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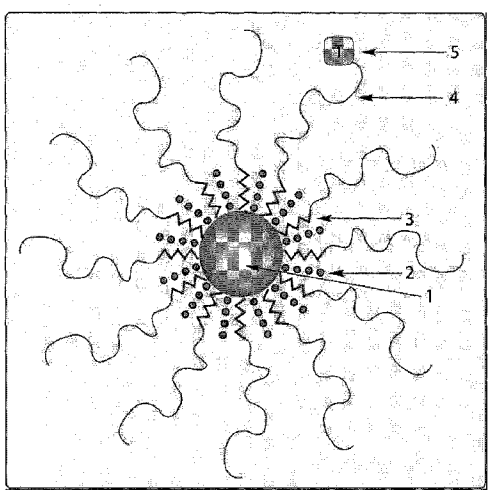
(54) Title: COATED NANOPARTICLES FOR AQUEOUS SYSTEMS

(57) Abstract: The invention is directed to nanoarticles comprising (i) a nanoparticle core, (ii) a plurality of polymer molecules, wherein the polymer molecules include one or more coordinating structures, and (iii) a plurality of non-core metal species. The nanoarticles may further comprise sterically stabilizing structures and/or targeting agents. The invention also includes methods for making the nanoarticles wherein the nanoparticle cores are mixed with the polymer molecules and the non-core metal species.

Illustration of nanoarticle



1 nanoparticle core
2 non-core metal species
3 coordinating structure
4 sterically stabilizing structure
5 targeting agent

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PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Coated Nanoparticles for Aqueous Systems

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application No. 60/867,040 filed on November 22, 2006, the entire contents of which is hereby incorporated by reference.

BACKGROUND

[0002] Nano-sized particles are particles exhibiting an average diameter, or major dimension, of less than about 1 micron. Due in part to their relatively small size and supramolecular structure, nano-sized particles are potentially useful for a variety of applications, such as diagnostic, therapeutic and vaccine applications. Certain coatings can provide for improved aqueous system dispersibility and can reduce undesirable biomolecular interactions of various nano-sized-particle cores, especially where the coatings are less hydrophobic than the cores.

SUMMARY OF INVENTION

[0003] Herein the inventors disclose nanoarticles, each nanoarticle comprising (i) a nanoparticle core, (ii) a plurality of polymer molecules, wherein the polymer molecules include one or more coordinating structures, and (iii) a plurality of non-core metal species. Optionally, the polymer molecules may also include one or more sterically stabilizing structures and/or targeting agents.

[0004] Without wishing to be bound by theory, it is believed that the polymer molecules, along with the non-core metal species as defined herein, form a thin coating or outer layer on the nanoparticle cores. A thin coating is helpful in producing a small overall nanoarticle structure, which may be desired for performance reasons, for instance for increasing tissue permeability when used in *in vivo* applications. When the core material is the source of the diagnostic signal or therapeutic activity, a thin coating (e.g., a coating about 1 to about 30 nm thick) as compared to a thicker coating may be desirable to maximize active core content. Unexpectedly, when polymers, nanoparticle cores, and non-core metal species are combined in the form of nanoarticles as disclosed herein, the nanoarticles are stably dispersible in aqueous solutions and in blood at nanoarticle concentrations up to 1 wt % or greater and are resistant to nonspecific protein binding and opsonization. In some embodiments, small nanoarticles of under about 40 nm in diameter comprise a plurality of

polymer molecules, a plurality of non-core metal species, and a nanoparticle core having an average diameter of about 25 nm or less. Such nanoarticle sizes may be desirable for certain applications, such as *in vivo* therapeutic and diagnostic applications, where the nanoarticles can more quickly penetrate tissues, such as tumors, compared to larger particles.

[0005] A coordinating structure as defined herein is a structure associated with the polymer molecules that forms or is capable of forming one or more coordinate bonds with one or more metal species in the nanoarticle. In some embodiments, the coordinating structure of the polymer molecules comprises an average in the range of about 2 to about 50 carboxylate functionalities per structure. In other embodiments, the coordinating structure of the polymer molecules comprises an average in the range of about 4 to about 40 carboxylate functionalities per structure.

[0006] The nanoarticles of the present invention may optionally further comprise sterically stabilizing structures. When present, the sterically-stabilizing structure may comprise a hydrophilic polymer that is hydrated in aqueous solutions, such as polyethylene glycol (PEG), for example. While not wishing to be bound by theory, it is believed that the sterically-stabilizing structures provide for nanoarticle dispersibility in aqueous systems. When a sterically-stabilizing structure that is attached to a nanoarticle is compressed, for instance due to the approach of another nanoarticle or a biomolecule such as a protein, there is an entropic penalty resulting from a reduction in conformational degree of freedom of the sterically-stabilizing structure. Thus, protein adsorption and/or nanoarticle agglomeration is on average thermodynamically unfavorable. For certain applications, for instance where it is desirable for nanoarticles to remain in the bloodstream for extended time or for instance where it is desirable for nanoarticles to localize to a pathological lesion, undesirably rapid opsonaization leads to an undesirably high rate reticuloendothelial system (RES) uptake.

[0007] The non-core metal species of the present invention may comprise platinum, cobalt, iron, calcium or other metal species as disclosed herein and may be radioactive or non-radioactive.

[0008] In certain embodiments of the present invention, some or all of the polymer molecules of each nanoarticle may further comprise one or more targeting agents.

[0009] The present invention further comprises a method of making a nanoarticle comprising the steps of mixing nanoparticle cores with a plurality of polymer molecules

having a coordinating structure, where the polymer molecules may further comprise a sterically-stabilizing region and/or a targeting agent. Non-core metal species may be added to the mixture before, while, or after the nanoparticle cores have been exposed to the coordinating structure-containing polymer molecules.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 shows a schematic of one embodiment of the nanoarticles of the invention.

DETAILED DESCRIPTION

[0010] In one aspect, the present invention provides nanoarticles with good water dispersability and resistance to non-specific protein binding and opsonization. As illustrated in FIG. 1, each nanoarticle includes a nanoparticle core, 1, and a plurality of non-core metal species, 2. The nanoarticles also comprise a plurality of polymer molecules. The polymer molecules include a coordinating structure, 3, and optionally, sterically stabilizing structures, 4, and/or targeting agents, 5. In other aspects the invention provides methods of making the nanoarticles, and for using the nanoarticles in formulations for *in vivo* uses including diagnostic imaging applications and as pharmaceutical formulations such as for chemotherapy.

Nanoparticle Core

[0011] The nanoarticles of the present invention comprise nanoparticle cores. A nanoparticle core of the invention is a material typically having an average diameter or major dimension of about 3 nm to about 1000 nm. In some embodiments, the particles are in a size range of about 5 nm to about 500 nm. In some embodiments the particles are in a size range of about 10 nm to about 100 nm. In some embodiments the particles are in a size range of about 20 to 50 nm. The nanoparticle core material is not particularly limited, except in that it will be a chemically and/or physically distinct composition from the polymer molecules and the non-core metal species. In some embodiments the nanoparticle cores aid in the assembly, uniformity, and/or stability of the nanoarticles disclosed herein. In some embodiments the nanoparticle core also has a therapeutic or diagnostic use or therapeutic or diagnostic value. Nanoparticle cores may be irregularly shaped or may be substantially in the shape of spheres, ellipsoids, disks, rods, wires, or various crystal structures. The nanoparticle cores may include an inorganic material, organic material, or both inorganic and organic materials. The core material may comprise an amorphous or crystalline structure, or

a combination of the two. The nanoparticle cores may comprise a solid material, or they may comprise an agglomeration of a plurality of smaller particles.

[0012] Nanoparticles that may be incorporated into nanoarticles as disclosed herein may be made using a variety of methods. For example, nanoparticle cores comprising inorganic nanoparticles may be synthesized using liquid-phase methods disclosed in Cushing, *et al.* (Chem. Rev. 2004, 104, 3893-3946). In another example, emulsion techniques may be used to form both inorganic and organic nanoparticles suitable for use as nanoparticle cores of the invention as disclosed by Uskokovic (Surface Review and letters 12 (2): 239-277 APR 2005).

[0013] In some embodiments the cores comprise or consist essentially of a metal and/or a metal oxide. The metal and/or metal oxide may be crystalline or amorphous. The nanoparticle cores may comprise or consist essentially of "metal/metal oxide" materials, herein denoting a material that comprises or consists essentially of both a metal crystal, for instance iron, and a metal oxide crystal, for instance iron oxide. Where the core material comprises a metal oxide, the metal oxide may be an iron oxide. A nanoparticle core comprising iron oxide may, among other possible structures have a hematite (α-Fe_2O_3), maghemite (γ-Fe_2O_3) or magnetite (Fe_3O_4) crystal structure. Nanoparticle cores may also comprise ferrite crystals with spinel structures of the general formula $MeFe_2O_4$, where Me denotes a divalent ion of the transition elements such as Cu, Zn, Mn, Co, Fe, or Mg; more than one of these elements may be incorporated into a spinel structure. Me may also comprise a combination of ions that have an average valence of about 2.

[0014] Ferrite cores, such as those including magnetite or maghemite, can be formed by a variety of methods. Non-limiting examples are provided below.

[0015] For instance, magnetite particles can be made by combining Fe(II) and Fe(III) salts in a basic solution from which Fe_3O_4 precipitates. Reverse microemulsions may also be utilized. For instance, Fe(II) can be prepared by dissolving $FeSO_47H_2O$ in water and an Fe(III) solution can be prepared by dissolving $FeCl_36H_2O$. These aqueous phases can then be combined into a single aqueous phase or in a reverse microemulsion with an appropriate organic continuous phase if desired. Addition of a base results in the formation of a magnetite colloid. The magnetic colloid can be encapsulated in another material, for instance silica prior to use as a nanoparticle core in a nanoarticle as disclosed herein. When silica encapsulation is used the nanoparticle may be further functionalized via alkoxysilane

derivatives. Silica encapsulation is discussed by Grasset, *et al.* in *European Cells and Materials*, Vol. 3, Suppl. 2, 2002, pp. 110-113.

[0016] Ferrite nanoparticle cores may also be formed using thermolysis procedures similar to those published by Hyeon, *et al.* (J Am Chem Soc (2001) **123** 12798-12801). This method results in oleic acid coupled to the surface of the iron oxide with a carboxylate moiety forming coordination bonds with iron atoms on the surface of the iron oxide core. If desired, the oleic acid chains can then be exchanged for water-soluble polymer molecules to give sterically stabilizing structures that allow for water dispersibility (i.e., steric-stabilization) as disclosed herein.

[0017] Ferrite nanoparticle cores may also be prepared by reacting metal acetylacetonates (acac) with long chain alcohols in the presence of oleic acid and oleyl amine using procedures similar to those described by Sun, *et al.* (J Am Chem Soc (2004) **126** 273-279). The hydrocarbon chains can then be exchanged for a water-soluble polymer molecules to the extent desired to allow for water dispersibility as disclosed herein.

[0018] Ferrite nanoparticle cores may also be prepared by reacting iron oxides and/or hydroxides with oleic acid using procedures similar to those described by Colvin, et al. (Chem Commun (2004) 2306). The hydrocarbon chains can then be exchanged for a water-soluble polymer molecules to the extent desired to allow for water dispersibility as disclosed herein.

[0019] In other embodiments the nanoparticle cores comprise or consist essentially of a noble metal, for instance gold, silver, tantalum, platinum, or rhodium, or a combination of these materials. Gold nanoparticles and nanoshells may be commercially obtained or may be synthesized according to well-described procedures (*see* Ramachandra Rao, *et al.* Chem. Soc. Rev.2000, **29**, 27-35).

[0020] In some embodiments the cores can also comprise or consist essentially of a combination of cadmium and selenium and may be in the form of a semiconductor crystal, sometimes termed a "quantum dot." In some embodiments the cores comprise or consist essentially of zinc oxide. In other embodiments the cores comprise or consist essentially of calcium phosphate.

[0021] In other embodiments the nanoparticle cores comprise or consist essentially of organic small molecules having a molecular weight of under about 1000. The organic

small molecule may be a drug. The drug may be a chemotherapeutic. Non-limiting examples of chemotherapeutics are paclitaxel, doxorubicin, irinotecan, cisplatin, and oxaliplatin.

Polymer Molecules

[0022] A plurality of certain polymer molecules, when in the presence of the nanoparticle cores, will form a coating on or around the nanoparticle cores, or will otherwise attach to or surround the exterior of the nanoparticles. The portion of the nanoarticles of the present invention outside of the core therefore comprises a plurality of polymer molecules. In certain embodiments, the plurality of polymer molecules have a number average molecular weight under about 20,000 Daltons and greater than about 1000 Daltons. In certain embodiments, the plurality of polymer molecules have a number-average molecular weight under about 15,000 Daltons and greater than about 1500 Daltons. In certain embodiments, the plurality of polymer molecules have a number-average molecular weight under about 12,000 Daltons and greater than about 1500 Daltons. In certain embodiments, the plurality of polymer molecules have a number-average molecular weight under about 10,000 Daltons and greater than about 1500 Daltons. In certain embodiments, the plurality of polymer molecules have a number-average molecular weight under about 8,000 Daltons and greater than about 1500 Daltons. In certain embodiments, the plurality of polymer molecules have a number-average molecular weight under about 6,000 Daltons and greater than about 1500 Daltons. In certain embodiments, the plurality of polymer molecules have a number-average molecular weight under about 4,000 Daltons and greater than about 1500 Daltons.

Coordinating Structures

[0023] Nanoarticles of the present invention comprise a plurality of polymer molecules that have coordinating structures. The coordinating structure as defined herein is a structure associated with the polymer molecules that forms, or is capable of forming, one or more coordinate bonds with one or more metal species (core or non-core). The resulting structure is sometimes called a coordination complex. In some embodiments, each coordinating structure is capable of forming about two or more coordinate bonds. In various embodiments, the polymer molecules may have an average of about 1, 2, 3, 4, or 5 coordinating structures per molecule.

[0024] The coordinating structures of the present invention may comprise or consist essentially of one or more chemical functionalities or elements capable of forming coordinate bonds by donating an electron pair to the core or non-core metal species, as described in

Advanced Inorganic Chemistry, F. A. Cotton, G. Wilkinson, R. N. Grimes, John Wiley & Sons Inc; 5th edition. By way of non-limiting examples, such elements include carbon, oxygen, nitrogen, sulfur, and halogens; exemplary chemical functionalities include carboxylates ($RCOO^-$), amines (R_nNH_{3-n} where n=0 to 3), hydroxyls (RO^-), and thiolates (RS^-), where R is a covalently-linked (to the polymer) alkyl-, alkenyl-, or aryl-derived group. Alkyl groups include straight or branched chain saturated hydrocarbons of 1 to 20 carbon atoms. Alkenyl groups include alkyl groups of 2 to 20 carbon atoms having at least one double bond between adjacent carbons. Aryl groups include mono-, bi- and tri-cyclic aromatic hydrocarbon ring systems of 6 to 20 carbons, e.g., phenyl, naphthyl and benzyl.

[0025] In certain embodiments it may also be beneficial to expose the nanoarticles to additional coordinating elements during or after formation, such as sulfide (S^{2-}), chloride (Cl^-), carbonate (CO_3^{2-}), phosphate (PO_4^{3-}), phosphonates (RPO_3^{2-}, R = alkyl, alkenyl or aryl, as defined herein), and cyanide (CN^-) ions. Without wishing to be bound by theory, it is believed that such coordinating elements that are not covalently bound to the polymer molecules can coordinate to one or more of the metal centers as monodentate, bidentate or multidentate ligands that may coordinate to a single metal ion, or bridge between two or more metal ions. In certain embodiments, the coordinating structure of the polymer molecules comprises or consists essentially of one or more carboxylate, amine, thiol, and/or alcohol functionalities. For example, where the coordinating structures comprise carboxylate functionalities and the nanoparticle core comprises a coordinate-bond forming material, the oxygen atom of the carboxylate group can donate a pair of electrons to the core and/or the non-core metal species, thus forming a coordination bond.

[0026] In some embodiments the number of carboxylates average in the range of about 1 to about 50 carboxylate functionalities per structure. In other embodiments the coordinating structures average in the range of about 2 to about 50 carboxylate functionalities per structure. In other embodiments coordinating structures average in the range of about 3 to about 15 carboxylate functionalities per structure. In other embodiments coordinating structures average in the range of about 4 to about 10 carboxylate functionalities per structure. The coordinating structures may also have an average of about 2 to about 5 carboxylate functionalities per structure. Also, in certain embodiments, the coordinating structures will have an average molecular weight in the range of about 100 to about 5000 Daltons. In other embodiments, the average molecular weight of the coordinating structure is in the range about 200 to about 1000 Daltons.

[0027] Butyl tetracarboxylate, cyclohexane hexacarboxylate, citric acid, the conjugates of these substances, and other multi-carboxylate molecules of defined structure may be used as coordinating structures.

[0028] In another embodiment, the coordinating structures at least partially comprise alkyl main chains of 4 carbons (C4), with carboxylate functionalities attached directly or indirectly to about half of the main chain carbons. Other embodiments comprise coordinating structures comprising alkyl main chains of 6, 8, 10, 12, 14, 16, 18, or 20 carbon atoms, with carboxylate functionalities attached to about 15% to about 50% of the main chain carbons. Non-limiting examples include coordinating structures comprised of an average of a 2-, 3-, or 4-mer of (meth)acrylate, or a 4-to-40-mer of (meth)acrylate, wherein at least one, and up to all, of the (meth)acrylate units have been hydrolyzed or otherwise substituted to yield the desired carboxylate or other coordination-bond-forming functionalities. Larger coordinating structures are also possible.

[0029] Carboxylate-containing coordinating structures can be made from (meth)acrylate and alkyl(meth)acrylate monomers, such as methyl(meth)acrylate, ethyl(meth)acrylate, and t-butyl (meth)acrylate, such that the resulting coordinating structure will contain (meth)acrylate or alkyl(meth)acrylate subunits. By "(meth)acrylate" and similarly denoted terms is meant either the acrylate form of a given monomer unit, the corresponding methacrylate form of the monomer unit, or a combination of the two. Polymer molecules made from the reaction of 2 or more (meth)acrylate or (alkyl)(meth)acrylate monomers are herein termed multi(alkyl)(meth)acrylates. When (meth)acrylate or (alkyl)(meth)acrylate monomers are used to form the polymer molecules of the present invention, the alkyl chains may be hydrolyzed or otherwise substituted after polymerization to yield the desired carboxylate functionalities or other coordinate-bond forming functionalities, if not already present in the monomer subunits.

[0030] Other coordinating-structure-containing polymer molecules can be made by using maleic acid in controlled radical polymerization methods. Combinations of monomers of alkyl(meth)acrylates and maleic acid may be reacted to form coordinating structures comprising 3 carboxylate functionalities or more.

[0031] Multi(alkyl)acrylates for use in the coordinating structures of the present invention may be fabricated using various methods known in the art, including free radical polymerization and controlled/living radical polymerization methods such as atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT), and

nitroxide-mediated polymerization (NMP). The number of distinct molecular entities of multi(alkyl)acrylates produced by any of these methods or others may be reduced using various purification techniques, including precipitation, extraction, electrophoretic and various chromatographic techniques, including gel permeation chromatography, ion exchange chromatography, and reverse phase high performance liquid chromatography, known in the art.

Sterically-Stabilizing Structures

[0032] The nanoarticles may optionally further comprise a plurality of polymer molecules that comprise one or more sterically-stabilizing structures. When present, the sterically-stabilizing structures may be part of the polymer molecules that contain the coordinating structures, or the sterically stabilizing structures may be independent of the coordinating-structure-containing polymer molecules. As used herein, the term sterically-stabilizing structure is used to denote a polymer or other high-molecular-weight structure that decreases the tendency of the nanoarticles to aggregate in aqueous solution. Typically, the sterically-stabilizing structures are hydrophilic and hydrated, and impart to the nanoarticles higher water dispersibility and/or lower nonspecific protein adhesion than the nanoarticles would exhibit without the sterically-stabilizing structure.

[0033] In one embodiment of the present invention, a plurality of polymer molecules surrounding or coating the core comprise a sterically-stabilizing structure. The polymer molecules may have an average of about 1, 2, 3, 4, or 5 sterically-stabilizing structures per molecule. In certain embodiments a plurality of the sterically-stabilizing structures comprise poly(ethylene glycol) (PEG). In such embodiments, the plurality of PEG stabilizing structures may have an average degree of polymerization in the range of about 20 to 200. In other embodiments the plurality of PEG structures may have an average degree of polymerization in the range of about 40 to 120. Sterically-stabilizing structures may be comprised of other materials such as PEG graft copolymers, polyhydroxyethyl methacrylate, polyhydroxypropyl methacrylate, polyvinyl alcohol, polyphosphazenes as well as carbohydrates such as dextran, inulin, hyaluronic acid, and sialic acid and their salts, and derivatives of carboxylates, for instance polyals. In certain embodiments, the plurality of sterically-stabilizing structures may have an average molecular weight of about 1000 to about 20,000. In other embodiments, the plurality of sterically stabilizing structures may have an average molecular weight of about 1000 to about 8000. In other embodiments, the sterically stabilizing structure may have an average molecular weight of about 1000 to about 2000.

[0034] In embodiments where both sterically-stabilizing structures and coordinating structures are present, the two structures may exist as part of a single homopolymer or may be combined into copolymer molecules. Copolymers may have block, graft, star, brush, or comb copolymer structures. Such polymer molecules may be formed in numerous ways, such as by first polymerizing the sterically stabilizing polymer from its monomer and then adding a second type of monomer and growing the coordinating structure or coordinating structure precursor, or vice-versa. Alternatively, one polymer may be functionalized so that it may be used as an initiator to grow the other polymer from this macroinitiator. Alternatively, one can conjugate coordinating structure polymers and sterically-stabilizing structure polymers or their precursors. In certain embodiments coordinating structures can be attached via a functionality located at a chain terminus. In one embodiment the multi(alkyl)acrylate (*e.g.*, multimethacrylate) has a terminal functionality and is attached to a PEG chain with a terminal functionality. For example an amine functionality located at a multimethacrylate terminal is reacted with an N-hydroxysuccinimide activated ester at a terminal of a PEG chain to form an amide bond covalently connecting multimethacrylate and PEG to produce multimethacrylate-PEG molecules.

Targeting Agents

[0035] The nanoarticles disclosed herein may further comprise targeting agents, also referred to in the literature by other terms such as targeting ligands, targeting vectors, and targeting moieties. Targeting agents selectively bind biomolecular targets, and may be included in the nanoarticles of the present invention to increase the accumulation of nanoarticles in certain tissues or cells. Targeting agents may additionally possess bioactivity. For instance, they may inhibit the binding of endogenous growth factors to certain type of receptors. Suitable targeting agents include small molecules, vitamins, carbohydrates, natural or synthetic peptides, hormones or natural or synthetic proteins such as but not limited to growth factors, lectins, antibodies and antibody fragments, and apatmers, provided that the targeting agent exhibits a preference or affinity for a particular biomolecule or target.. By small molecules is meant small organic molecules having a molecular weight of under about 1000. Discussions of targeting agents have been provided in many publications, including Gregoriadis, *Nature* (1977) 265, 407-411, and Fahmy, *et al.*, *Materials Today*, (2005) 8, 18-26.

[0036] In some embodiments targeting agents bind to biomolecules such as oligonucleotides, carbohydrates, glycoproteins, or proteins such as but not limited to certain cellular receptors that are overexpressed on the surface of targeted cells.

[0037] Biomolecular targets to which the targeting agents may bind include but are not limited to folate receptors, carbohydrate receptors, transferrin receptors, erbB1, erbB2, erbB3, erbB4, CMET, CEA, EphA2, carcinoembryonic (CEA) antigen, mucin antigens such as Muc-1, cellular adhesion molecules such as selectins and integrins, including integrin $\alpha v\beta 3$, integrin $\alpha v\beta 1$, receptor tyrosine kinases such as Tie-1 and Tie-2, including cleaved forms of Tie-1, interleukin receptors, members of the cluster differentiation (CD) antigen family, LHRH receptors, LH/CG receptors, estrogen receptors, somatostatin receptors, as well as other hormone receptors. Vascular targets associated with multiple pathologies, including cancer, include VEGFR-1, VEGFR-2, integrins, including integrin $\alpha v\beta 3$, and integrin $\alpha v\beta 1$. Additional targets are for example extracellular proteins such as matrix metalloproteinases (MMPs), the collagen family, and fibrin.

[0038] In certain embodiments, targeting agents are attached to the free terminus of one or more of the polymer molecules that comprise a nanoarticle. For example, where the polymer molecules comprise PEG segments with one PEG one terminus conjugated to a coordinating structure, the second terminus of some of the PEG segments may be conjugated to a targeting agent, resulting in a (targeting agent)-(sterically-stabilizing structure)-(coordinating-structure) configuration. The number of polymer molecules having a covalently-attached targeting agent may range from about 1 to over 100 per nanoarticle. There may be more than one type of targeting agent attached to a single nanoarticle, for example one or more targeting agents that bind to a hormone receptor and one or more targeting agents that binds to Her2 may both be attached to a single nanoarticle.

Types of polymers

[0039] Non-limiting embodiments of polymers that may be used in the nanoarticles of the present invention are: C type polymers which comprise coordinating (abbreviated "C") structures; C-S type polymers which comprise coordinating C structures linked to sterically stabilizing (abbreviated "S") structures; and C-S-T type structures which comprise coordinating C structures linked to stabilizing S structures linked to targeting (abbreviated "T" structures. In one embodiment the linkages between C, S, and T structures in a given type of polymer are through covalent bonds, such as amide bonds.

[0040] The polymer molecules may also be comprised of sterically-stabilizing structures (S structures) attached to each end of a coordinating structure (C structures), yielding a block-copolymer configuration of S-C-S or vice-versa, yielding a block-copolymer configuration of C-S-C. Other block copolymer configurations and block copolymer

fabrication techniques are well-known in the art, and it will be appreciated that where desired, T structures can be attached at the ends or at desired locations along the polymer molecules.

[0041] More that one type of polymer may be incorporated into a nanoarticle. For example, a nanoarticle formulation may be comprised of 90 % C type polymer chains, 5 % C-S type polymer chains, and 5 % C-S-T polymer chains. In another example, more than one kind of a certain type of polymer may be incorporated into a nanoarticle. In another example, a nanoarticle formulation may include 90 % C-S type polymer chains where the S structure comprises PEG with an average molecular weight of 1000, 5 % C-S type polymer chains were the S structure comprises PEG with an average molecular weight of 5000, and 5 % C-S-T type polymer chains.

[0042] While not wishing to be bound by theory, these multi-structures may orient in a polarized fashion around the nanoparticle core, where the coordinating structure is predominantly near the exterior of the nanoparticle core, the sterically stabilizing structure is predominantly outside of the coordinating structure, forming a palisade or corona, and the targeting agent is predominantly near the outer surface of this stabilizing-structure palisade, one possible embodiment of which is shown in Fig. 1. In certain embodiments, the polymer molecules may form a thin coating around the nanoparticle core, e.g., a coating about 1 to about 30 nm thick.

Non-core Metal Species

[0043] The nanoarticles disclosed herein further comprise one or more metal atoms that are not part of the nanoparticle core, herein termed "non-core metal species." Without wishing to be bound by theory, such non-core metal species are believed to form coordination bonds with the coordinating structures disclosed herein. Where the coordinating structures comprise carboxylate functionalities, for example, the oxygen atom of a carboxylate group is believed to donate a pair of electrons to a non-core metal species, thus forming a coordination bond, which may also be referred to as a coordination complex. Non-core metal species may thus aid in the formation of cross-links between polymer molecules comprising coordinating structures, thereby stabilizing the overall nanoarticle structure. Non-limiting examples of non-core metal species are iron, platinum, manganese, cobalt, ruthenium, copper and calcium. In various embodiments, these non-core metal species include platinum (II), for example cis or trans diammino platinum (II) and cis or trans diaminocyclohexane platinum (II), platinum(IV) species, and multinuclear platinum

structures. In other embodiments the non-core metal species include cobalt, such as cobalt(III). In other embodiments non-core metal species includes iron(II), iron (III) and combinations of iron (II) and iron (III). The non-core metal species may or may not be mineralized.

[0044] In certain embodiments, additional ligands may be added to the metal cross-linked polymer to reduce metal ion extraction from mineralized, coordinated non-core metal species into the surrounding solution phase, and thus decrease the disintegration of the nanoarticle structure. For example, ligands capable of binding to more than one metal ion may bridge between metal ions on different polymer chains. Coordinating ligands may be added to render the metal-polymer bonds less labile. Additionally, without wishing to be bound by theory, it is believed that certain counter ions such as phosphate, carbonate and sulfide may form insoluble metal ion derivatives that partially or completely mineralize the non-core metal species around the core, coordinating with and/or entrapping the polymer chains. Examples of such additional ligands include sulfide (S^{2-}), chloride (Cl^-), carbonate (CO_3^{2-}), phosphate (PO_4^{3-}), phosphonates (RPO_3^{2-}, R = alkyl, alkenyl or aryl, as defined herein), and cyanide (CN^-) ions. Such ligands may be introduced through the addition of appropriate salts, such as sodium bicarbonate for the carbonate ions, for example.

[0045] The non-core metal species may be pharmacologically-active or substantially non- pharmacologically active. By pharmacologically active it is meant that the non-core metal species interacts beneficially with, or has a beneficial effect on, cells or tissue within the human body. The non-core metal species may act as an anti-neoplastic agent. The non-core metal species may be radioactive or non-radioactive

[0046] It has been found that a plurality of polymer molecules, each molecule comprising, e.g., PEG and several carboxylates, can associate with metal oxide nanoparticles. For example, nanoarticle formulations comprising (*i*) maghemite nanoparticle cores with an average diameter of about 10 nm, (*ii*) carboxylate-containing PEG-multimethacrylate polymer molecules of under about 8000 MW, and (*iii*) diammino platin moieties, in one embodiment, had about 500 polymer molecules and about 2000 Pt atoms per nanoarticle. Without wishing to be bound by theory, it is believed that the coordinating structures form coordinate bonds with non-core metal species causing the nanoarticles thus formed to be unexpectedly stable, dispersible, and relatively unaggregated in aqueous solutions, as compared to nanoparticles that had been exposed such polymer molecules in the absence of any non-core metal species.

[0047] The nanoarticles of the present invention can be fabricated by mixing a plurality of nanoparticle cores, a plurality of polymer molecules, and a plurality of non-core metal species. In certain embodiments, the nanoparticle cores and the polymer molecules are mixed first for some finite period of time sufficient to allow for substantially homogeneous mixing, after which the non-core metal species is added. In other embodiments, the nanoparticle cores may be mixed with the non-core metal species first, and then the polymer molecules may be added. In yet another embodiment, the polymer molecules and the non-core metal species may be mixed together in the absence of nanoparticle cores, and after substantially homogeneous mixing has occurred, then the nanoparticles can be added to the solution. Other aspects of the invention may include a waiting period between the time the first two components are mixed together and when the third component is added. In any of the above approaches, precursors to the ultimate non-core metal species or polymer molecules may be added to the solution instead, such that the desired non-core metal species or polymer molecules form at some later point.

[0048] In some embodiments, nanoarticles of the invention remain substantially integrated under physiological conditions or conditions resembling physiological conditions over time periods useful for pharmacologic activity and/or diagnostic testing. For example, less than about 30 % of non-core metal species is released from the nanoarticle when incubated in chloride solutions, blood plasma, or whole blood for 24 hours at 37 °C. Certain embodiments of the nanoarticles disclosed herein additionally exhibit low binding of blood proteins to the nanoarticles when incubated in blood plasma or whole blood (for example, a protein to nanoarticle weight ratio of less than or equal to about 0.05 after a 24 hour plasma incubation assay). The nanoarticles disclosed herein may in some embodiments also circulate for an extended length of time in mammals (for example, greater than 10 % of nanoarticles in bloodstream 24 hours after IV injection in mouse) and have low liver uptake (for example, less than 20 % of nanoarticles sequestered in the liver 24 hours after IV injection in mouse).

[0049] The nanoarticles disclosed herein can be designed to substantially disintegrate in a mammalian body into its component nanoparticle, polymer, and non-core metal species, or sub-units thereof, in a desirable timeframe, for instance a disintegration half life of less than one week, less than 5, 4, 3, or 2 days, or less than 24 hours. Nanoarticle components may then be metabolized or cleared by the kidneys.

[0050] The nanoarticles disclosed herein may find utility as *in vivo* diagnostic agents, such as MRI contrast agents and as therapeutic agents, such as anti-cancer agents, anti-infectious agents and anti-inflammatory agents and as *in vitro* diagnostic agents, and as laboratory reagents, for instance, useful in screening assays that identify the presence of certain biomolecules.

[0051] Nanoarticles may be incorporated into various materials and formulations for use *in vivo*. For example nanoarticles may be dispersed in aqueous solutions for use in diagnostic applications as MRI contrast agents. In other examples, nanoarticles are incorporated into liquid or solid pharmaceutical formulations for medicinal use. Diseases that are particularly amenable to treatment by the nanoarticles disclosed herein are those that form lesions with poorly constructed, or "leaky" vasculature. Such diseases include but are not limited to many cancers and autoimmune and other inflammatory diseases.

[0052] Non-limiting nanoarticle compositions for treating these diseases are as follows. For treating cancer, platinum agents may be used as the non-core metal species. For treating arthritis, anti-TNF antibodies or antibody fragments may be incorporated as targeting agents.

[0053] When administered to mammalian bodies, the nanoarticle formulations may be administered by various routes, including topical, enteral, and parenteral routes. Parenteral routes include inhalation, transmucosal, transdermal and injection. Routes of injection include intravascular, intraarterial, intradermal, intraperitoneal, intramuscular, intratumoral, intravitreal, intracerebral and subcutaneous.

[0054] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

EXAMPLES

[0055] The following abbreviations are used herein.

AIBN	2,2'azobisisobutylnitrile

tBuMA	t-Butylmethacrylate
CPDB	2-(2-Cyanopropyl) Dithiobenzoate
DCM	Dichloromethane
DI	Deionized
DIPEA	Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMF	N,N-Dimethylformamide
MeOH	Methanol
PBS	Phosphate Buffer Solution, pH 7
PMAA	Poly(methacrylic acid), in acid or salt form
TFA	Trifluoroacetic acid

Example 1. Multimethacrylate-amine synthesis:

[0056] 0.5 g tBuMA and 0.05 g methyl-2-bromopropionate initiator were combined in 2mL acetone and sparged 5 minutes with N2. This was added to a solution of CuBr (0.04 g) and 2-2'-bipyridyl (0.14g) in acetone and the contents were heated to 60oC for four hours. Afterward, the contents were precipitated into 40mL of 50/50 MeOH/H2O solution to give solid polymer. The material was collected by filtration, washed several times with MeOH/H2O, and dried overnight in a vacuum desicator to give over 300 mg of a white powder. This powder was dissolved in 2 mL of 50 % TFA in DCM and allowed to stand one hour. Vacuum removal of solvent yielded over 200 mg of off-white powder. Complete carboxylate deprotection was confirmed by 1H NMR.

[0057] 200 Mg of this Br-terminated material and 200 mg NaN_3 were dissolved in 3mL distilled water and stirred at 60°C for 4 hours. Precipitation into acetone yielded a gummy solid that was dried overnight in vacuo to give a hard white solid (a film deposited from a MeOH / H_2O solution onto a KBr crystal showed a strong azide signal by FTIR at 2065cm^{-1}). The white solid precipitate and 100 mg PPh_3 was added to 3mL MeOH. After heating to 60°C, the contents were dried, then stirred in DMF. A white solid was collected by filtration, washed first with DMF and then with DCM and dried to give about 200 mg of a pale pink powder. The presence of PPh_3 in the product was confirmed by ^1H NMR. This material was dissolved in 1mL H_2O and a basic solution of NaOH in 2mL H_2O was added, causing immediate precipitation of a white solid. After stirring 30 minutes at 60°C, the solids were removed with a 0.2μm filter and the filtrate was stirred over Dowex 650 resin until the pH measured ~3. The resin was filtered off and the filtrate that tested positive for the presence

of a primary amine by ninhydrin test. MALDI-MS characterization of product material indicated an average of about 10 methacrylate moieties per molecule.

Example 2. Multimethacrylate-thiol synthesis

[0058] 10 Ml of t-BuMA is added to 10 ml anisole in a Schlenck flask. AIBN at a 0.005 molar ratio to t-BuMA and of CPDB at a 0.1 molar ratio to t-BuMA are added to the flask. Oxygen is remove using three freeze-pump-thaw cycles, and the material is heated to 70 °C under a nitrogen atmosphere and the reaction proceeds overnight. Polymer from this reaction is dissolved in THF and precipitated in methanol/water. Dithiobenzoate is removed from the polymer by reacting with ethylene diamine in chloroform overnight at 40 °C to produce a thiol-terminated polymer. Acid hydrolysis of the t-Butyl moiety is accomplished by reacting with 10% HCl in dioxane for 24 hours to yield thiol terminated multimethacrylate material.

Example 3. Multimethacrylate-PEG conjugation

[0059] 100 mg of multimethacrylate-NH_2 prepared as in Example 1 is dissolved in 2 ml of 100 mM PBS and reacted overnight with a molar equivalent of MeO-PEG_{2K} -NHS. The multimethacrylate-PEG product is purified by spin filtration through a 3K MWCO filter.

Example 4. Multimethacrylate-PEG conjugation

[0060] 100 mg of multimethacrylate-NH_2 prepared as in Example 1 is dissolved at in 2 ml of 100 mM PBS and reacted overnight with a molar equivalent of Boc-NH-PEG_{2K} -NHS. The multimethacrylate-PEG-NH-Boc is purified by spin filtration through a 3K MWCO filter. The Boc group is removed by dissolving polymer in a solution of 55% TFA in DCM for one hour and evaporating to dryness to give PMAA-PEG-NH_2.

Example 5. Attachment of targeting ligand to multimethacrylate-PEG

[0061] 400 Mg of Ethylene glycol bis-succinic acid N-hydroxy succinimide ester was dissolved in 12 ml DMA. To this solution, 50 μL DIPEA and 100 mg of a peptide comprising the RGD sequence and lysine were added and the solution was stirred. After 4 h the reaction was stopped and the solvent was evaporated. The obtained residue was washed with acetonitrile to afford the activated peptide product as a colorless solid (103 mg). 100 Mg of this material was dissolved in DMA (7.0 mL) and 300 mg multimethacrylate-PEG_{2K}–amine prepared as described in Example 4 was added to the solution and stirred for 15 min. DIPEA (400 μL) was added to the reaction and stirred at room temperature. After 5 h the reaction was stopped and the solvent was evaporated. A dense liquid was obtained and dissolved in MeOH/ H_2O and this solution was filtered with a 5000 MWCO spin filter. A

qualitative analysis using BCA colorimetric analysis (Pierce) of the product confirmed the presence of RGD-peptide in the polymer product.

Example 6. Iron oxide core formation using acac ligands

[0062] $Fe(acac)_3$ (4.71g), $Zn(acac)_2$ (1.75g), 1,2-dodecandiol (20 g), oleic acid (20 mL) and oleylamine (20mL) were combined in dibenzyl ether (200 mL) and heated at 300 °C for 1 hr to form nanoparticles. When cooled to room temperature, the nanoparticles were precipitated with 2 volumes of ethanol and magnetically collected. The collected precipitate was re-dispersed in hexane followed by re-precipitation and magnetic collection. The solid material was washed with ethanol and then dried at 40 °C to give 1.4g of product.

[0063] TEM measurements to characterize particle size were carried out on a Hitachi HF-2000 electron microscope and the images were collected at a magnification of 60,000 to 500,000. Typically, the sample was prepared by applying a drop of approximately 0.5 mg/mL solutions of nanoparticles on to a 300 mesh carbon coated copper grid. TEM indicated an average diameter of less than 10 nm.

Example 7. Iron oxide core formation method

[0064] Fe(OH)O (Aldrich, 50-80 mesh, further ground to >100 mesh, 7.12g, 1 equiv.) is stirred in a reaction mixture of oleic acid (5 equiv) in octadecene to a total volume of 300 mL. The reaction mixture is heated to 320 °C over 1 h. Heating is discontinued after 90 min and the reaction is allowed to cool to room temperature. The particles are isolated by precipitation with ethylacetate/ethanol followed by magnetic concentration. The material is reprecipitated from hexanes/ethanol This procedure yields 7-8 g of nanoparticles.

Example 8. Coated ferrite nanoparticle formation

[0065] Warm a solution of 9.5 mL DI water and 0.5 mL 20% Et4NOH to 50-60 °C and add 150 mg particles prepared according to Example 6, stirring until the material is dissolved. Filter the solution using a 5 micron syringe filter, and wash the filtered solution three times with ~5 mL dichloromethane. The pH of the solution should be >11. Perform multiple cycles of spin filtration or other ultrafiltration methods (30K MWCO membranes). Pass the solution through a 0.2 micron filter and dilute this solution with DI water to produce about 5 ml solution of 2 wt% ferrite material.

[0066] Add 50 mg MMA-PEG product material from Example 4 and if a targeting agent is desired, 10 mg MMA-PEG product material from Example 5 to 5 ml of water and add this solution to the ferrite solution and incubate overnight. Coated ferrite nanoparticles

thus formed may be separated from materials that are not associated with the ferrite nanoparticles by adding steel shot, placing the vial on a FeNdB magnet, incubating for 24 hours, and pipetting away solution not in the vicinity of the steel shot. This magnetic separation may be repeated as desired by adding water to the vial, mixing the vial contents and incubating the solution on the magnet to further separate nanoparticle product from non-magnetic material.

Example 9. Pt-Nanoarticle formation

[0067] Polymer-coated nanoparticles from Example 8 were solubilized at 1 wt % of particle in water. Diamminoplatinum dinitrate was added to this solution at a ratio of 1 mole Pt to 2 mole carboxylate. Particles were incubated overnight at 40 °C and materials not associated with the ferrite nanoparticle core were removed using magnetic purification as described in Example 8. Dynamic light scattering indicated a diameter of 18 nm for these nanoarticles.

Example 10. Pt-nanoarticle formation

[0068] Nanoarticles formed using 10.0 nm maghemite cores and polymer molecules with each molecule comprising PEG_{2K} and a multimethacrylate with an average of eight methacrylate moieties were prepared using methods similar to those described in Example 8, and Pt was incorporated using similar methods as described in Example 9. With knowledge of the number of iron atoms in the ferrite core gained through TEM image and crystal structure stoichiometry, elemental analysis indicated that there are on average about 460 polymer molecules and about 1600 Pt atoms per nanoarticle.

Example 11. Co-nanoarticle formation

[0069] To a aqueous solution of 1%wt/vol polymer-coated ferrite (0.5mmol in Fe, coated with 0.35 mmol of carboxylates in a polycarboxylate-PEG), $Co(NO_3)_2 \cdot 6H_2O$(0.175mmol) dissolved in a minimal volume of water is added. After 1hr at 40 °C, the pH is adjusted to 6 and the solution returned to a 40 °C incubator. After a further hour, pentamethyldiethylenetriamine (0.175mmol) is added and the reaction continued overnight at 40 °C. The solution is neutralized to pH 6. Purification by two cycles of magnetic separation leads to (Me_5dienCo)-MagNaGel with a Co content of 6.8 wt % (dry weight).

Example 12. Co-nanoarticle formation

[0070] To a aqueous solution of 1%wt/vol nanoarticle (0.5mmol in Fe, coated with 0.35 mmol of carboxylates in a polycarboxylate-PEG),) $Co(NO_3)_2 \cdot 6H_2O$(0.175mmol)

dissolved in a minimal volume of water was added. After 2 hours, tris(2-aminoethyl)amine (0.175mmol) was added and the reaction continued overnight at 40 °C. The solution was brought to pH 6, and purification by two cycles of magnetic separation produced nanoarticles with a Co content of 3.1 wt % (dry weight).

Example 13. Fe-nanoarticle formation

[0071] To an aqueous solution of 1%wt/vol polymer-coated nanoparticles (0.5mmol in Fe, coated with 0.35 mmol of carboxylates in a polycarboxylate-PEG),) $FeCl_3 \cdot 6H_2O$(0.117mmol) dissolved in a minimal volume of water was added. After 2 hours, sodium bicarbonate (0.35mmol) was added and the reaction continued overnight at 40 °C. Purification by two cycles of magnetic separation produced nanoarticle material that eluted as a single species by GPC.

Example 14. In vitro plasma protein binding to nanoarticles

[0072] Nanoarticles (0.5mg) comprising diammino platin and PMAA(2K)- PEG(5K) polymer was incubated with 1ml fresh mouse plasma for 24h with continuous mix at 37C. The mixture was then run through a PBS pre-rinsed magnetic LD column (Miltenyi) placed between two FeNdB magnets (each 2" x 2" x 1"). 8ml of PBS is then applied to wash column. Collect the first 9ml that has passed through the column (fraction 1). The column was then rinsed with two 5 ml PBS wash steps the passed though fractions were collected (fraction 2 and fraction 3). Column was removed from magnetic field and 5ml PBS was used to elute nanoarticle (fraction 4); protein in this fraction is characterized as bound to nanoarticle. Protein content was assayed by CBQCA protein quantitation kit (Molecular Probes). To determine how much plasma protein bound to the column material and not to nanoarticles, one milliliter plasma without nanoarticle was subjected to the same magnetic purification procedure. The nanoarticle bound protein amount was calculated by subtracting the amount of protein found in fraction 4 when using plasma only from the amount of protein found in fraction 4 of nanoarticle-plasma material. There was approximately 22 microgram protein bound per mg nanoarticle. For comparison, for nanoparticle that was not coated as disclosed herein, over 100 microgram of protein was bound per mg nanoparticle.

Example 15. Non-core metal species release in plasma

[0073] Two ml of pure HNO_3 was added to fraction 1 from Example 14 and this material was heated to 80 °C, and volume was reduced to 0.5 to 1 ml. Another 3ml of pure HNO3 was added and material was again heated and volume reduced to 0.5 to 1 ml. This step was repeated, then material was dissolved in 3ml of water and platinum content was

measured using ICP. The percentage of platinum released, calculated as the amount of platin in fraction 1 divided by the total amount of platin in the starting nanoarticle material, was less than 30 %.

[0074] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the invention in its broader aspects as defined in the following claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A nanoarticle comprising

   (i) a nanoparticle core having a major dimension of about 3 nm to about 1000 nm;

   (ii) a plurality of polymer molecules, wherein the polymer molecules include a coordinating structure; and

   (iii) a plurality of non-core metal species.

2. A nanoarticle according to claim 1 wherein the nanoparticle core comprises iron and/or iron oxide.

3. A nanoarticle according to claim 2 wherein the nanoparticle core comprises a ferrite with a spinel structure of the general formula $MeFe_2O_4$, where Me denotes a divalent ion selected from copper, zinc, manganese, cobalt, iron, or magnesium, or a combination of ions that have an average valence of about 2.

4. A nanoarticle according to claim 1 wherein the nanoparticle core comprises one or more materials selected from the group consisting of gold, silver, tantalum, platinum, rhodium, cadmium, selenium, zinc oxide, and calcium phosphate.

5. A nanoarticle according to claim 1 wherein the nanoparticle core comprises an organic small molecule.

6. A nanoarticle according to claim 1 wherein the coordinating structure comprises one or more functionalities selected from the group consisting of carboxylates, amines, hydroxyls, and thiolates.

7. A nanoarticle according to claim 1 wherein the coordinating structure comprises about 2 to about 50 carboxylate functionalities.

8. A nanoarticle according to claim 1 wherein the coordinating structure comprises a 4-to-40-mer of (meth)acrylate, wherein at least one, and up to all, of the (meth)acrylate units have been hydrolyzed or otherwise substituted to yield the desired coordination-bond-forming functionalities.

9. A nanoarticle according to claim 1 wherein the non-core metal species forms cross-links between two or more of said polymer molecules.

10. A nanoarticle according to claim 1 wherein the non-core metal species comprises one or more materials selected from the group consisting of iron, platinum, manganese, cobalt, ruthenium, copper and calcium.

11. A nanoarticle according to claim 1 wherein at least a fraction of the polymer molecules further comprise a sterically stabilizing structure such that the tendency of the nanoarticles to aggregate in aqueous solution is decreased.

12. A nanoarticle according to claim 12 wherein the sterically stabilizing structure comprises PEG having a degree of polymerization in the range of about 20 to 200.

13. A nanoarticle according to claim 1 wherein the polymer molecules comprise a coordinating structure and a sterically stabilizing structure.

14. A nanoarticle according to claim 1 further comprising a targeting agent.

15. A nanoarticle according to claim 15 wherein the targeting agent is selected from the group consisting of small molecules, vitamins, carbohydrates, natural or synthetic peptides, hormones, and natural or synthetic proteins.

16. A nanoarticle according to claim 1 wherein the polymer molecules comprise a coordinating structure, a sterically stabilizing structure, and a targeting structure, and wherein the coordinating structure is predominantly near the nanoparticle core, the sterically stabilizing structure is predominantly outside of the coordinating structure, forming a palisade or corona, and the targeting agent is predominantly near the outer surface of this stabilizing-structure palisade.

17. A nanoarticle according to claim 1 wherein the nanoparticle core comprises maghemite nanoparticles with an average diameter of about 10 nm, the polymer molecules comprise carboxylate-containing PEG-multimethacrylate polymer molecules of under about 8000 MW, and the non-core metal species comprises diammino platin.

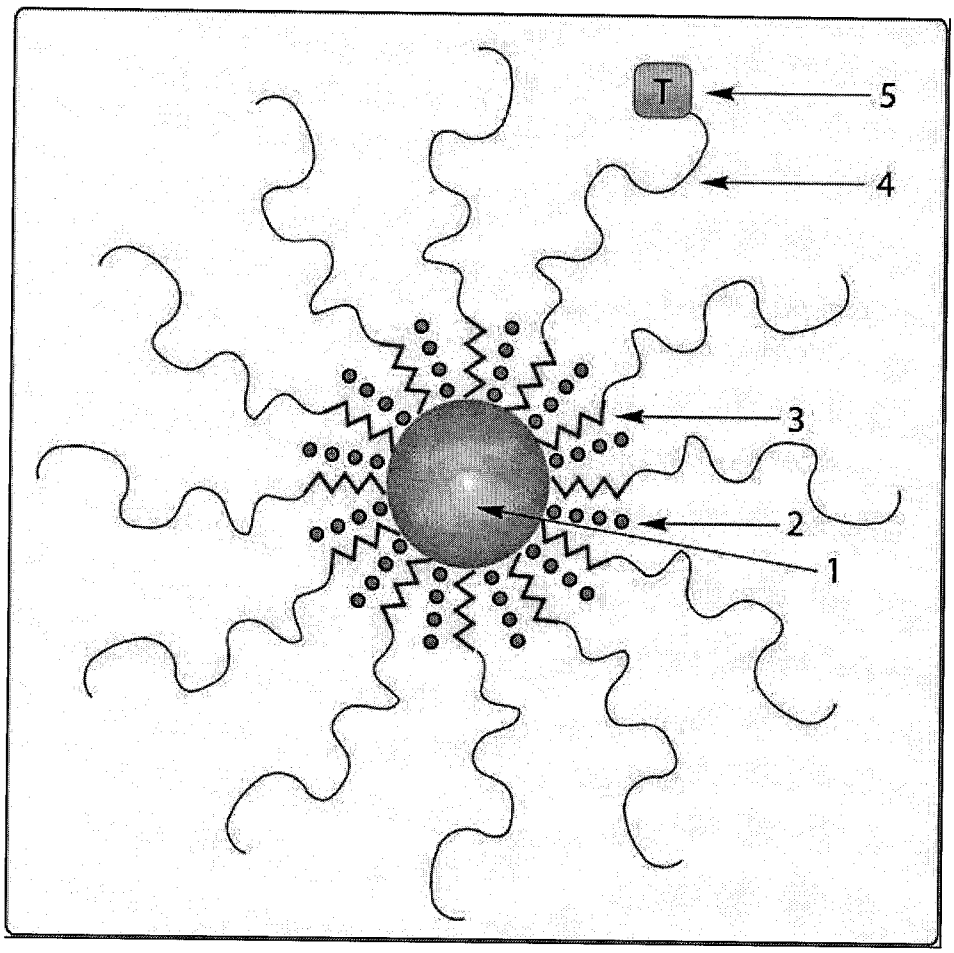
18. A method of making the nanoarticles of claim 1, wherein the nanoparticle cores and the plurality of polymer molecules are mixed first for some finite period of time sufficient to allow for substantially homogeneous mixing, and then the non-core metal species is added to the mixture of nanoparticle cores and polymer molecules.

19. A pharmaceutical formulation comprising a plurality of nanoarticles of claim 1.

20. A method for treating cancer by administering the nanoarticles of claim 1 topically, enterally, or parenterally.

FIG. 1

Illustration of nanoarticle



1 nanoparticle core

2 non-core metal species

3 coordinating structure

4 sterically stabilizing structure

5 targeting agent