folic acid analogs, purine analogs or pyrimidine analogs; paclitaxel, docetaxel, sirolimus; platinum compounds such as carboplatin, cisplatin or oxaliplatin; amsacrin, irinotecan, imatinib,
- 10 topotecan, interferon-alpha 2a, interferon-alpha 2b, hydroxycarbamide, miltefosine, pentostatin, porfimer, aldesleukin, bexaroten, tretinoin; antiandrogens and antiestrogens; antiarrhythmics in particular class I antiarrhythmic such as antiarrhythmics of the quinidine type, quinidine, dysopyramide, ajmaline, prajmalium bitartrate, detajmium bitartrate; antiarrhythmics of the lidocaine type,
- 15 e.g., lidocaine, mexiletin, phenytoin, tocainid; class Ic antiarrhythmics, e.g., propafenon, flecainid(acetate); class II antiarrhythmics beta-receptor blockers such as metoprolol, esmolol, propranolol, metoprolol, atenolol, oxprenolol; class III antiarrhythmics such as amiodarone, sotalol; class IV antiarrhythmics such as diltiazem, verapamil, gallopamil; other antiarrhythmics such as adenosine,
- 20 orciprenaline, ipratropium bromide; agents for stimulating angiogenesis in the myocardium such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), non-viral DNA, viral DNA, endothelial growth factors: FGF-1, FGF-2, VEGF, TGF; antibiotics, monoclonal antibodies, anticalins; stem cells, endothelial progenitor cells (EPC); digitalis glycosides, such as acetyl
- 25 digoxin/metildigoxin, digitoxin, digoxin; cardiac glycosides such as ouabain, proscillaridin; antihypertensives such as CNS active antiadrenergic substances, e.g., methyl dopa, imidazoline receptor agonists; calcium channel blockers of the dihydropyridine type such as nifedipine, nitrendipine; ACE inhibitors: quinaprilate,

cilazapril, moexipril, trandolapril, spirapril, imidapril, trandolapril; angiotensin II antagonists: candesartancilexetil, valsartan, telmisartan, olmesartanmedoxomil, eprosartan; peripherally active alpha-receptor blockers such as prazosin, urapidil, doxazosin, bunazosin, terazosin, indoramin; vasodilators such as dihydralazine,

5 diisopropylamine dichloracetate, minoxidil, nitroprusside sodium; other antihypertensives such as indapamide, co-dergocrine mesylate, dihydroergotoxin methanesulfonate, cicletanin, bosentan, fludrocortisone; phosphodiesterase inhibitors such as milrinone, enoximon and antihypotensives such as in particular

10 adrenergic and dopaminergic substances such as dobutamine, epinephrine, etilefrine, norfenefrine, norepinephrine, oxilofrine, dopamine, midodrine, pholedrine, ameziniummetil; and partial adrenoceptor agonists such as dihydroergotamine; fibronectin, polylysine, ethylene vinyl acetate, inflammatory cytokines such as:

15 TGF β , PDGF, VEGF, bFGF, TNF α , NGF, GM-CSF, IGF-a, IL-1, IL-8, IL-6, growth hormone; as well as adhesive substances such as cyanoacrylates, beryllium, silica;

20 and growth factors such as erythropoietin, hormones such as corticotropins, gonadotropins, somatotropins, thyrotrophins, desmopressin, terlipressin, pxytocin, cetorelix, corticorelin, leuprorelin, triptorelin, gonadorelin, ganirelix, buserelin, nafarelin, goserelin, as well as regulatory peptides such as somatostatin, octreotide; bone and cartilage stimulating peptides, bone morphogenetic proteins (BMPs), e.g.

25 recombinant BMPs, such as recombinant human BMP-2 (rhBMP-2), bisphosphonate (e.g., risedronate, pamidronate, ibandronate, zoledronic acid, clodronic acid, etidronic acid, alendronic acid, tiludronic acid), fluorides such as disodium fluorophosphate, sodium fluoride; calcitonin, dihydrotachystyrol; growth factors and cytokines such as epidermal growth factor (EGF), platelet-derived growth factor

(PDGF), fibroblast growth factors (FGFs), transforming growth factors-b (TGFs-b), transforming growth factor-a (TGF-a), erythropoietin (EPO), insulin-like growth factor-I (IGF-I), insulin-like growth factor-II (IGF-II), interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-

a (TNF-a), tumor necrosis factor-b (TNF-b), interferon-g (INF-g), colony stimulating factors (CSFs); monocyte chemotactic protein, fibroblast stimulating factor 1, histamine, fibrin or fibrinogen, endothelin-1, angiotensin II, collagens, bromocriptine, methysergide, methotrexate, carbon tetrachloride, thioacetamide and ethanol; as well as silver (ions), titanium dioxide, antibiotics and anti-infective drugs such as in particular β -lactam antibiotics, e.g., β -lactamase-sensitive penicillins such as benzyl penicillins (penicillin G), phenoxymethylpenicillin (penicillin V); β -lactamase-resistant penicillins such as aminopenicillins, e.g., amoxicillin, ampicillin, bacampicillin; acylaminopenicillins such as mezlocillin, piperacillin; carboxy-penicillins, cephalosporins such as cefazoline, cefuroxim, cefoxitin, cefotiam, cefaclor, cefadroxil, cefalexin, loracarbef, cefixim, cefuroximaxetil, ceftibuten, cefpodoximproxetil, cefpodoximproxetil; aztreonam, ertapenem, meropenem; β -lactamase inhibitors such as sulbactam, sultamicillintosylate; tetracyclines such as doxycycline, minocycline, tetracycline, chlorotetracycline, oxytetracycline; aminoglycosides such as gentamicin, neomycin, streptomycin, tobramycin, amikacin, netilmicin, paromomycin, framycetin, spectinomycin; macrolide antibiotics such as azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin, josamycin; lincosamides such as clindamycin, lincomycin; gyrase inhibitors such as fluoroquinolones, e.g., ciprofloxacin, ofloxacin, moxifloxacin, norfloxacin, gatifloxacin, enoxacin, fleroxacin, levofloxacin; quinolones such as pipemidic acid; sulfonamides, trimethoprim, sulfadiazine, sulfalene; glycopeptide antibiotics such as vancomycin, teicoplanin; polypeptide antibiotics such as polymyxins, e.g., colistin, polymyxin-b, nitroimidazole derivatives, e.g., metronidazole, tinidazole; aminoquinolones such as chloroquin, mefloquin, hydroxychloroquin; biguanids such as proguanil; quinine alkaloids and diaminopyrimidines such as pyrimethamine; amphenicols such as chloramphenicol; rifabutin, dapson, fusidic acid, fosfomycin, nifuratel, telithromycin, fusafungin, fosfomycin, pentamidine diisethionate, rifampicin, taurolidin, atovaquon, linezolid; virus static such as aciclovir, ganciclovir, famciclovir, foscarnet, inosine-

(dimepranol-4-acetamidobenzoate), valganciclovir, valaciclovir, cidofovir, brivudin; antiretroviral active ingredients (nucleoside analog reverse-transcriptase inhibitors and derivatives) such as lamivudine, zalcitabine, didanosine, zidovudin, tenofovir, stavudin, abacavir; non-nucleoside analog reverse-transcriptase inhibitors: ampre-
5 navir, indinavir, saquinavir, lopinavir, ritonavir, nelfinavir; amantadine, ribavirine, zanamivir, oseltamivir or lamivudine, and any combinations and mixtures thereof.

Encapsulation

The active agents as described above are in a first step of the inventive process encapsulated in a polymeric shell or in vesicles, liposomes, micelles or the like. The
10 encapsulation of the active agents into polymers may be achieved by various polymerisation techniques known in the art, e.g. dispersion-, suspension- or emulsion-polymerisation. Preferred encapsulating polymers are biopolymers as further described herein below, or acrylic polymers such as polymethylmethacrylate (PMMA) or other latex-forming polymers.

15 The resulting polymer capsules, which contain the active agents, can further be optionally modified, for example by crosslinking the capsules and/or further encapsulation with several shells of polymer. Techniques to modify the polymers, if necessary, are well known to those skilled in the art, and may be employed depending on the requirements of the individual composition to be used in the
20 inventive process. The use of encapsulated active agents prevents aggregation and the encapsulated active agents can be uniformly distributed in a sol/gel process without agglomerating.

The encapsulation of the active agents can lead to covalently or non-covalently encapsulated active agents, depending on the individual materials used. For
25 combining with the sol, the encapsulated active agents may be provided in the form of polymer spheres, particularly microspheres, or in the form of dispersed, suspended or emulgated particles or capsules. Conventional methods suitable for providing or manufacturing encapsulated active agents, dispersions, suspensions or emulsions,

- particularly preferred mini-emulsions, thereof can be utilized. Suitable encapsulation methods are described, for example, in Australian publication AU 9169501, European Patent Publications EP 1205492, EP 1401878, EP 1352915 and EP 1240215, U.S. Patent No. 6380281, U.S. Patent Publication 2004192838, Canadian
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The encapsulated active agents can be preferably produced in a size of about 1 nm to 500 nm, or in the form of microparticles having sizes from about 5 nm to 5 μ m. Active agents may be further encapsulated in mini- or micro-emulsions of suitable polymers. The term mini- or micro-emulsion may be understood as dispersions comprising an aqueous phase, an oil phase and one or more surface active substances. Such emulsions may comprise suitable oils, water, one or several surfactants, optionally one or several co-surfactants and one or several hydrophobic substances. Mini-emulsions may comprise aqueous emulsions of monomers, oligomers or other pre-polymeric reactants stabilised by surfactants, which may be easily polymerized, and wherein the particle size of the emulgated droplets is between about 10 nm to 500 nm or larger.

Furthermore, mini-emulsions of encapsulated active agents can be made from non-aqueous media, for example, formamide, glycol or non-polar solvents. In principle, pre-polymeric reactants may be selected from thermosets, thermoplastics, plastics, synthetic rubbers, extrudable polymers, injection molding polymers, moldable polymers, and the like or mixtures thereof, including pre-polymeric reactants from which poly(meth)acrylics can be used.

- Examples of suitable polymers for encapsulating the active agents can include, but are not limited to, homopolymers or copolymers of aliphatic or aromatic polyolefins such as polyethylene, polypropylene, polybutene, polyisobutene, polypentene; polybutadiene; polyvinyls such as polyvinyl chloride or polyvinyl alcohol, poly(meth)acrylic acid, polymethylmethacrylate (PMMA), polyacrylocyanoacrylate; polyacrylonitril, polyamide, polyester, polyurethane, polystyrene, polytetrafluoroethylene; particularly preferred are biopolymers such as collagen, albumin, gelatine, hyaluronic acid, starch, celluloses such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose phthalate; casein, dextrans, polysaccharides, fibrinogen, poly(D,L-lactides), poly(D,L-lactide coglycolides), polyglycolides, polyhydroxybutylates, polyalkyl carbonates, polyorthoesters, polyesters, polyhydroxyvaleric acid, polydioxanones, polyethylene terephthalates, polymaleate acid, polytartronic acid, polyanhydrides, polyphosphazenes, polyamino acids; polyethylene vinyl acetate, silicones; poly(ester urethanes), poly(ether urethanes), poly(ester ureas), polyethers such as polyethylene oxide, polypropylene oxide, pluronics, polytetramethylene glycol; polyvinylpyrrolidone, poly(vinyl acetate phthalate), shellac, and combinations of these homopolymers or copolymers; with the exception of cyclodextrine and derivatives thereof or similar carrier systems.
- Further encapsulating materials that may be used include poly(meth)acrylate, unsaturated polyester, saturated polyester, polyolefines such as polyethylene, polypropylene, polybutylene, alkyd resins, epoxypolymers, epoxy resins, polyamide, polyimide, polyetherimide, polyamideimide, polyesterimide, polyesteramideimide, polyurethane, polycarbonate, polystyrene, polyphenole, polyvinylester, polysilicone, polyacetale, cellulosic acetate, polyvinylchloride, polyvinylacetate, polyvinylalcohol, polysulfone, polyphenylsulfone, polyethersulfone, polyketone, polyetherketone, polybenzimidazole, polybenzoxazole, polybenzthiazole, polyfluorocarbons,

polyphenylenether, polyarylate, cyanatoester-polymere, and mixtures or copolymers of any of the foregoing are preferred.

In certain exemplary embodiments of the present invention, the polymers for encapsulating the active agents may be selected from mono(meth)acrylate-,
 5 di(meth)acrylate-, tri(meth)acrylate-, tetra-acrylate- and pentaacrylate-based poly(meth)acrylates. Examples for suitable mono(meth)acrylates are hydroxyethyl acrylate, hydroxyethyl methacrylate, hydroxypropyl methacrylate, hydroxypropyl acrylate, 3-chloro-2-hydroxypropyl acrylate, 3-chloro-2-hydroxypropyl methacrylate, 2,2-dimethylhydroxypropyl acrylate, 5-hydroxypentyl acrylate, diethylene glycol
 10 monoacrylate, trimethylolpropane monoacrylate, pentaerythritol monoacrylate, 2,2-dimethyl-3-hydroxypropyl acrylate, 5-hydroxypentyl methacrylate, diethylene glycol monomethacrylate, trimethylolpropane monomethacrylate, pentaerythritol mono-methacrylate, hydroxy-methylated N-(1,1-dimethyl-3-oxobutyl)acrylamide, N-methylolacrylamide, N-methylolmethacrylamide, N-ethyl-N-methylolmethacryl-
 15 amide, N-ethyl-N-methylolacrylamide, N,N-dimethylol-acrylamide, N-ethanol-acrylamide, N-propanolacrylamide, N-methylolacrylamide, glycidyl acrylate, and glycidyl methacrylate, methyl acrylate, ethyl acrylate, propyl acrylate, butyl acrylate, amyl acrylate, ethylhexyl acrylate, octyl acrylate, t-octyl acrylate, 2-methoxyethyl acrylate, 2-butoxyethyl acrylate, 2-phenoxyethyl acrylate, chloroethyl acrylate,
 20 cyanoethyl acrylate, dimethylaminoethyl acrylate, benzyl acrylate, methoxybenzyl acrylate, furfuryl acrylate, tetrahydrofurfuryl acrylate and phenyl acrylate; di(meth)-acrylates may be selected from 2,2-bis(4-methacryloxyphenyl)propane, 1,2-butane-diol-diacrylate, 1,4-butanediol-diacrylate, 1,4-butanediol-dimethacrylate, 1,4-cyclohexanediol-dimethacrylate, 1,10-decanediol-dimethacrylate, diethylene-glycol-
 25 diacrylate, dipropylene glycol-diacrylate, dimethylpropanediol-dimethacrylate, tri-ethyleneglycol-dimethacrylate, tetraethyleneglycol-dimethacrylate, 1,6-hexanediol-diacrylate, Neopentylglycol-diacrylate, polyethyleneglycol-dimethacrylate, tripropyl-eneglycol-diacrylate, 2,2-bis[4-(2-acryloxyethoxy)phenyl]propane, 2,2-bis[4-(2-

hydroxy-3-methacryloxypropoxy)phenyl]propane, bis(2-methacryloxyethyl)N,N-1,9-nonylene-biscarbamate, 1,4-cyclohexanedimethanol-dimethacrylate, and diacrylic urethane oligomers; tri(meth)acrylates may be selected from tris(2-hydroxyethyl)-isocyanurate-trimethacrylate, tris(2-hydroxyethyl)isocyanurate-triacrylate, tri-
5 methylolpropane-trimethacrylate, trimethylolpropane-triacrylate or pentaerythritol-triacrylate; tetra(meth)acrylates may be selected from pentaerythritol-tetraacrylate, di-trimethylpropane-tetraacrylate, or ethoxylated pentaerythritol-tetraacrylate; suitable penta(meth)acrylates may be selected from dipentaerythritol-pentaacrylate or pentaacrylate-esters; and mixtures, copolymers and any combinations thereof.

- 10 In medical applications, biopolymers or acrylics may be preferably selected as polymers for encapsulating the active agents. In agricultural or other non-medical applications, acrylics, starch-based or cellulose derived polymers may be preferably selected as polymers for encapsulating the active agents.

- Encapsulating polymer reactants may be selected from polymerisable
15 monomers, oligomers or elastomers such as polybutadiene, polyisobutylene, polyisoprene, poly(styrene-butadiene-styrene), polyurethanes, polychloroprene, natural rubber materials, gums such as gum arabica, locust bean gum, gum caraya, or silicone, and mixtures, copolymers or combinations of any of the foregoing. The active agents may be encapsulated in elastomeric polymers solely or in mixtures of
20 thermoplastic and elastomeric polymers or in a sequence of shells/layers alternating between thermoplastic and elastomeric polymer shells.

- The polymerization reaction for encapsulating the active agents may be any suitable conventional polymerisation reaction, for example, a radical or non-radical polymerization, enzymatical or non-enzymatical polymerization, including a poly-
25 condensation reaction. The emulsions, dispersions or suspensions used may be in the form of aqueous, non-aqueous, polar or unpolar systems. By adding suitable surfactants, the amount and size of the emulgated or dispersed droplets can be adjusted as required.

The surfactants may be anionic, cationic, zwitter-ionic or non-ionic surfactants or any combinations thereof. Preferred anionic surfactants may include, but are not limited to, soaps, alkylbenzolsulphonates, alkansulphonates, olefinsulphonates, alkyethersulphonates, glycerinethersulphonates, α -methylestersulphonates, 5 sulphonated fatty acids, alkylsulphates, fatty alcohol ether sulphates, glycerine ether sulphates, fatty acid ether sulphates, hydroxyl mixed ether sulphates, monoglyceride(ether)sulphates, fatty acid amide(ether)sulphates, mono- and di-alkylsulfosuccinates, mono- and dialkylsulfosuccinamates, sulfotriglycerides, amidsoaps, ethercarboxylicacid and their salts, fatty acid isothionates, fatty acid 10 arcosinates, fatty acid taurides, N-acylaminoacid such as acyllactylates, acyltartrates, acylglutamates and acylaspartates, alkyloligoglucosidsulfates, protein fatty acid condensates, including plant derived products based on wheat; and alky(ether)phosphates.

Cationic surfactants suitable for encapsulation reactions in certain 15 embodiments of the present invention may be selected from the group of quaternary ammonium compounds such as dimethyldistearylammoniumchloride, Stepanex® VL 90 (Stepan), esterquats, particularly quaternised fatty acid trialkanolaminester salts, salts of long-chain primary amines, quaternary ammonium compounds such as hexadecyltrimethyl-ammoniumchloride (CTMA-Cl), Dehyquart® A (cetrimonium- 20 chloride, Cognis), or Dehyquart® LDB 50 (lauryldimethylbenzylammoniumchloride, Cognis).

Further specifically preferred surfactants may be lecithine, poloxamers, i.e. block copolymers of ethylene oxide and propylene oxide, e.g. those available from BASF Co. under the tradename pluronic®, including pluronic® F68NF, alcohol 25 ethoxylate based surfactants from the TWEEN® series, available from Sigma Aldrich or Krackeler Scientific Inc., and the like.

The active agent can be added before or during the start of the polymerization reaction and may be provided as a dispersion, emulsion, suspension or solid solution,

or solution of the active agents in a suitable solvent or solvent mixture, or any mixtures thereof. The encapsulation process can require the polymerization reaction, optionally with the use of initiators, starters or catalysts, wherein an *in-situ* encapsulation of the active agents in the polymer produced by the polymerisation in
5 polymer capsules, spheroids or droplets is provided. The solids content of the active agents in such encapsulation mixtures may be selected such that the solids content in the polymer capsules, spheroids or droplets is at about 10 weight-% to about 80 weight-% of active agent within the polymer particles.

Optionally, the active agents may also be added after completion of the
10 polymerisation reaction, either in solid form or in a liquid form. In such instance the active agents are selected from those compounds which are able to bind to the polymer spheroids or droplets covalently or non-covalently. Preferably, the droplet size of the polymers and the solids content of active agents is selected such that the solid content of the active agents is in the range of from about 5 weight-% to about
15 90 weight-%, referring to the total weight of the encapsulated active agents.

In a preferred embodiment, the *in-situ* encapsulation of the active agents during the polymerisation can be repeated at least once by addition of further monomers, oligomers or pre-polymeric agents after completion of the first
polymerisation/encapsulation step. By at least one repetition step such as this
20 multilayer coated polymer capsules can be produced. Also, active agents bound to polymer spheroids or droplets may be encapsulated by subsequently adding monomers, oligomers or pre-polymeric reactants to overcoat the active agents with a polymer capsule. Repetition of such method steps leads to multilayered polymer capsules comprising the active agent.

25 Any of these encapsulation steps may be combined with each other. In a especially preferred embodiment, polymer encapsulated active agents are further coated with release modifying agents.

In further exemplary embodiments of the present invention, the polymer encapsulated active agents can be further encapsulated in vesicles, liposomes or micelles, or overcoatings. Suitable surfactants for this purpose include the surfactants described above, and compounds having hydrophobic groups which may include

5 hydrocarbon residues or silicon residues, for example polysiloxane chains, hydrocarbon based monomers, oligomers and polymers or lipids or phospholipids or any combinations thereof, particularly glycerylester such as phosphatidyl-ethanolamine, phosphatidylcholine, polyglycolide, polylactide, polymethacrylate, polyvinylbutylether, polystyrene, polycyclopentadienyl-methylnorbornene,

10 polypropylene, polyethylene, polyisobutylene, polysiloxane, or any other type of surfactant.

Furthermore, depending on the polymeric shell, surfactants for encapsulating the polymer encapsulated active agents in vesicles, overcoats and the like may be selected from hydrophilic surfactants or surfactants having a hydrophilic residues or

15 hydrophilic polymers such as polystyrenesulfonic acid, poly-N-alkylvinylpyridinium-halogenide, poly(meth)acrylic acid, polyaminoacids, poly-N-vinylpyrrolidone, polyhydroxyethylmethacrylate, polyvinylether, polyethyleneglycol, polypropylene-oxide, polysaccharides such as agarose, dextrane, starch, cellulose, amylase, amylo-pektin or polyethyleneglycols or polyethylenimines of a suitable molecular weight.

20 Also mixtures from hydrophobic or hydrophilic polymer materials or lipid polymer compounds may be used for encapsulating the polymer encapsulated active agents in vesicles or for further over-coating the polymer encapsulating active agents.

Additionally, the encapsulated active agents may be chemically modified by functionalization with suitable linker groups or coatings which are capable to react

25 with the sol/gel forming components. For example, they may be functionalized with organosilane compounds or organo-functional silanes. Such compounds for modification of the polymer encapsulating active agents are further described in the below sol/gel component section.

- The particle size and particle size distribution of the encapsulated active agents in dispersed or suspended form typically correspond to the particle size and particle size distribution of the particles of finished encapsulated active agents, and have e.g. a significant influence on the release properties of the drug delivery material
- 5 produced. The encapsulated active agents can be characterised by dynamic light scattering methods with regard to their particle size and monodispersity.

Sol/gel forming components

- The polymer encapsulated active agents may be combined with a sol before subsequently being converted into a solid or semi-solid drug delivery material.
- 10 The sol utilized in the process of the present invention can be prepared from any type of sol/gel forming components in a conventional manner. The skilled person will –depending on the desired properties and requirements of the material to be produced – select the suitable components / sols for combination with the polymer encapsulated active agents based on his professional knowledge.
- 15 The sol/gel forming components may be selected from alkoxides, oxides, acetates, nitrates of various metals, e.g. silicon, aluminum, boron, magnesium, zirconium, titanium, alkaline metals, alkaline earth metals, or transition metals, and from platinum, molybdenum, iridium, tantalum, bismuth, tungsten, vanadium, cobalt, hafnium, niobium, chromium, manganese, rhenium, iron, gold, silver, copper,
- 20 ruthenium, rhodium, palladium, osmium, lanthanum and lanthanides, as well as combinations thereof.

- In some exemplary embodiments of the present invention, the sol/gel forming components can be selected from metal oxides, metal carbides, metal nitrides, metaloxynitrides, metacarbonitrides, metaloxycarbides, metaloxynitrides, and
- 25 metaloxycarbonitrides of the above mentioned metals, or any combinations thereof. These compounds, which may be in the form of colloidal particles, can be reacted with oxygen containing compounds, e.g. alkoxides to form a sol/gel, or may be added as fillers if not in colloidal form.

In other exemplary embodiments of the present invention, the sols may be derived from at least one sol/gel forming component selected from alkoxides, metal alkoxides, colloidal particles, particularly metal oxides and the like. The metal alkoxides that may be used as sol/gel forming components may be conventional
5 chemical compounds that may be used in a variety of applications. These compounds have the general formula $M(OR)_x$ wherein M is any metal from a metal alkoxide which e.g. may hydrolyze and polymerize in the presence of water. R is an alkyl radical of 1 to 30 carbon atoms, which may be straight chained or branched, and x has a value equivalent to the metal ion valence. Metal alkoxides such as $Si(OR)_4$,
10 $Ti(OR)_4$, $Al(OR)_3$, $Zr(OR)_3$ and $Sn(OR)_4$ may be used. Specifically, R can be the methyl, ethyl, propyl or butyl radical. Further examples of suitable metal alkoxides can include $Ti(isopropoxy)_4$, $Al(isopropoxy)_3$, $Al(sec-butoxy)_3$, $Zr(n-butoxy)_4$ and $Zr(n-propoxy)_4$.

Sols can be made from silicon alkoxides such as tetraalkoxysilanes, wherein
15 the alkoxy may be branched or straight chained and may contain 1 to 25 carbon atoms, e.g. tetramethoxysilane (TMOS), tetraethoxysilane (TEOS) or tetra-n-propoxysilane, as well as oligomeric forms thereof. Also suitable are alkylalkoxysilanes, wherein alkoxy is defined as above and alkyl may be a substituted or unsubstituted, branched or straight chain alkyl having about 1 to 25 carbon atoms,
20 e.g., methyltrimethoxysilane (MTMOS), methyltriethoxysilane, ethyltriethoxysilane, ethyltrimethoxysilane, methyltripropoxysilane, methyltributoxysilane, propyltrimethoxysilane, propyltriethoxysilane, isobutyltriethoxysilane, isobutyltrimethoxysilane, octyltriethoxysilane, octyltrimethoxysilane, which is commercially available from Degussa AG, Germany, methacryloxydecyltrimethoxysilane
25 (MDTMS); aryltrialkoxysilanes such as phenyltrimethoxysilane (PTMOS), phenyltriethoxysilane, which is commercially available from Degussa AG, Germany; phenyltripropoxysilane, and phenyltributoxysilane, phenyl-tri-(3-glycidyloxy)-silane-oxide (TGPSO), 3-aminopropyltrimethoxysilane, 3-aminopropyl-triethoxysilane,

2-aminoethyl-3-aminopropyltrimethoxysilane, triaminofunctional propyltri-
methoxysilane (Dynasylan[®] TRIAMO, available from Degussa AG, Germany), N-
(n-butyl)-3-aminopropyltrimethoxysilane, 3-aminopropylmethyl-diethoxysilane, 3-
glycidyloxypropyltrimethoxysilane, 3-glycidyloxypropyltriethoxy-silane, vinyl-
5 trimethoxysilane, vinyltriethoxysilane, 3-mercaptopropyltrimethoxy-silane,
Bisphenol-A-glycidylsilanes; (meth)acrylsilanes, phenylsilanes, oligomeric or
polymeric silanes, epoxysilanes; fluoroalkylsilanes such as fluoroalkyltrimethoxy-
silanes, fluoroalkyltriethoxysilanes with a partially or fully fluorinated, straight chain
or branched fluoroalkyl residue of about 1 to 20 carbon atoms, e.g. tridecafluoro-
10 1,1,2,2-tetrahydrooctyltriethoxysilane and modified reactive fluoroalkylsiloxanes
which are available from Degussa AG under the trademarks Dynasylan[®] F8800 and
F8815; as well as any mixtures of the foregoing. Such sols may be easily converted
into solid porous aerogels by drying.

In another exemplary embodiment of the present invention, the sol may be
15 prepared from carbon-based nano-particles and organic alkaline or earth alkaline
metal salts, e.g. their formates, acetates, propionates, malates, maleates, oxalates,
tartrates, citrates, benzoates, salicylates, phtalates, stearates, phenolates, sulfonates,
and amines, as well as acids, such as phosphorous acids, pentoxides, phosphates, or
organo phosphorous compounds such as alkyl phosphonic acids. Further substances
20 that may be used to form sols for e.g. bioerodible or dissolvable drug delivery
materials include sols made from magnesium acetate, calcium acetate, phosphorous
acid, P₂O₅ as well as triethyl phosphite as a sol in ethanol or ethanediol, whereby
biodegradable composites can be prepared from physiologically acceptable organic
or inorganic components. For example, by varying the stoichiometric Ca/P-ratio, the
25 degeneration rate of such composites can be adjusted. A molar ratio of Ca to P can be
about 0.1 to 10, or preferably about 1 to 3.

In some exemplary embodiments of the present invention, the sols can be
prepared from colloidal solutions, which may comprise carbon-based nanoparticles,

preferably in solution, dispersion or suspension in polar or nonpolar solvents, including aqueous solvents as well as cationically or anionically polymerizable polymers as precursors, such as alginate. By addition of suitable coagulators, e.g. inorganic or organic acids or bases, including acetates and diacetates, carbon

5 containing composite materials can be produced by precipitation or gel formation. Optionally, further additives can be added to adjust the properties of the resultant drug delivery material.

The sol/gel components used in the sols may also comprise colloidal metal oxides, preferably those colloidal metal oxides which are stable long enough to be

10 able to combine them with the other sol/gel components and the polymer-encapsulated active agents. Such colloidal metal oxides may include, but are not limited to, SiO_2 , Al_2O_3 , MgO , ZrO_2 , TiO_2 , SnO_2 , ZrSiO_4 , B_2O_3 , La_2O_3 , Sb_2O_5 and $\text{ZrO}(\text{NO}_3)_2$. SiO_2 , Al_2O_3 , ZrSiO_4 and ZrO_2 may be preferably selected. Further examples of the at least one sol/gel forming component include aluminumhydroxide

15 sols or -gels, aluminumtri-sec-butylat, AlOOH -gels and the like.

Some of these colloidal sols may be acidic in the sol form and, therefore, when used during hydrolysis, it may not be necessary to add additional acid to the hydrolysis medium. These colloidal sols can also be prepared by a variety of methods. For example, titania sols having a particle size in the range of about 5 to

20 150 nm can be prepared by the acidic hydrolysis of titanium tetrachloride, by peptizing hydrous TiO_2 with tartaric acid and, by peptizing ammonia washed $\text{Ti}(\text{SO}_4)_2$ with hydrochloric acid. Such processes are described, for example, by Weiser in Inorganic Colloidal Chemistry, Vol. 2, p. 281 (1935). In order to preclude the incorporation of contaminants in the sols the alkyl orthoesters of the metals can

25 be hydrolized in an acid pH range of about 1 to 3, in the presence of a water miscible solvent, wherein the colloid is present in the dispersion in an amount of about 0.1 to 10 weight percent.

In some exemplary embodiments of the present invention, the sols can be made of sol/gel forming components such as metal halides of the metals as mentioned above, which are reacted with oxygen functionalized polymer-encapsulated active agents to form the desired sol. In this case, the sol/gel forming components may be
5 oxygen-containing compounds, e.g., alkoxides, ethers, alcohols or acetates, which can be reacted with suitably functionalized polymer-encapsulated active agents. However, normally the encapsulated active agents can be dispersed into the sol by suitable blending methods such as stirring, shaking, extrusion, or the like.

Where the sol is formed by a hydrolytic sol/gel-process, the molar ratio of the
10 added water and the sol/gel forming components, such as alkoxides, oxides, acetates, nitrides or combinations thereof, may be in the range of about 0.001 to 100, preferably from about 0.1 to 80, more preferred from about 0.2 to 30.

In a typical hydrolytic sol/gel processing procedure which can be used in exemplary embodiments of the invention, the sol/gel components are blended with
15 the (optionally chemically modified) encapsulated active agents in the presence of water. Optionally, further solvents or mixtures thereof, and/or further additives may be added, such as surfactants, fillers and the like, as described in more detail hereinafter. The solvent may contain salts, buffers such as PBS buffer or the like to adjust the pH value, the ionic strength etc. Further additives such as crosslinkers
20 may be added, as well as catalysts for controlling the hydrolysis rate of the sol or for controlling the crosslinking rate. Such catalysts are also described in further detail hereinbelow. Such processing is similar to conventional sol/gel processing.

Non-hydrolytic sols may be similarly made as described above, but likely essentially in the absence of water.

25 When the sol is formed by a non-hydrolytic sol/gel-process or by chemically linking the components with a linker, the molar ratio of the halide and the oxygen-containing compound may be in the range of about 0.001 to 100, or preferably from

about 0.1 to 140, even more preferably from about 0.1 to 100, particularly preferably from about 0.2 to 80.

In nonhydrolytic sol/gel processes, the use of metal alkoxides and carboxylic acids and their derivatives or carboxylic acid functionalized polymer-encapsulated
5 active agents may also be suitable. Suitable carboxylic acids include acetic acid, acetoacetic acid, formic acid, maleic acid, crotonic acid, succinic acid, their anhydrides, esters and the like.

Non-hydrolytic sol/gel processing in the absence of water may be accomplished by reacting alkylsilanes or metal alkoxides with anhydrous organic
10 acids, acid anhydrides or acid esters, or the like. Acids and their derivatives may be suitable as sol/gel components and/or for modifying/functionalizing the encapsulated active agents.

In certain exemplary embodiments of the present invention, the sol may also be formed from at least one sol/gel forming component in a nonhydrous sol/gel
15 processing, and the reactants can be selected from anhydrous organic acids, acid anhydrides or acid esters such as formic acid, acetic acid, acetoacetic acid, succinic acid, maleic acid, crotonic acid, acrylic acid, methacrylic acid, partially or fully fluorinated carboxylic acids, their anhydrides and esters, e.g. methyl- or ethylesters, and any mixtures of the foregoing. It is often preferred to use acid anhydrides in
20 admixture with anhydrous alcohols, wherein the molar ratio of these components determines the amount of residual acetoxy groups at the silicon atom of the alkylsilane employed.

Typically, according to the degree of crosslinking desired in the resulting sol or combination of sol and encapsulated active agents, either acidic or basic catalysts
25 may be applied, particularly in hydrolytic sol/gel processes. Suitable inorganic acids include, for example, hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid as well as diluted hydrofluoric acid. Suitable bases include, for example, sodium hydroxide, ammonia and carbonate as well as organic amines. Suitable catalysts in

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non-hydrolytic sol/gel processes include anhydrous halide compounds, for example BCl_3 , NH_3 , AlCl_3 , TiCl_3 or mixtures thereof.

To affect the hydrolysis in hydrolytic sol/gel processing steps of the present invention, the addition of solvents may be used, including water-miscible solvents, such as water-miscible alcohols or mixtures thereof. Alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol and lower molecular weight ether alcohols such as ethylene glycol monomethyl ether may be used. Small amounts of non-water-miscible solvents such as toluene may also be advantageously used. These solvents can also be used in polymer encapsulation reactions such as those described above.

Additives

In certain exemplary embodiments of the present invention, the sol or combination network may be further modified by the addition of at least one crosslinking agent to the sol, the encapsulated active agent or the combination. The crosslinking agent may comprise, for example, isocyanates, silanes, diols, dicarboxylic acids, (meth)acrylates, for example such as 2-hydroxyethyl methacrylate, propyltrimethoxysilane, 3-(trimethylsilyl)propyl methacrylate, isophorone diisocyanate, polyols, glycerine and the like. Biocompatible crosslinkers such as glycerine, diethylene triamino isocyanate and 1,6-diisocyanato hexane may be preferably used.

Fillers can be used to modify the pore sizes and the degree of porosity, if desired. Some preferred fillers include inorganic metal salts, such as salts from alkaline and/or alkaline earth metals, preferably alkaline or alkaline earth metal carbonates, -sulfates, -sulfites, -nitrates, -nitrites, -phosphates, -phosphites, -halides, -sulfides, -oxides, as well as mixtures thereof. Further suitable fillers include organic metal salts, e.g. alkaline or alkaline earth and/or transition metal salts, such as formiates, acetates, propionates, malates, maleates, oxalates, tartrates, citrates,

benzoates, salicylates, phthalates, stearates, phenolates, sulfonates, and amines as well as mixtures thereof.

Preferably, porosity in the resultant composite materials can be produced by treatment processes such as those described in German Patent publication DE 103 35
5 131 and in PCT Application No. PCT/EP04/00077.

Further additives may include, e.g., drying-control chemical additives such as glycerol, DMF, DMSO or any other suitable high boiling point or viscous liquids that can be suitable for controlling the conversion of the sols to gels and solid or semi-solid materials.

10 Solvents that can be used e.g. for the removal of fillers include, for example, (hot) water, diluted or concentrated inorganic or organic acids, bases and the like. Suitable inorganic acids include, for example, hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid as well as diluted hydrofluoric acid. Suitable bases include, for example, sodium hydroxide, ammonia, carbonate as well as organic
15 amines. Suitable organic acids include, for example, formic acid, acetic acid, trichloromethane acid, trifluoromethane acid, citric acid, tartaric acid, oxalic acid and mixtures thereof.

In exemplary embodiments of the present invention, coatings made of the drug delivery materials producible in accordance with the processes described in the
20 present invention may be applied as a liquid solution or dispersion or suspension of the combination in a suitable solvent or solvent mixture, with subsequent drying / evaporation of the solvent. Suitable solvents comprise, for example, methanol, ethanol, N-propanol, isopropanol, butoxydiglycol, butoxyethanol, butoxyisopropanol, butoxypropanol, n-butyl alcohol, t-butyl alcohol, butylene glycol, butyl
25 octanol, diethylene glycol, dimethoxydiglycol, dimethyl ether, dipropylene glycol, ethoxydiglycol, ethoxyethanol, ethyl hexane diol, glycol, hexane diol, 1,2,6-hexane triol, hexyl alcohol, hexylene glycol, isobutoxy propanol, isopentyl diol, 3-methoxybutanol, methoxydiglycol, methoxyethanol, methoxyisopropanol,

methoxymethylbutanol, methoxy PEG-10, methylal, methyl hexyl ether, methyl propane diol, neopentyl glycol, PEG-4, PEG-6, PEG-7, PEG-8, PEG-9, PEG-6-methyl ether, pentylene glycol, PPG-7, PPG-2-buteth-3, PPG-2 butyl ether, PPG-3 butyl ether, PPG-2 methyl ether, PPG-3 methyl ether, PPG-2 propyl ether, propane diol, propylene glycol, propylene glycol butyl ether, propylene glycol propyl ether, tetrahydrofurane, trimethyl hexanol, phenol, benzene, toluene, xylene; as well as water, any of which may be mixed with dispersants, surfactants or other additives and mixtures of the above-named substances.

Any of the above- and below-mentioned solvents can also be used in the sol/gel process itself or in the encapsulation process, as outlined above. Solvents may also comprise one or several organic solvents from the group of ethanol, isopropanol, *n*-propanol, dipropylene glycol methyl ether and butoxyisopropanol (1,2-propylene glycol-*n*-butyl ether), tetrahydrofurane, phenol, benzene, toluene, xylene, preferably ethanol, isopropanol, *n*-propanol and/or dipropylene glycol methyl ether.

The fillers can be partly or completely removed from the resultant drug delivery material depending on the nature and time of treatment with the solvent. A complete removal of the filler may be sometimes preferred.

Conversion

The combination of the sol and the encapsulated active agents formed in the process according to the invention can be converted into a solid or semi-solid drug delivery material. Conversion of the combination into a gel, preferably an aerogel or xerogel, may be accomplished by, e.g., aging, curing, raising of pH, evaporation of solvent or any other conventional method. The combination may be preferably converted into the material at room temperature, particularly where the materials used result in polymeric glassy composites, aerogels or xerogels.

The conversion step can be achieved by drying the combination or the gel derived thereof. In exemplary embodiments of the present invention, this drying step includes a thermal treatment of the sol/combination or gel, in the range of about -200

C to +200 °C, preferably in the range of about -100 °C to 100 °C, more preferably in the range of about -50 °C to 100 °C, about 0 °C to 90 °C, and most preferably from about 10 °C to 80 °C or at about room temperature. Drying or aging may also be performed at any of the above temperatures under reduced pressure or *in vacuo*.

- 5 The conversion of the sol/combination into the solid or semi-solid material can be performed under various conditions. The conversion can be performed in different atmospheres, e.g. inert atmospheres such as nitrogen, SF₆, or noble gases such as argon, or any mixtures thereof, or it may be performed in an oxidizing atmosphere such as normal air, oxygen, carbon monoxide, carbon dioxide, or nitrogen oxide.
- 10 Furthermore, an inert atmosphere may be blended with reactive gases, e.g. hydrogen, ammonia, C₁-C₆ saturated aliphatic hydrocarbons such as methane, ethane, propane and butene, mixtures thereof or other oxidizing gases.

- In exemplary embodiments of the present invention, the atmosphere used in any of the steps of the process according to the invention is substantially free of
- 15 oxygen, particularly where oxygen sensitive components are used, e.g. organometallic compounds or certain alkoxides in non-hydrolytic sols. The oxygen content may be preferably below about 10 ppm, more preferred below about 1 ppm.

- In further exemplary embodiments of the present invention, high pressure may be applied to form the drug delivery material. The conversion step may be
- 20 performed by drying under supercritical conditions, for example in supercritical carbon dioxide, which can lead to highly porous aerogel materials. Reduced pressure or a vacuum may also be applied to convert the sol/gel into the drug delivery material.

- Suitable conditions such as temperature, atmosphere and/or pressure may be
- 25 applied depending on the desired property of the final material and the components used to form the material.

 By the incorporation of additives, fillers or functional materials, the properties of the materials produced can be influenced and/or modified in a controlled manner.

For example, it is possible to render the surface properties of the material hydrophilic or hydrophobic by incorporating inorganic nanoparticles or nanocomposites such as layer silicates.

Coatings or bulk materials including the encapsulated active agents may be
5 processed or structured in a suitable way before or after conversion into the resultant material by folding, embossing, punching, pressing, extruding, gathering, injection molding and the like, either before or after being applied to a substrate or being molded or formed. In this way, certain structures of a regular or irregular type can be incorporated into the active agent containing coating produced with the drug delivery
10 material.

The combination materials can be further processed by conventional techniques, e.g., they can be used to build molded paddings and the like, or to form coatings on any substrates. Molded paddings can be produced in almost any desired form. The molded paddings may be in the form of pipes, bead-mouldings, plates,
15 blocks, cuboids, cubes, spheres or hollow spheres or any other three-dimensional structure, which may be, for example longish, circle-shaped, polyether-shaped, e.g. triangular, bar-shaped, plate-shaped, tetrahedral, pyramidal, octahedral, dodecahedral, icosahedral, rhomboidal, prismatic or in round shapes such as ball-shaped, spheroidal or cylindrical, lens-shaped, ring-shaped, honeycomb-shaped, and
20 the like.

The material can be brought into the desired form by applying any appropriate conventional technique, including, but not limited to, casting processes such as sand casting, shell moulding, full mould processes, die casting, centrifugal casting or by pressing, sintering, injection moulding, compression moulding, blow moulding,
25 extrusion, calendaring, fusion welding, pressure welding, jiggering, slip casting, dry pressing, drying, firing, filament winding, pultrusion, lamination, autoclave, curing or braiding.

Coatings formed from sols/combinations may be applied in liquid, pulpy or pasty form, for example, by painting, furnishing, phase-inversion, dispersing atomizing or melt coating, extruding, slip casting, dipping, or as a hot melt. Where the combination is in a solid or semi-solid state, it may be applied as a coating onto a
5 suitable substrate by, e.g., powder coating, flame spraying, sintering or the like. Dipping, spraying, spin coating, ink-jet-printing, tampon and microdrop coating or 3-D-printing may also be used.

Combination sols or gels can be processed by any appropriate conventional technique. Preferred techniques may include folding, stamping, punching, printing,
10 extruding, die casting, injection moulding, reaping, and the like. Coatings may also be obtained by a transfer process, in which the combination gels are applied to the substrates as a lamination. The coated substrates can be cured, and subsequently the coating can be released from the substrate to be thermally treated. The coating of the substrate can be provided by using suitable printing procedures, e.g. gravure printing,
15 scraping or blade printing, spraying techniques, thermal laminations or wet-in-wet laminations. It is possible to successively apply a plurality of thin layers to provide a more uniform and thicker coating, and/or to control a correct dosing of the active agent.

By applying the above-mentioned transfer procedure, it is also possible to form
20 multi-layer gradient films by using different material layers and/or different sequences of layers. Conversion of these multilayer coatings into a composite material can provide gradient materials, wherein the density, the release properties and/or the active agent concentration in the material may vary from place to place. With this, non-linear release profiles of the active agents may be achieved, as may be
25 desired for specific drugs and/or applications.

In another exemplary embodiment of the present invention, the combination according to the invention may be dried or thermally treated and commuted by suitable conventional techniques, for example by grinding in a ball mill or roller mill

and the like. The commuted material can be used as a powder, a flat blank, a rod, a sphere, a hollow sphere in different grainings, and the like, and can be further processed by conventional techniques to form granulates or extrudates in various forms.

- 5 Additional processing options can include, but are not limited to, the formation of powders by other conventional techniques, such as spray-pyrolysis, precipitation, and the formation of fibers by spinning-techniques, such as gel-spinning.

 The porosity and the pore sizes may also be varied over a wide range, simply by varying the components in the sol and/or by varying the particle size of the
10 encapsulated active agents, which may be used to control the release properties. Depending on the active agents used, their in vivo and/or in vitro release can be controlled by adjusting suitable pore sizes in the sol/gel matrix.

 Furthermore, by suitable selection of components and processing conditions, bioerodible coatings, or coatings and materials which are dissolvable or may be
15 peeled off from substrates in the presence of physiologic fluids can be produced. For example, coatings comprising the drug delivery material may be used for coronary implants such as stents, wherein the coating optionally further comprises, besides the active agent, an encapsulated or not encapsulated marker such as a metal compound having signaling properties, and thus may produce signals detectable by physical,
20 chemical or biological detection methods such as x-ray, nuclear magnetic resonance (NMR), computer tomography methods, scintigraphy, single-photon-emission computed tomography (SPECT), ultrasonic, radiofrequency (RF), and the like. Metal compounds used as markers may also be encapsulated in a polymer shell together or independently from the active agents, and thus can be prevented from
25 interfering with the implant material, which can also be a metal, where such interference can often lead to electrocorrosion or related problems.

 Coated implants may be produced with drug delivery coatings, wherein the coating remains permanently on the implant. In one exemplary embodiment of the

present invention, the coating may be slowly or rapidly dissolved or peeled off from the stent after implantation under physiologic conditions, thus providing for a controlled release of the active agent. Additionally, with the suitable selection of the encapsulating material, the release of the active agents can be further modified, e.g.
5 by using dissolvable or swellable encapsulating materials which slowly release the active agent in the presence of water, solvents or physiologic fluids.

Further possibilities for the modification of the release rate of the active agents encapsulated in the shells from the drug delivery materials are, for example, the incorporation of fillers such as porogenous fillers, hydrophilic or hydrophobic fillers,
10 which, in the presence of solvents such as water or physiologic fluids, have an influence on the elution rate of the encapsulated active agents. Also, with the incorporation of such fillers or surface active substances, the surface tension at the interfaces between encapsulated active agents and the sol/gel matrix can be modified, which may also directly influence the release rate of the active agents.

15 The active agents may be eluted from the drug delivery materials by eluting or releasing the whole capsules/polymeric shells, which may then subsequently be dissolved or degraded, or the shell of the encapsulated active agent may be degraded under the influence of physiologic fluids or solvents already within the sol/gel matrix and the active agents may then be directly released from the drug delivery materials.

20 The specific advantages of the drug delivery materials, especially when compared to prior art drug delivery systems where the active agent is simply dispersed in the sol/gel matrix without encapsulation are as follows:

The encapsulation of the active agents allows a separation of the active agents in a substantially inert surrounding, so that interactions with the sol/gel materials or
25 an interaction with substances used during the sol/gel process such as solvents, salts and the like are avoided. Such interactions may, in case of sensitive active agents, lead to degradation reactions or even inactivation of the active agents, for example proteins may be denaturated by sol/gel components. This can be effectively avoided

by encapsulating the proteins in polymeric or surfactant shells, as in the present invention. Also, the formation of intermediates of polycyclic active agents with sol/gel components can be avoided by the inventive encapsulation step.

Furthermore, it is possible with the process of the present invention to adjust
5 the release kinetics of the active agent from the inventive material independently from the sol/gel material used, simply by suitable selection of the encapsulation material, the thickness of the encapsulation shell, a suitable selection of the encapsulating polymer and its characteristic properties and the like. By selecting hydrophilic or hydrophobic encapsulation polymers, the release characteristics may
10 be suitably influenced and adapted to the media wherein the release occurs. Also the number of side chains of cross-linked or branched polymers as the encapsulation materials may have a direct influence on the release kinetics.

Further advantages of the drug delivery materials, particularly when used in coatings, may be that the combination from sol/gel materials, particularly those
15 which are bioresorbable or biodegradable, allow for the incorporation of fillers and the simultaneous incorporation of the encapsulated active agents, which provide new possibilities for individually adjusting the release rate and the release kinetics of the inventive drug delivery materials.

Furthermore, the method of producing the drug delivery materials is simplified
20 and also better reproducible when compared to prior art methods, since the formulation of active agents in polymer capsules can be done separately from the formulation of the sol/gel matrix. There is a particular advantage if with resorbable implant materials of the present invention or coatings made therewith, the release kinetics of the active agent are decoupled from the degradation kinetics of the
25 implant or the coating of the implant itself. This advantage is particularly relevant if the substrate or carrier of the drug delivery material is resorbed faster in vivo (as is the case with e.g., some magnesium or zinc alloys), and the action of the drug should follow a different release kinetic or release profile, respectively. In this case, the

present invention comprises in an exemplary embodiment a combined first carrier/second carrier mechanism, i.e., the sol/gel matrix used in the drug delivery materials is the first carrier (which transports the encapsulated active agents), and the shells/capsules carrying the encapsulated active agents are the second carrier, which
5 control the release of the active agent itself.

A further advantage of the invention is that if the implant comprising the inventive material can only reach a specific compartment of the organism (for example, the intra-vascular space in case of endoluminal coronary stents), the second carrier in the inventive materials, i.e., the polymer encapsulated active agent may,
10 however, provide physiological pathways to another compartment (for example, the extra vascular space). The latter is particularly desired with local drug delivery applications, if the drug itself is not enriched primarily in such a compartment where the implant is placed, which may be, for example, the case with hydrophilic proteins as the active agents which are transported from the intravascular space to the local
15 surrounding extra vascular space.

The drug delivery materials can be specifically used for the production or coating of medical implants such as coronary stents consisting of corrosive materials, for example, implants consisting of magnesium or zinc alloys, bone grafts made of biocorrosive material or degradable material or other stents. It is specifically
20 advantageous to use the drug delivery material for the manufacture of medical implants for replacement of organs or tissue, e.g. bone grafts, prostheses and the like, wherein the implants are manufactured in part or totally from the drug delivery material.

Examples

25 The invention will now be further described by way of the following non-limiting examples. Analyses and parameter determination in these examples were performed by the following methods:

Particle sizes are provided as mean particle sizes, as determined on a CIS Particle Analyzer (Ankersmid) by the TOT-method (Time-Of-Transition), X-ray powder diffraction, or TEM (Transmission-Electron-Microscopy). Average particle sizes in suspensions, emulsions or dispersions were determined by dynamic light scattering methods. Average pore sizes of the materials were determined by SEM (Scanning Electron Microscopy). Porosity and specific surface areas were determined by N₂ or He absorption techniques, according to the BET method.

Example 1 - Coating

20 mg of poly(DL-lactide-co-glycolide) and 2 mg of paclitaxel were added to 3 ml of acetone. The resulting solution was added at a constant flow rate of 10 ml per minute to a stirred (400 rpm) solution of 0.1% poloxamer 188 surfactant (pluronic® F68, available from BASF Co., N.J., US) in 0.05 M PBS buffer (phosphate-buffered saline), and the resulting colloidal suspension was stirred for additional 3 hours under a slight vacuum for evaporating the solvent. Then, the mixture was dried for 14 hours in vacuo. The resulting nano-particles comprising encapsulated paclitaxel had a mean particle size of 140 to 170 nm.

300 gm of tetraethylorthosilane TEOS (obtained from Degussa AG, Germany) in 300 g of deionized water and 1 g of 1N HCl as the catalyst were stirred for 30 minutes at room temperature in a glass vessel in order to produce a homogeneous sol. 5 ml of this sol were combined with 2 ml of a 5 mg per ml suspension of the above-produced capsules in ethanol, and 0.1 wt. % of lecithin was added as a surfactant. The suspension was stirred for 6 hours at room temperature and subsequently sprayed onto a commercially available coronary stent obtained from Fortimedix Co. (KAON 18.5 mm). The sprayed layer was dried for two hours at room temperature and had a gel-like, semi-solid consistency. The resulting layer had a thickness of about 3 µm.

Three coronary stents coated as described above were incubated in an Eppendorf-cup while shaking (75 rpm) at 37.5°C for 30 days in 4 ml of PBS buffer,

and the supernatant buffer solution was removed once a day and replaced by fresh buffer. In the removed supernatant solution, the amount of released paclitaxel was determined via HPLC. After 1 day about 30%, after 5 days about 50%, after 30 days about 70% of the total amount of the paclitaxel present in the coating were released.

5 **Example 2**

In this example, encapsulated paclitaxel was prepared in accordance with the procedure as outlined above in Example 1.

300 g tetramethylorthosilane (TMOS) (Degussa AG) were combined with 300 g of deionized water, 3 g TWEEN[®]20 (polyoxyethylene sorbitan monolaurate, obtained from Sigma Aldrich) as the surfactant and 1 ml of 1N HCl as a catalyst were added, and the mixture was stirred for 30 minutes at room temperature in a glass vessel in order to produce a homogeneous sol. 5 ml of this sol and 2 ml of a 5 mg per ml suspension of the encapsulated paclitaxel in ethanol were combined, stirred for 6 hours at room temperature and subsequently aged for five days at room temperature in 2 ml Eppendorf-cups. Then, the material was dried in vacuo. The aerogels so obtained had the form of a spheroidal powder of milky appearance. The aerogels had biodegradable properties and released the paclitaxel in a controlled manner which was determined as follows: The aerogel particles were incubated in 4 ml of PBS buffer while shaking at 75 rpm for thirty days at 37.5°C. An 1.2 ml volume of the aerogel particles was used. The buffer supernatant was removed daily and replaced by fresh buffer. The amount of paclitaxel released was determined in the supernatant via HPLC. The average release rate of paclitaxel was relatively constant at about 6 to about 8wt.-% of the total amount per day.

Example 3

Encapsulated paclitaxel was prepared in accordance with Example 1. A homogenous sol was prepared from 100 ml from a 20 wt.% solution of magnesium acetate tetrahydrate ($\text{Mg}(\text{CH}_3\text{COO})_2 \cdot 4 \text{H}_2\text{O}$) in ethanol, 10 ml of a 10% nitric acid and stirring for three hours at room temperature. 4 ml of tetraethylorthosilane TEOS

(obtained from Degussa AG) were added to the sol and the mixture was stirred for further two hours at room temperature (20 rpm). 5 ml of the sol was combined with 2 ml of a 5 mg per ml suspension of the encapsulated paclitaxel in ethanol, 0.1 wt.% lecithin as a surfactant were added and the combination was stirred for 6 hours at
5 room temperature and subsequently sprayed onto a commercially available coronary stent of Fortimedix Co. (KAON 18.5 mm). The homogeneous layer was dried for 10 minutes at about 40°C in a hot air stream.

The coated coronary stents were incubated in an Eppendorf-cup in 4 ml of PBS buffer while shaking at 75 rpm for 30 days at 37.5°C. The buffer supernatant was
10 removed daily and was replaced by fresh buffer. The amount of the released paclitaxel in the supernatant was determined by HPLC. 10 wt.% of the paclitaxel was released after the first day, 15% was released after 5 days and 40% of the total amount of the paclitaxel was released after 30 days.

Example 4

15 The encapsulated paclitaxel was prepared as described in Example 1. A homogeneous sol was prepared from 100 ml of a 20 wt.% solution of magnesium acetate tetrahydrate in ethanol and 10 ml of a 10% nitric acid at room temperature and stirring for 3 hours. 4 ml of TEOS (obtained from Degussa AG) were added and the mixture was stirred for further 2 hours at room temperature (20 rpm). 5 ml of the
20 so-obtained gel was combined with 2 ml of a 5 mg per ml suspension of paclitaxel capsules in ethanol, 2 wt.% of lecithine and 5 wt.% of polyethylene glycol PEG 400 as the surfactant or filler, respectively. The combination was stirred for 6 hours at room temperature and aged for 5 days in 2 ml Eppendorf-cups. Thereafter, the material was dried in vacuo. The so-obtained gel had the form of spheroidal particles
25 having a milky appearance. The aerogels had biodegradable and controlled release properties. The release rate was determined by incubating the aerogels in 4 ml of PBS buffer, while shaking at 75 rpm for thirty days at 37.5°C. The buffer supernatant was removed daily and replaced by fresh buffer. The amount of

paclitaxel released into the supernatant was determined via HPLC. The average release rate of paclitaxel in this example was constantly at about 2 % of the total amount per day.

Having thus described in detail several exemplary embodiments of the present invention, it is to be understood that the invention described above is not to be limited to particular details set forth in the above description, as many apparent variations thereof are possible without departing from the spirit or scope of the present invention. The embodiments of the present invention are disclosed herein or are obvious from and encompassed by the detailed description. The detailed description, given by way of example, is not intended to limit the invention solely to the specific embodiments described.

The foregoing applications and all documents cited therein or during their prosecution ("appln. cited documents") and all documents cited or referenced in the appln. cited documents, and all documents, references and publications cited or referenced herein ("herein cited documents"), and all documents cited or referenced in the herein cited documents, together with any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention. Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention. It is noted that in this disclosure and particularly in the claims, terms such as "comprises," "comprised," "comprising" and the like can have the broadest possible meaning; e.g., they can mean "includes," "included," "including" and the like; and that terms such as "consisting essentially of" and "consists essentially of" can have the broadest possible meaning, e.g., they allow for elements not explicitly recited, but exclude elements that are found in the prior art or that affect a basic or novel characteristic of the invention. The invention is further described by the following claims.

Claims:

1. A process for manufacturing a drug delivery material, the process comprising the following steps:
 - 5 a) encapsulating at least one biologically and/or therapeutically active agent in a shell;
 - b) combining the encapsulated active agent with a sol; and
 - c) converting the resulting combination into a solid or semi-solid drug delivery material.
- 10 2. The process according to claim 1, wherein the biologically and/or therapeutically active agent is encapsulated in a polymeric shell.
3. The process according to any one of claims 1 or 2, wherein the sol is formed by using a hydrolytic sol/gel-process in the presence of water.
4. The process according to any one of claims 1 to 3, wherein the sol is
15 formed by using a non-hydrolytic sol/gel-process in the absence of water.
5. The process according to any one of the preceding claims, wherein the active agent is a therapeutically active agent which is capable to provide a direct or indirect therapeutic, physiologic and/or pharmacologic effect in a human or animal organism.
- 20 6. The process according to claim 5, wherein the active agent is a medicament, drug, pro-drug, or a drug or pro-drug comprising at least one targeting group.
7. The process according to any one of claims 1 to 6, wherein the active agent is encapsulated in a polymer material selected from at least one of
25 poly(meth)acrylate, poly(DL-lactide-co-glycolide), poly(D,L-lactide), polyglycolide, unsaturated polyester, saturated polyester, polyolefines such as polyethylene, polypropylene, polybutylene, alkyd resins, epoxy-polymers, epoxy resins, polyamide, polyimide, polyetherimide, polyamideimide, polyesterimide, polyesteramideimide, polyurethane, polycarbonate, polystyrene, polyphenole,
30 polyvinylester, polysilicone, polyacetale, cellulosic acetate, polyvinylchloride,

polyvinylacetate, polyvinylalcohol, polysulfone, polyphenylsulfone, polyethersulfone, polyketone, polyetherketone, polybenzimidazole, polybenzoxazole, polybenzthiazole, polyfluorocarbons, polyphenylenether, polyarylate, cyanatoester-polymere, or copolymers of any of the foregoing.

5 8. The process according to claim 7, wherein the polymer material is selected from at least one of poly(D,L-lactide), polyglycolide, and poly(DL-lactide-co-glycolide), or polymethylmethacrylate (PMMA).

 9. The process according to any one of claims 7 or 8, wherein the encapsulation is provided by dispersion-, suspension-, or emulsion-polymerization,
10 enzymatic or radical polymerization techniques.

 10. The process according to claim 9, wherein the active agent is added to the polymerization mixture before or during start of the polymerization reaction.

 11. The process according to any one of claims 7 to 10, wherein the active agent is encapsulated in several shells or layers of organic material.

15 12. The process according to any one of the preceding claims, wherein the encapsulated active agents are chemically modified by functionalization with suitable linker groups or coatings which are capable to react with sol/gel forming components.

 13. The process according to any one of claims 1 to 12, wherein the sol is
20 prepared by using sol/gel forming components selected from the group comprising alkoxides, metal alkoxides, metal oxides, metal acetates, metal nitrates, metal halides, wherein the metal includes at least one of silicon, aluminum, boron, magnesium, zirconium, titanium, alkaline metals, alkaline earth metals, or transition metals, platinum, molybdenum, iridium, tantalum, bismuth, tungsten, vanadium,
25 cobalt, hafnium, niobium, chromium, manganese, rhenium, iron, gold, silver, copper, ruthenium, rhodium, palladium, osmium, lanthanum and lanthanides.

 14. The process according to claim 13, wherein the sol/gel forming components are selected from the group comprising silicon alkoxides such as tetraalkoxysilanes, as well as oligomeric forms thereof; alkylalkoxysilanes;
30 aryltrialkoxysilanes; aminoalkylalkoxysilanes, alkenylalkoxysilanes; bisphenol-A-

glycidylsilanes; (meth)acrylsilanes, epoxysilanes; fluoroalkylalkoxysilanes; as well as any mixtures of the foregoing.

15. The process according to any of the preceding claims, wherein the sol is formed in the presence of an organic solvent, and the organic solvent content of
5 the sol is from about 0.1 % and 90 %, preferably from about 1 % and 90 %, more preferably from about 5 % and 90 % and most preferably from about 20 % and 70 %.

16. The process according to any one of the preceding claims, wherein further additives are added to the encapsulated active agent, to the sol or to the combination thereof, the additives including at least one of further biologically or
10 therapeutically active compounds, fillers, surfactants, acids or bases, crosslinkers, pore-forming agents, plasticizers, lubricants, flame resistants, glass or glass fibers, carbon fibers, cotton, fabrics, metal powders, metal compounds, silicon, silicon oxides, zeolites, titanium oxides, zirconium oxides, aluminum oxides, aluminum silicates, talcum, graphite, soot, phyllosilicates, or drying-control chemical additives
15 such as glycerol, DMF or DMSO.

17. The process according to any one of the preceding claims, wherein the conversion of the combination of the encapsulated active agent and the sol into a solid or semi-solid material is performed by hydrolysis of the sol, aging, crosslinking and/or drying.

20 18. The process according to claim 17, wherein the drying is obtained by a thermal treatment in the range of about -200 °C to 100 °C, optionally under reduced pressure or vacuum.

19. The process according to any one of the preceding claims, additionally comprising the addition of at least one crosslinking agent to the encapsulated active
25 agent, to the sol or to the combination thereof, wherein the crosslinking agent includes at least one of an isocyanate, a silane, a (meth)acrylate, 2-hydroxyethyl methacrylate, propyltrimethoxysilane, 3-(trimethylsilyl)propyl methacrylate, isophoron diisocyanate, HMDI, diethylenetriaminoisocyanate, 1,6-diisocyanato-hexane.

20. The process according to any one of the precedings claims, additionally comprising the addition of at least one filler to the encapsulated active agent, to the sol or to the combination thereof, wherein the filler is incapable of reacting with the other components of the sol/gel.

5 21. The process according to claim 20, wherein the fillers are polymer encapsulated fullerenes.

22. The process according to any one of claims 20 or 21, further comprising at least partially removing the filler from the solid drug delivery material.

23. A solid or semi-solid drug delivery material obtainable by a process
10 according to any one of claims 1 to 22, in the form of a coating or as a bulk material.

24. The material according to claim 23, wherein the material is dissolvable in physiologic fluids and/or has bioerodible properties in the presence of physiologic fluids.

25. An implant comprising a drug delivery material according to any one
15 of claims 23 or 24.

26. The implant according to claim 25, providing a sustained release of the biologically active compound when inserted into the human or animal body.