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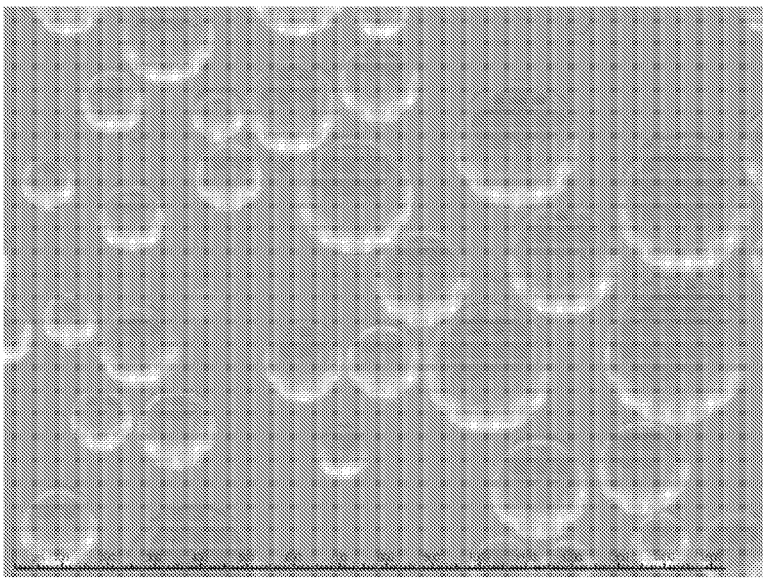

FIG. 2A

(57) Abstract: Biomaterials suitable for use as drug eluting, Magnetic Resonance Imaging ("MRI") detectable implants for vascular occlusion are provided, as are methods of producing such biomaterials. Further, methods of treating an individual suffering from a solid tumor are provided.

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BIOMATERIALS SUITABLE FOR USE AS DRUG ELUTING, MAGNETIC RESONANCE IMAGING DETECTABLE IMPLANTS FOR VASCULAR OCCLUSION

Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 61/651,389 filed on May 24, 2012, titled Biomaterials Suitable for Use as Drug Eluting, Magnetic Resonance Imaging Detectable Implants for Vascular Occlusion, which is hereby incorporated by reference in its entirety.

Technical Field

[0002] The present disclosure relates to biomaterials suitable for use as a drug eluting, Magnetic Resonance Imaging ("MRI") detectable implants for vascular occlusion, as well as methods of producing such biomaterials. Further, the disclosure relates to methods of treating an individual suffering from a solid tumor.

Brief Description of the Drawings

[0003] Figure 1 is a histogram showing the size distribution of microspheres from Example 1.

[0004] Figures 2A and 2B are microscope images of microspheres of Example 1.

[0005] Figure 3 is a graph depicting the drug loading behavior data collected in Example 3.

[0006] Figure 4 is a graph depicting the drug release behavior data collected in Example 3.

[0007] Figure 5 is a depiction of a generalized dialysis membrane experiment to test drug release from a biomaterial. Figure 5A depicts the apparatus used during dialysis, and Figure 5B depicts some of the steps in setting up the dialysis experiment.

[0008] Figure 6 is a graph depicting the drug release behavior data collected in Example 4.

[0009] Figure 7 is a histogram showing the size distribution of microspheres from Example 5.

[0010] Figures 8A, 8B, 8C and 8D are microscope images of microspheres of Example 5.

[0011] Figure 9 is a histogram showing the size distribution of microspheres from Example 6.

[0012] Figures 10A and 10B are microscope images of microspheres of Example 6.

[0013] Figure 11 is a histogram showing the size distribution of microspheres from Example 7.

[0014] Figures 12A and 12B are microscope images of microspheres of Example 7.

[0015] Figure 13 is a graph depicting the drug loading behavior data collected in Example 8.

[0016] Figure 14 is a graph depicting the drug release behavior data collected in Example 9.

[0017] Figure 15 is a graph depicting the drug loading behavior data collected in Example 10.

[0018] Figure 16 is a graph depicting the drug release behavior data collected in Example 11.

Detailed Description of Certain Embodiments

[0019] The present disclosure relates to drug eluting, Magnetic Resonance Imaging ("MRI") detectable implants for vascular occlusion, as well as methods of producing such biomaterials. Further, the disclosure relates to methods of treating an individual suffering from a solid tumor.

[0020] It will be readily understood that the embodiments, as generally described herein, are exemplary. The following more detailed description of various embodiments is not intended to limit the scope of the present disclosure, but is merely representative of various embodiments. Moreover, the order of the steps or actions of the methods disclosed herein may be changed by those skilled in the art without departing from the scope of the present disclosure. In other words, unless a specific order of steps or actions is required for proper operation of the embodiment, the order or use of specific steps or actions may be modified.

[0021] In a first aspect, the present disclosure is related to biomaterials suitable for use as a drug eluting, Magnetic Resonance Imaging ("MRI") detectable implant for vascular occlusion. In an embodiment, the biomaterial comprises: a polymer; an iron oxide particle; and a drug. In an embodiment, the drug is a chemotherapeutic drug.

[0022] In one embodiment, the biomaterial comprises: a polymer comprising at least one of an acrylate or vinyl sulfonate; an iron oxide particle; and a drug. In an embodiment, the drug is a chemotherapeutic drug.

[0023] In another embodiment, the biomaterial is in the form of a microsphere. In a related embodiment, the microsphere is substantially spherical. In another related embodiment, the microsphere has a major axis of from about 15 micrometers to about 1000 micrometers. In another embodiment, the microsphere has a major axis of from about 100 micrometers to about 300 micrometers.

[0024] In another embodiment, the biomaterial comprises a copolymer. In a related embodiment, the copolymer comprises an acrylate, such as sodium acrylate, and an acrylamide. In one embodiment, the copolymer comprises at least one of: sodium acrylate, vinyl sulfonate, AMPS or CEA; and an acrylamide. In a related embodiment, the copolymer comprises: at least one of: sodium acrylate, vinyl sulfonate, AMPS or CEA; and N-[tris-(hydroxymethyl)methyl] acrylamide. It is understood that the copolymers disclosed herein may comprise any of the recited monomer components, individually, together with any acrylamide. Thus, any one of sodium acrylate, vinyl sulfonate, AMPS or CEA may comprise a copolymer with any acrylamide, including N-[tris-(hydroxymethyl)methyl] acrylamide.

[0025] In another embodiment, the polymer comprises a crosslinking agent. In a related embodiment, the crosslinking agent is N,N-methylene-bis-acrylamide. It is understood that the polymers disclosed herein may comprise any of the recited monomer components, individually, together with any crosslinking agent. Thus, any one of sodium acrylate, vinyl sulfonate, AMPS or CEA may comprise a polymer with any crosslinking agent, including N,N-methylene-bis-acrylamide.

[0026] The biomaterial, comprising a polymer; an iron oxide particle; and a drug, may comprise a polymer which comprises any of the recited monomer components, individually, together with any acrylamide and any crosslinking agent. Thus, any one of sodium acrylate, vinyl sulfonate, AMPS or CEA may comprise a polymer with any acrylamide, including N-[tris-(hydroxymethyl)methyl] acrylamide, and any crosslinking agent, including N,N-methylene-bis-acrylamide. This includes, for example, a polymer comprising sodium acrylate, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide; a polymer comprising vinyl sulfonate, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide; a polymer comprising AMPS, N-[tris-(hydroxymethyl)methyl] acrylamide,

and N,N-methylene-bis-acrylamide; and a polymer comprising CEA, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide.

[0027] In one embodiment, the biomaterial comprises: 0 wt% to 90 wt% sodium acrylate; 0 wt% to 90 wt% vinyl sulfonate; 0 wt% to 90 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0 wt% to 90 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 0 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide.

[0028] In a related embodiment, the biomaterial comprises: 5 wt% to 50 wt% sodium acrylate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In an embodiment, the biomaterial comprises: 5 wt% to 50 wt% vinyl sulfonate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In an additional embodiment, the biomaterial comprises: 5 wt% to 50 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In a further embodiment, the biomaterial comprises: 5 wt% to 50 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide.

[0029] In an embodiment, the drug is a chemotherapeutic drug. In one embodiment, the drug is irinotecan. In one embodiment, the drug is doxorubicin. In certain embodiments, the drug is at least one of doxorubicin or irinotecan. In one embodiment, a chemotherapeutic drug is releasably associated with a microsphere. In one embodiment, doxorubicin is releasably associated with a microsphere. In one embodiment, irinotecan is releasably associated with a microsphere. In a related embodiment, a drug is added to a suspension of microspheres in an amount of between about 0.5 mg to about 50 mg per milliliter of the suspension.

[0030] In an embodiment, the drug may be a charged drug, or a drug that is charged within the range of physiological pH values, including the pH values in and near tumors. In an embodiment, the drug is a cationic drug. The biomaterial may comprise a polymer which is also charged, by for example, containing ionic groups.

In an embodiment, the biomaterial contains anionic groups. In one embodiment, the association of a drug to the biomaterial comprises an ionic interaction.

[0031] In one embodiment, the iron oxide is Fe_3O_4. In one embodiment, the iron oxide is a mixture of both iron(II) oxide and iron(III) oxide. In one embodiment, the iron oxide particle is a nanoparticle. In a related embodiment, the iron oxide nanoparticle is superparamagnetic. In an embodiment, the iron oxide is in a colloidal form.

[0032] In a second aspect, the present disclosure is related to methods of producing a biomaterial suitable for use as a drug eluting, MRI detectable implant for vascular occlusion.

[0033] In one embodiment, the method comprises providing a polymer comprising at least one of an acrylate, vinyl sulfonate, AMPS or CEA, wherein the polymer is associated with an iron oxide particle; and associating the polymer with a chemotherapeutic drug. In an embodiment, the acrylate is sodium acrylate.

[0034] In one embodiment, providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition comprises at least one of an acrylate such as sodium acrylate, vinyl sulfonate, AMPS or CEA. In another embodiment, providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition comprises: at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA; and one other monomer.

[0035] It is understood that providing the polymer may comprise polymerizing a polymer which comprises any of the recited monomer components, individually, together with any acrylamide or any crosslinking agent, or both an acrylamide and a crosslinking agent, in the presence of an iron oxide particle. Thus, providing the polymer may comprise polymerizing any one of sodium acrylate, vinyl sulfonate, AMPS or CEA, optionally with any acrylamide, including N-[tris-(hydroxymethyl)methyl] acrylamide, and optionally with any crosslinking agent, including N,N-methylene-bis-acrylamide.

[0036] In another embodiment, providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition comprises: at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA; and N-[tris-(hydroxymethyl)methyl] acrylamide. In another embodiment, providing the polymer comprises polymerizing a monomer composition

in the presence of an iron oxide particle, wherein the monomer composition comprises: at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA; N-[tris-(hydroxymethyl)methyl] acrylamide; and a crosslinking agent. In another embodiment, providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition comprises: at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA; N-[tris-(hydroxymethyl)methyl] acrylamide; and N,N-methylene-bis-acrylamide.

[0037] In one embodiment, providing the polymer comprises providing a mixture comprising: 0 wt% to 90 wt% sodium acrylate; 0 wt% to 90 wt% vinyl sulfonate; 0 wt% to 90 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0 wt% to 90 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 0 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture.

[0038] In a related embodiment, providing the polymer comprises providing a mixture comprising: 5 wt% to 50 wt% sodium acrylate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture. In an embodiment, providing the polymer comprises providing a mixture comprising: 5 wt% to 50 wt% vinyl sulfonate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture. In an additional embodiment, providing the polymer comprises providing a mixture comprising: 5 wt% to 50 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture. In a further embodiment, providing the polymer comprises providing a mixture comprising: 5 wt% to 50 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture.

[0039] In one embodiment, the monomer composition and the iron oxide particle are mixed to form a mixture before polymerizing the monomer composition in the presence of the iron oxide particle. In a related embodiment, the method further comprises heating the mixture before polymerizing the monomer composition in the presence of the iron oxide particle. In a related embodiment, heating the mixture

comprises heating the mixture to a temperature of from about 20°C to about 80°C. In a related embodiment, heating the mixture comprises heating the mixture to about 50°C.

[0040] In another embodiment, polymerizing the monomer composition in the presence of the iron oxide particle further comprises forming a polymeric microsphere associated with an iron oxide particle. In a related embodiment, polymerizing the monomer composition in the presence of the iron oxide particle takes place in oil, such that a polymeric microsphere associated with an iron oxide particle is formed. In a related embodiment, the oil is at a temperature of from about 30°C to about 100°C. In a related embodiment, the oil is at a temperature of about 60°C. In a related embodiment, the polymeric microspheres are sieved to obtain polymeric microspheres with a major axis of from about 15 micrometers to about 1000 micrometers. In a related embodiment, the polymeric microspheres are sieved to obtain polymeric microspheres with a major axis of from about 100 micrometers to about 300 micrometers.

[0041] In one embodiment, the iron oxide is Fe_3O_4. In one embodiment, the iron oxide particle is a nanoparticle. In a related embodiment, the iron oxide nanoparticle is superparamagnetic.

[0042] In one embodiment, the chemotherapeutic drug is doxorubicin. In one embodiment, the chemotherapeutic drug is irinotecan. In an embodiment, the chemotherapeutic drug is at least one of doxorubicin or irinotecan.

[0043] In one embodiment, the polymer is in the form of a microsphere.

[0044] In one embodiment, the method further comprises: suspending the microsphere in a liquid and adding a drug to the suspension in an amount of between about 0.5 mg to about 50 mg per milliliter of the suspension.

[0045] In a third aspect, the present disclosure is related to methods of treating an individual suffering from a solid tumor comprising: administering to the individual a drug eluting, MRI detectable implant for vascular occlusion, comprising: a polymer comprising at least one of an acrylate, such as sodium acrylate, vinyl sulfonate, AMPS or CEA; an iron oxide particle; and a chemotherapeutic drug, wherein administering to the individual the drug eluting, MRI detectable implant for vascular occlusion leads to occlusion of a blood vessel associated with the solid tumor and delivery of the chemotherapeutic agent to the solid tumor.

[0046] In one embodiment, the method further comprises identifying the location of the drug eluting, MRI detectable implant for vascular occlusion through MRI after administering to the individual the drug eluting, MRI detectable implant for vascular occlusion.

[0047] In one embodiment, the drug eluting, MRI detectable implant for vascular occlusion is in the form of one or more microspheres. In a related embodiment, administering to the individual the drug eluting, MRI detectable implant for vascular occlusion comprises introducing the one or more microspheres into the lumen of a blood vessel associated with the solid tumor through a catheter. In another related embodiment, the drug eluting, MRI detectable implant for vascular occlusion is suspended in a liquid and a drug is added to the suspension of the drug eluting, MRI detectable implant in an amount of between about 0.5 mg to about 50 mg per milliliter of the suspension.

[0048] In one embodiment, the polymer comprises a copolymer. In a related embodiment, the copolymer comprises: at least one of an acrylate, such as sodium acrylate, vinyl sulfonate, AMPS or CEA; and N-[tris-(hydroxymethyl)methyl] acrylamide. In another embodiment, the copolymer comprises: at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA; N-[tris-(hydroxymethyl)methyl] acrylamide; and N,N-methylene-bis-acrylamide.

[0049] It is understood that the copolymer may comprise any of the recited monomer components, individually, together with any acrylamide or any crosslinking agent, or both an acrylamide and a crosslinking agent. Thus, the copolymer may comprise any one of sodium acrylate, vinyl sulfonate, AMPS or CEA, optionally with any acrylamide, including N-[tris-(hydroxymethyl)methyl] acrylamide, and optionally with any crosslinking agent, including N,N-methylene-bis-acrylamide.

[0050] In one embodiment, the drug eluting, MRI detectable implant for vascular occlusion comprises: 0 wt% to 90 wt% sodium acrylate; 0 wt% to 90 wt% vinyl sulfonate; 0 wt% to 90 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0 wt% to 90 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 0 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide.

[0051] In a related embodiment, the drug eluting, MRI detectable implant for vascular occlusion comprises: 5 wt% to 50 wt% sodium acrylate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1

wt% to 30 wt% N,N-methylene-bis-acrylamide. In an embodiment, the drug eluting, MRI detectable implant for vascular occlusion comprises: 5 wt% to 50 wt% vinyl sulfonate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In an additional embodiment, the drug eluting, MRI detectable implant for vascular occlusion comprises: 5 wt% to 50 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In a further embodiment, the drug eluting, MRI detectable implant for vascular occlusion comprises: 5 wt% to 50 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide.

[0052] In one embodiment, the iron oxide is Fe_3O_4. In one embodiment, the iron oxide particle is a nanoparticle. In a related embodiment, the iron oxide nanoparticle is superparamagnetic. In an embodiment, the iron oxide is in a colloidal form.

[0053] Definitions

[0054] Unless specifically defined otherwise, technical terms, as used herein, have their normal meaning as understood in the art. The following terms are specifically defined with examples for the sake of clarity.

[0055] A “biomaterial” means any composition that is suitable for introducing into the body of an individual.

[0056] A “microsphere” means a composition having a generally ellipsoid shape and a major axis in the size range of from about 15 μm to about 1000 μm. In some embodiments, the microsphere will have a spheroid shape, in other embodiments, the microsphere will have a spherical shape. In other embodiments, the microsphere will be substantially spherical.

[0057] In the context of a microsphere, “major axis” means the longest axis that can be drawn through the ellipsoid shape of the microsphere.

[0058] In the context of a microsphere, “minor axis” means the shortest axis that may be drawn through the ellipsoid shape of the microsphere perpendicular to the major axis.

[0059] In the context of a microsphere, “substantially spherical” means that the length of the minor axis of the microsphere is at least 80% of the length of the major axis of the microsphere. In some embodiments, the length of the minor axis of the

microsphere is at least 85% of the length of the major axis of the microsphere. In some embodiments, the length of the minor axis of the microsphere is at least 90% of the length of the major axis of the microsphere. In some embodiments, the length of the minor axis of the microsphere is at least 95% of the length of the major axis of the microsphere. In some embodiments, the length of the minor axis of the microsphere is at least 99% of the length of the major axis of the microsphere.

[0060] In some embodiments, the microsphere will appear smooth at up to 1000X (times) magnification, (i.e., the surface of the microsphere does not include an irregularity which would cause the minor axis to be less than 95% of the length of the major axis). In another embodiment, the microspheres do not have irregularities on the surface. In another embodiment, the microspheres do not have indentations on the surface.

[0061] In the context of a polymer, a polymer "comprises" a monomer if the polymer has at least one of the monomer covalently bound to the polymer (i.e., a polymerized monomer).

[0062] A "monomer composition" means any composition comprising at least one monomer that may be polymerized to form a polymer. The monomer composition may optionally comprise other components besides the at least one monomer. For example, the monomer composition may comprise additional agents to aid in the polymerization process, or it may comprise non-monomer compositions that should be incorporated or associated with the final polymer after polymerization.

[0063] "Polymerize" or "polymerizing" means any action taken to cause one or more monomers to become covalently bound to a polymer. For example, a monomer composition or mixture may be polymerized by adding an activating agent to the monomer composition or mixture to induce formation of a polymer. In some embodiments, the activating agent comprises N,N,N',N'-tetramethylethylenediamine ("TEMED").

[0064] A compound is "incorporated into" a composition when the compound is covalently or non-covalently bound to the composition, such that in at least some conditions, the compound will not be released from the composition. For example a compound, such as iron oxide, may be incorporated into a composition, such as a polymer, so that when the polymer is introduced into an individual, at least a portion of the iron oxide will remain bound to the polymer.

[0065] A compound is "releasably associated" with a composition when the compound is covalently or non covalently bound to the composition such that in at least some conditions, the compound will not remain bound to the composition. For example, a compound, such as a drug, may be releasably bound to a composition, such as a microsphere, so that when the microsphere is introduced into an individual, at least a portion of the drug will not remain bound to the microsphere.

[0066] **Biomaterials**

[0067] In a first aspect, the present disclosure is related to biomaterials suitable for use as a drug eluting, Magnetic Resonance Imaging ("MRI") detectable implant for vascular occlusion.

[0068] In some embodiments, the biomaterial comprises a polymer. In some embodiments, the polymer comprises an acrylate, such as sodium acetate. In some embodiments, the polymer comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA. When reciting that a polymer comprises an acrylate, vinyl sulfonate or some other monomer, it is understood to mean that the polymer comprises a polymerized form of such monomer.

[0069] In another embodiment, the polymer is a copolymer. In some embodiments, the copolymer comprises an acrylate, such as sodium acrylate, and another monomer. In some embodiments, the copolymer comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, and another monomer. In some embodiments, the additional monomer comprises an acrylamide, such as N-[tris-(hydroxymethyl)methyl] acrylamide.

[0070] In another embodiment, the polymer further comprises a crosslinking agent. In some embodiments, the crosslinking agent comprises N,N-methylene-bis-acrylamide. In other embodiments, the crosslinking agent may comprise 1-(acryloyloxy)-3-(methacryloyloxy)-2-propanol, 1,4-diacryloylpiperazine, diethylene glycol diacrylate, ethylene glycol dimethacrylate, piperazine diacrylate, N,N'-bisacrylylcystamide, or N,N'-diallyl tartardiamide.

[0071] It is understood that the polymer may comprise any of the recited monomer components, individually, with any acrylamide or any crosslinking agent, or with both an acrylamide and a crosslinking agent. Thus, any one of sodium acrylate, vinyl sulfonate, AMPS or CEA may comprise a polymer with optionally any acrylamide, including N-[tris-(hydroxymethyl)methyl] acrylamide, and optionally any crosslinking agent, including N,N-methylene-bis-acrylamide.

[0072] In some embodiments, the polymer comprises an acrylate, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In other embodiments, the polymer comprises sodium acrylate, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In other embodiments, the polymer comprises vinyl sulfonate, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In other embodiments, the polymer comprises AMPS, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In other embodiments, the polymer comprises CEA, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In other embodiments, the polymer comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide.

[0073] In some embodiments, the biomaterial comprises an iron oxide particle. In some embodiments, the biomaterial comprises Fe_3O_4. In some embodiments, the biomaterial comprises an iron oxide nanoparticle. In some embodiments, the biomaterial comprises a superparamagnetic iron oxide particle. In some embodiments, the superparamagnetic iron oxide particle is an iron oxide nanoparticle. In an embodiment, the iron oxide is in a colloidal form. In some embodiments, the iron oxide particle is associated with the polymer. In some embodiments, the iron oxide particle is incorporated into the polymer.

[0074] In some embodiments, the biomaterial comprises: 0 wt% to 90 wt% sodium acrylate; 0 wt% to 90 wt% vinyl sulfonate; 0 wt% to 90 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0 wt% to 90 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 0 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide.

[0075] In a related embodiment, the biomaterial comprises: 5 wt% to 50 wt% sodium acrylate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In an embodiment, the biomaterial comprises: 5 wt% to 50 wt% vinyl sulfonate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In an additional embodiment, the biomaterial comprises: 5 wt% to 50 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0.01 wt% to 10 wt% iron

oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In a further embodiment, the biomaterial comprises: 5 wt% to 50 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide.

[0076] In some embodiments, the biomaterial is formed so that it is in an appropriate shape to occlude a blood vessel. In some embodiments, the biomaterial is in the form of a microparticle. In some embodiments, the biomaterial is in the form of a microsphere. In other embodiments, the microsphere is substantially spherical. In some embodiments, the microspheres may have an average major axis of from about 15 micrometers to about 1000 micrometers. In some embodiments, the microspheres may have an average major axis of from about 100 micrometers to about 800 micrometers. In some embodiments, the microspheres may have an average major axis of from about 200 micrometers to about 600 micrometers. In some embodiments, the microspheres may have an average major axis of from about 100 micrometers to about 300 micrometers. In some embodiments, the microspheres may have an average major axis of from about 50 micrometers to about 150 micrometers. In certain embodiments, the microspheres may have an average major axis of from about 50 micrometers to about 100 micrometers. In some embodiments, the microspheres may have an average major axis of from about 30 micrometers to about 100 micrometers.

[0077] In some embodiments, the biomaterial comprises a drug. In some embodiments, the drug is releasably associated with the biomaterial. In some embodiments, the drug is releasably associated to a microsphere. In some embodiments, the drug is doxorubicin. In some embodiments, the drug is irinotecan. The drug may be at least one of doxorubicin or irinotecan. In some embodiments, the biomaterial is suspended in a liquid and a drug is added to a suspension of microspheres in an amount of between about 0.5 mg to about 50 mg per milliliter of the suspension.

[0078] Methods of Producing Biomaterials

[0079] In a second aspect, the present disclosure is related to methods of producing a biomaterial suitable for use as a drug eluting, MRI detectable implant for vascular occlusion.

[0080] In some embodiments, the method comprises providing a polymer associated with an iron oxide particle, and associating the polymer with a drug. In an embodiment, the drug is a chemotherapeutic drug.

[0081] The polymer associated with an iron oxide polymer may be provided in various ways. For example, the polymer may be sourced from a third party, or it may be generated prior to associating the polymer with the drug.

[0082] In some embodiments, providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle. The monomer composition may be polymerized according using an appropriate activating agent. For example, an amide may be used as an activating agent. In an embodiment, N,N,N',N'-tetramethylethylenediamine ("TEMED") may be used as an activating agent. In an embodiment, triethyl amine may be used as an activating agent.

[0083] In some embodiments, the monomer composition comprises acrylate, such as sodium acrylate. In some embodiments, the monomer composition comprises vinyl sulfonate. In some embodiments, the monomer composition comprises AMPS. In certain embodiments, the monomer composition comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA.

[0084] In some embodiments, the monomer composition comprises acrylate and an additional monomer. In some embodiments, the monomer composition comprises vinyl sulfonate and an additional monomer. In some embodiments, the monomer composition comprises AMPS and an additional monomer. In some embodiments, the monomer composition comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, and an additional monomer.

[0085] It is understood that the polymer may comprise any of the recited monomer components, individually, with any acrylamide or any crosslinking agent, or with both an acrylamide and a crosslinking agent. Thus, any one of sodium acrylate, vinyl sulfonate, AMPS or CEA may comprise a polymer with optionally any acrylamide, including N-[tris-(hydroxymethyl)methyl] acrylamide, and optionally any crosslinking agent, including N,N-methylene-bis-acrylamide.

[0086] In some embodiments, the monomer composition comprises acrylate and an acrylamide, such as N-[tris-(hydroxymethyl)methyl] acrylamide. In some embodiments, the monomer composition comprises sodium acrylate and an acrylamide. In some embodiments, the monomer composition comprises vinyl sulfonate and an acrylamide, such as N-[tris-(hydroxymethyl)methyl] acrylamide. In

some embodiments, the monomer composition comprises AMPS and an acrylamide. In some embodiments, the monomer composition comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, and N-[tris-(hydroxymethyl)methyl] acrylamide.

[0087] In some embodiments, the monomer composition comprises acrylate, such as sodium acrylate, and a crosslinking agent. In some embodiments, the monomer composition comprises vinyl sulfonate and a crosslinking agent. In some embodiments, the monomer composition comprises AMPS and a crosslinking agent. In some embodiments, the monomer composition comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, and a crosslinking agent.

[0088] In some embodiments, the monomer composition comprises acrylate and N,N-methylene-bis-acrylamide. In some embodiments, the monomer composition comprises sodium acrylate and N,N-methylene-bis-acrylamide. In some embodiments, the monomer composition comprises vinyl sulfonate and N,N-methylene-bis-acrylamide. In some embodiments, the monomer composition comprises AMPS and N,N-methylene-bis-acrylamide. In some embodiments, the monomer composition comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, and N,N-methylene-bis-acrylamide.

[0089] In some embodiments, the monomer composition comprises acrylate, an additional monomer and a crosslinking agent. In some embodiments, the monomer composition comprises sodium acrylate, an additional monomer and a crosslinking agent. In some embodiments, the monomer composition comprises vinyl sulfonate, an additional monomer and a crosslinking agent. In some embodiments, the monomer composition comprises AMPS, an additional monomer and a crosslinking agent. In some embodiments, the monomer composition comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, an additional monomer and a crosslinking agent.

[0090] In some embodiments, the monomer composition comprises acrylate, N-[tris-(hydroxymethyl)methyl] acrylamide and N,N-methylene-bis-acrylamide. In some embodiments, the monomer composition comprises sodium acrylate, N-[tris-(hydroxymethyl)methyl] acrylamide and N,N-methylene-bis-acrylamide. In some embodiments, the monomer composition comprises vinyl sulfonate, N-[tris-(hydroxymethyl)methyl] acrylamide and N,N-methylene-bis-acrylamide. In some embodiments, the monomer composition comprises AMPS, N-[tris-

(hydroxymethyl)methyl] acrylamide and N,N-methylene-bis-acrylamide. In some embodiments, the monomer composition comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, N-[tris-(hydroxymethyl)methyl] acrylamide and N,N-methylene-bis-acrylamide.

[0091] In some embodiments, the monomer composition is polymerized in the presence of an iron oxide nanoparticle. In an embodiment, the monomer composition is polymerized in the presence of colloidal iron oxide. In some embodiments, the monomer composition is polymerized in the presence of Fe_3O_4. In some embodiments, the monomer composition is polymerized in the presence of a superparamagnetic iron oxide particle. In some embodiments, the monomer composition is polymerized in the presence of the iron oxide particle such that the iron oxide particle is incorporated into the resulting polymer.

[0092] In some embodiments, the monomer composition and the iron oxide particle are mixed to form a mixture before polymerizing the monomer composition. In some embodiments, the mixture is heated, before polymerizing the monomer composition. The mixture may be heated to a temperature of from about 20°C to about 100°C. In one embodiment, the mixture is heated to from about 30°C to about 80°C. In an embodiment, the mixture is heated to about 50°C.

[0093] In some embodiments, obtaining the polymer comprises providing a mixture comprising: 0 wt% to 90 wt% sodium acrylate; 0 wt% to 90 wt% vinyl sulfonate; 0 wt% to 90 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0 wt% to 90 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 0 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture.

[0094] In a related embodiment, obtaining the polymer comprises providing a mixture comprising: 5 wt% to 50 wt% sodium acrylate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture. In an embodiment, obtaining the polymer comprises providing a mixture comprising: 5 wt% to 50 wt% vinyl sulfonate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture. In an additional embodiment, obtaining the polymer comprises providing a mixture comprising: 5 wt% to 50 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0.01 wt% to 10 wt% iron oxide;

10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture. In a further embodiment, obtaining the polymer comprises providing a mixture comprising: 5 wt% to 50 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide; and polymerizing the mixture.

[0095] In some embodiments, additional agents may be added to the monomer composition or mixture prior to polymerization. For example in some embodiments, one or more salts are added. In another embodiment, one or more buffers are added. In some embodiments, at least one of sodium chloride, sodium acetate or glycerol are added. In some embodiments, the pH is adjusted prior to polymerization. In some embodiments, the pH is adjusted to a range of from about 2 to about 10 prior to polymerization. In some embodiments, the pH is adjusted to between 5.9 and 6.1.

[0096] In some embodiments, polymerizing the monomer composition or polymerizing the mixture, comprises forming a polymeric microsphere associated with an iron oxide particle. In some embodiments, polymerizing the monomer composition or polymerizing the mixture, comprises adding the monomer composition or the mixture to oil, such that a polymeric microsphere associated with an iron oxide particle is formed. In some embodiments, the oil is paraffin oil. Other oils that may be used include, for example, silicon oil.

[0097] In some embodiments, the oil is heated before adding the monomer composition or the mixture to the oil. The oil may be heated to a temperature of from about 20°C to about 100°C. In one embodiment, the mixture is heated to from about 30°C to about 80°C. In a related embodiment, the oil is at a temperature of about 60°C.

[0098] In some embodiments, after adding the monomer composition or the mixture to the oil, the resulting suspension is stirred. In some embodiments, the speed at which the suspension is stirred will change the distribution of the lengths of the major axis of the microspheres that are formed. In some embodiments, the oil contains a surfactant. In some embodiments, the oil contains sorbitan sesquioleate. In some embodiments, sorbitan sesquioleate is present in the oil in an amount of from about 0.075% v/v to about 0.1% v/v. In some embodiments, sorbitan

sesquioleate is present in the oil in an amount of from about 0.01% v/v to about 5% v/v.

[0099] In some embodiments, the monomer composition or mixture is allowed to polymerize for between about 15 minutes to about 24 hours. In some embodiments, the monomer composition or mixture is allowed to polymerize for between about 30 minutes to about 90 minutes. In one embodiment, the monomer composition or mixture is allowed to polymerize for about 45 minutes.

[0100] In some embodiments, the microspheres are washed after polymerization. In some embodiments, the microspheres are washed in water. In some embodiments, the microspheres are washed in a salt solution. In some embodiments, the salt solution comprises sodium chloride. In some embodiments, the water or solution used to wash the microspheres is at a temperature of from about 20°C to about 90°C.

[0101] In some embodiments, the microspheres may have an average major axis of from about 15 micrometers to about 1000 micrometers. In some embodiments, the microspheres may have an average major axis of from about 100 micrometers to about 800 micrometers. In some embodiments, the microspheres may have an average major axis of from about 200 micrometers to about 600 micrometers. In some embodiments, the microspheres may have an average major axis of from about 100 micrometers to about 300 micrometers.

[0102] In some embodiments, a sieve is used to obtain a polymeric microsphere with a desired major axis. In some embodiments, the method comprises sieving the polymeric microsphere to obtain a polymeric microsphere with a major axis as recited previously.

[0103] In some embodiments, associating the polymer with the drug comprises releasably associating the drug with the biomaterial. In some embodiments, the drug is doxorubicin. In some embodiments the drug is irinotecan. In some embodiments, the drug is an anti-angiogenic drug. In some embodiments, the drug is a chemotherapeutic drug. In some embodiments, the chemotherapeutic drug is at least one of: doxorubicin, irinotecan and sunitinib. The drug may be at least one of doxorubicin or irinotecan. In some embodiments, the chemotherapeutic drug is associated with a polymeric microsphere. In some embodiments, the polymer microsphere is suspended in a liquid and a drug is added to the suspension in an amount of between about 0.5 mg to about 50 mg per milliliter of the suspension.

[0104] In some embodiments, contacting the biomaterial with the drug comprises adding the biomaterial to a solution of the drug. In some embodiments, after adding the biomaterial to the solution of the drug, the solution of the drug is agitated. In some embodiments, the solution of the drug contains the drug in an amount of from about 10 mg to about 50 mg. In some embodiments, the biomaterial is incubated with the solution of the drug for a period of from about 15 minutes to about 2 hours. In some embodiments, the biomaterial is incubated with the solution of the drug for a period of at least 15, 30, 45, 60, 90, 120 or 180 minutes.

[0105] **Methods of treatment**

[0106] In a third aspect, the present disclosure is directed to methods of treating an individual suffering from a solid tumor. In one embodiment, the solid tumor is a hepatic tumor.

[0107] In one embodiment, the method comprises administering to the individual a drug eluting, MRI detectable implant for vascular occlusion.

[0108] In one embodiment, administering to the individual the drug eluting, MRI detectable implant for vascular occlusion leads to occlusion of a blood vessel associated with the solid tumor. In another embodiment, administering to the individual the drug eluting, MRI detectable implant for vascular occlusion leads to delivery of a chemotherapeutic agent to the solid tumor. In one embodiment, administering to the individual the drug eluting, MRI detectable implant for vascular occlusion leads to occlusion of a blood vessel associated with the solid tumor and delivery of a chemotherapeutic agent to the solid tumor.

[0109] In one embodiment, the drug eluting, MRI detectable implant for vascular occlusion comprises a polymer. In one embodiment, the drug eluting, MRI detectable implant for vascular occlusion comprises an iron oxide particle. In one embodiment, the drug eluting, MRI detectable implant for vascular occlusion comprises a chemotherapeutic drug.

[0110] In one embodiment, the drug- eluting, MRI detectable implant for vascular occlusion comprises, a polymer, an iron oxide particle and a chemotherapeutic drug.

[0111] In one embodiment, the polymer comprises acrylate, such as sodium acrylate. In other embodiments, the polymer comprises vinyl sulfonate. In other embodiments, the polymer comprises AMPS. In some embodiments, the polymer comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA.

[0112] In another embodiment, the polymer is a copolymer. In some embodiments, the copolymer comprises acrylate, such as sodium acrylate, and another monomer. In some embodiments, the copolymer comprises vinyl sulfonate and another monomer. In some embodiments, the copolymer comprises AMPS and another monomer. In some embodiments, the copolymer comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, and another monomer. In some embodiment, the additional monomer comprises an acrylamide, such as N-[tris-(hydroxymethyl)methyl] acrylamide.

[0113] In another embodiment, the polymer further comprises a crosslinking agent. In some embodiments, the crosslinker comprises N,N-methylene-bis-acrylamide. In other embodiments, the crosslinking agent may comprise 1-(acryloyloxy)-3-(methacryloyloxy)-2-propanol, 1,4-diacryloylpiperazine, diethylene glycol diacrylate, ethylene glycol dimethacrylate, piperazine diacrylate, N,N'-bisacrylylcystamide, or N,N'-diallyl tartardiamide.

[0114] In some embodiments, the polymer comprises acrylate, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In some embodiments, the polymer comprises sodium acrylate, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In other embodiments, the polymer comprises vinyl sulfonate, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In other embodiments, the polymer comprises AMPS, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide. In other embodiments, the polymer comprises at least one of sodium acrylate, vinyl sulfonate, AMPS or CEA, N-[tris-(hydroxymethyl)methyl] acrylamide, and N,N-methylene-bis-acrylamide.

[0115] It is understood that the polymer may comprise any of the recited monomer components, individually, with any acrylamide or any crosslinking agent, or with both an acrylamide and a crosslinking agent. Thus, any one of sodium acrylate, vinyl sulfonate, AMPS or CEA may comprise a polymer with optionally any acrylamide, including N-[tris-(hydroxymethyl)methyl] acrylamide, and optionally any crosslinking agent, including N,N-methylene-bis-acrylamide.

[0116] In some embodiments, the biomaterial comprises an iron oxide particle. In some embodiments, the biomaterial comprises Fe_3O_4. In some embodiments, the biomaterial comprises an iron oxide nanoparticle. In some embodiments, the biomaterial comprises a superparamagnetic iron oxide particle. In some

embodiments, the superparamagnetic iron oxide particle is an iron oxide nanoparticle. In an embodiment, the biomaterial comprises iron oxide in a colloidal form. In some embodiments, the iron oxide particle is associated with the polymer. In some embodiments, the iron oxide particle is incorporated into the polymer.

[0117] In some embodiments, the biomaterial comprises: 0 wt% to 90 wt% sodium acrylate; 0 wt% to 90 wt% vinyl sulfonate; 0 wt% to 90 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0 wt% to 90 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 0 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide.

[0118] In a related embodiment, the biomaterial comprises: 5 wt% to 50 wt% sodium acrylate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In an embodiment, the biomaterial comprises: 5 wt% to 50 wt% vinyl sulfonate; 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In an additional embodiment, the biomaterial comprises: 5 wt% to 50 wt% 2-acrylamido-2-methylpropane sulfonic acid (AMPS); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide. In a further embodiment, the biomaterial comprises: 5 wt% to 50 wt% 2-carboxyethyl acrylate (CEA); 0.01 wt% to 10 wt% iron oxide; 10 wt% to 50 wt% N-[tris-(hydroxymethyl)methyl] acrylamide; and 1 wt% to 30 wt% N,N-methylene-bis-acrylamide.

[0119] In another embodiment, the method further comprises subjecting the individual to MRI. In one embodiment, the individual is subjected to MRI to determine where in the individual the drug eluting, MRI detectable implant for vascular occlusion is located.

[0120] In some embodiments, the drug eluting, MRI detectable implant for vascular occlusion is formed so that it is in an appropriate shape to occlude a blood vessel. In some embodiments, the drug eluting, MRI detectable implant for vascular occlusion is in the form of one or more microparticles. In some embodiments, the drug eluting, MRI detectable implant for vascular occlusion is in the form of one or more microspheres. In other embodiments, the one or more microspheres are substantially spherical. In some embodiments, the one or more microspheres have

a major axis of from about 15 micrometer to about 1000 micrometers. In some embodiments, the one or more microspheres have a major axis of from about 100 micrometers to about 800 micrometers. In some embodiments, the one or more microspheres have a major axis of from about 200 micrometers to about 600 micrometers. In some embodiments, the one or more microspheres have a major axis of from about 100 micrometers to about 300 micrometers.

[0121] In one embodiment, administering to the individual the drug eluting, MRI detectable implant for vascular occlusion comprises introducing the one or more microspheres into the lumen of a blood vessel associated with the solid tumor through a catheter. In one embodiment, when treating an individual with a hepatic tumor, a catheter is inserted via the femoral or brachial artery and advanced into the hepatic artery by steering it through the arterial system under fluoroscopic guidance. Alternatively or in addition, the catheter may be inserted and advanced by steering it through the arterial system under MRI guidance. The catheter is advanced into the hepatic arterial tree as far as necessary to allow complete blockage of the blood vessels supplying the tumor(s), while sparing as many of the arterial branches supplying normal structures as possible. This may be a segmental branch of the hepatic artery, but it could be the entire hepatic artery distal to the origin of the gastroduodenal artery, or even multiple separate arteries. The artery that will need to be blocked depends on the extent of tumor and its individual blood supply. Once the desired catheter position is achieved, the artery is embolized by injecting the therapeutic compositions as described herein through the arterial catheter until flow in the artery to be blocked ceases, for example, after observation for 5 minutes. Occlusion of the artery may be confirmed by subjecting an individual to MRI to determine where in the individual the drug eluting, MRI detectable implant for vascular occlusion is located, and/or injecting radiopaque contrast through the catheter and demonstrating by fluoroscopy or X-ray film that the vessel which previously filled with contrast no longer does so. The same procedure may be repeated with each feeding artery to be occluded.

[0122] In some embodiments, the drug eluting, MRI detectable implant for vascular occlusion comprises a chemotherapeutic drug. In some embodiments, the chemotherapeutic drug is releasably associated with the drug eluting, MRI detectable implant for vascular occlusion. In some embodiments, the chemotherapeutic drug is releasably associated to a microsphere. In some

embodiments, the chemotherapeutic drug is doxorubicin. In some embodiments, the chemotherapeutic drug is irinotecan. In some embodiments, the biomaterial is suspended in a liquid and a drug is added to the suspension in an amount of between about 0.5 mg to about 50 mg per milliliter of the suspension.

[0123] To further illustrate these embodiments, the following examples are provided. These examples are not intended to limit the scope of the claimed invention, which should be determined solely on the basis of the attached claims.

[0124] Example 1 – Preparation of MRI Detectable Microspheres using Sodium Acrylate Monomers

[0125] In a beaker containing 300 ml of demineralized water, 58 g of sodium chloride and 27 g of sodium acetate were dissolved. Next 400 ml of glycerol was added and the pH of the solution was adjusted to between 5.9 and 6.1 with acetic acid. Then, 90 g of N-[tris-(hydroxymethyl)methyl] acrylamide, 19.4 g of sodium acrylate and 10 g of N,N-methylene-bis-acrylamide were added. The volume was adjusted to 1 liter by addition of water and the monomer solution was then heated to 50°C.

[0126] Separately, a suspension of 25 ml of iron oxide (ferucarbotran – equivalent to 0.5 mol Fe/L) was filtered. After all monomers were dissolved, the monomer solution was filtered, and the filtered solution of iron oxide was added along with 20 ml of a 70 mg/ml ammonium persulfate solution. This resulting solution was rapidly poured into 4 liters of paraffin oil at 60°C containing 3 ml of Arlacel 83 (sorbitan sesquioleate) and 4 ml of TEMED (N,N,N',N' – tetramethylethylenediamine) under stirring.

[0127] The suspension was left for 45 minutes at 60°C and the microspheres were then recovered by decanting, and washed with 60°C water and saline solution to remove the excess oil.

[0128] The microspheres were then sieved into different size ranges. The sieved microspheres were then stored in saline. Figure 1 is a histogram showing the size distribution of microspheres from Example 1. The X axis denotes the size of the microsphere and the Y axis the percentage of microspheres in a given size bin.

[0129] Microspheres from Example 1 were subjected to granulometry. As shown, the sieved microspheres formed in Example 1 fall within a particular size distribution of about 200 μm. The results of the granulometry experiments are shown in Table 1.

[0130] Table 1. Characteristics of MRI Detectable Microspheres from Example 1

	Number	Minimum	Maximum	Average
Length [μm]	1259	80.18	604.83	192.41
Width [μm]		75.02	590.91	188.14

[0131] Microspheres from Example 1 were further subjected to microscopy using a microscope linked to a computer for analysis of the images. The microscopy results for Example 1 are shown in Figures 2A and 2B. As shown in the images, the microspheres formed in Example 1 are substantially spherical.

[0132] Example 2 – Preparation of Additional MRI-Detectable Microspheres using Sodium Acrylate Monomers

[0133] In a beaker containing 300 ml of demineralized water, 58 g of sodium chloride and 27 g of sodium acetate were dissolved. Next 400 ml of glycerol was added and the pH of the solution was adjusted to between 5.9 and 6.1 with acetic acid. Then, 90 g of N-[tris-(hydroxymethyl)methyl] acrylamide, 70 g of sodium acrylate and 10 g of N,N-methylene-bis-acrylamide were added. The volume was adjusted to 1 liter by addition of water and the monomer solution was then heated to 50°C.

[0134] Separately, a suspension of 25 ml of iron oxide (ferucarbotran – equivalent to 0.5 mol Fe/L) was filtered. After all monomers were dissolved, the monomer solution was filtered, and the filtered solution of iron oxide was added along with 20 ml of a 70 mg/ml ammonium persulfate solution. This resulting solution was rapidly poured into 4 liters of paraffin oil at 60°C containing 3 ml of Arlacel 83 (sorbitan sesquioleate) and 4 ml of TEMED (N,N,N',N' – tetramethylethylenediamine) under stirring.

[0135] The suspension was left for 45 minutes at 60°C and the microspheres were then recovered by decanting, and washed with 60°C water and saline solution to remove the excess oil.

[0136] The microspheres were then sieved into different size ranges. The sieved microspheres were then stored in a solution of equal parts ethanol and water.

[0137] Example 3 – Drug Loading of MRI Detectable Microspheres of Example 2, Varying the Mass of the Drug

[0138] Vials containing 2 ml of the microspheres synthesized in Example 2 were washed two times with a saline solution (0.9 % NaCl). The excess supernatant was removed and 8 ml of a doxorubicin (Yick Vic lot #IF-DO-071116) solution was added to each vial. Each vial received a solution with a different concentration of doxorubicin such that one vial received 25 mg, one 50 mg, one 75 mg and one 100 mg of doxorubicin. After addition of doxorubicin, the vials were agitated every minute for the first 10 minutes. Samples of 150 µl of supernatant were drawn from each vial at 15, 30, 45, 60, 90, 120 and 180 minutes.

[0139] The concentration of doxorubicin in the supernatant was analyzed by reverse phase high performance liquid chromatography (Uptisphere C18 column, 150 mm x 4.6 mm). The elution phase consisted in 30% (v/v) acetonitrile and 0.1% (v/v) trifluoroacetic acid in water. UV detection was at λ_{max} 480 nm.

[0140] The loading efficiency was calculated by using the following equation:

$$\%\ \text{loading at time t} = \frac{(\text{initial drug mass}) - (\text{drug mass in the supernatant at time t})}{\text{initial drug mass}} \times 100$$

with mass at time t = concentration at time t x volume of solution at time t.

[0141] The results of the experiment are shown in Figure 3. The X axis denotes the amount of time the biomaterials were incubated with the doxorubicin solution, and the Y axis denotes the percentage of doxorubicin in the solution that has become associated with the biomaterials. As depicted in the figure, varying amounts of the drug doxorubicin are loaded onto the microspheres in 3 hours or less. Some amounts were loaded in very short times. For example, about 80% loading or greater was achieved in 15 minutes or less.

[0142] Example 4 – Drug Loading and Release Dynamics for MRI Detectable Microspheres of Example 2, Varying the Mass of the Drug

[0143] To determine both the loading and release dynamics of the MRI detectable microspheres, microspheres from Example 2 were loaded with 25 or 50 mg of pharmaceutical grade doxorubicin.

[0144] In vials containing 2 ml of the microspheres of Example 2, the excess supernatant was removed and 8 ml of a doxorubicin (Adriblastin, Pfizer, lot #8PL007-H) solution was added to each vial. After addition of doxorubicin, the vials were agitated every minute for the first 10 minutes. Samples of 100 µl of supernatant were drawn from each vial at 15, 30, 45, 60, 90 and 120 minutes.

[0145] The concentration of doxorubicin in the supernatant was analyzed by reverse phase high performance liquid chromatography (YMC C18 column, 250 mm x 4.6 mm). The elution phase consisted in 54% (v/v) water, 29% (v/v) acetonitrile, 17% (v/v) methanol, 2ml/l phosphoric acid and 1g/l sodium dodecyl sulfate (pH is adjusted at 3.6). UV detection was at λ_{max} 480 nm.

[0146] The loading efficiency was calculated using the following equation:

$$\% \text{ loading at time t} = \frac{(\text{initial drug mass}) - (\text{drug mass in the supernatant at time t})}{\text{initial drug mass}} \times 100$$

with the mass at time t = concentration at time t x volume of solution at time t.

[0147] Figure 4 shows the loading behavior for this experiment, confirming the data of Example 3. The X axis denotes the amount of time the biomaterials were incubated with the doxorubicin solution, and the Y axis denotes the percentage of doxorubicin in the solution that has become associated with the biomaterials.

[0148] A dialysis membrane model was used to analyze the release of doxorubicin from the microspheres over time. Although this model does not simulate the pressure and flow rate from vasculature, for measuring embolization, it is a good model for measuring drug release because the embolic, *in vivo*, prevents blood flow and the drug release is due to diffusion phenomena.

[0149] Previously obtained results from dialysis experiments assaying the release of peptides from biodegradable microspheres are more predictive of the *in vivo* onset and duration of release than data obtained from experiments using the extraction method, although the overall *in vitro* release rate was still somewhat slower than the estimated *in vivo* release. (See J W Kotanski, P. P. DeLuca, AAPS PharSciTech, 2000, article 4, which is hereby incorporated by reference in its entirety.) The microspheres of the present example were non-degradable microspheres, and the dialysis model was found to be the most appropriate to simulate the release behaviour of implanted microspheres after embolization procedure. Figures 5A and 5B show schematics of a typical dialysis membrane model experiment.

[0150] The study was performed at room temperature. Two ml of drug loaded MRI detectable microspheres from Example 2 were introduced into a 3 ml dialysis membrane (Spectra Por dialysis membrane - MWCO 100,000 Da), which was then introduced in a 250 ml graduated cylinder filled with 250 ml of saline. About 150 µl of the saline solution was sampled periodically from the 250 ml reservoir and the drug content was analysed by HPLC as described in Example 3. The results of the

experiment are depicted in Figure 6. The X axis denotes the amount of time the biomaterial was dialyzed, and the Y axis denotes the percentage of doxorubicin originally associated with the biomaterial that has been released from the from the biomaterial.

[0151] Example 5 – Preparation of MRI-Detectable Microspheres using Vinyl Sulfonate Monomers

[0152] In a beaker containing 300 ml of demineralized water, 58 g of sodium chloride and 27 g of sodium acetate were dissolved. Next 400 ml of glycerol was added and the pH of the solution was adjusted to between 5.9 and 6.1 with acetic acid. Then, 90 g of N-[tris-(hydroxymethyl)methyl] acrylamide, 26.8 g of sodium vinyl sulfonate and 10 g of N,N-methylene-bis-acrylamide were added. The volume was adjusted to 1 liter by addition of water and the monomer solution was then heated to 50°C.

[0153] Separately, a suspension of 25 ml of iron oxide (ferucarbotran – equivalent to 0.5 mol Fe/L) was filtered. After all monomers were dissolved, the monomer solution was filtered, and the filtered solution of iron oxide was added along with 20 ml of a 70 mg/ml ammonium persulfate solution. This resulting solution was rapidly poured into 4 liters of paraffin oil at 60°C containing 3ml of Arlacel 83 (sorbitan sesquioleate) and 4 ml of TEMED (N,N,N',N' – tetramethylethylenediamine) under stirring.

[0154] The suspension was left for 45 minutes at 60°C and the microspheres were then recovered by decanting, and washed with 60°C water and saline solution to remove the excess oil.

[0155] The microspheres were then sieved into different size ranges. The sieved microspheres were then stored in saline. Figure 7 is a histogram showing the size distribution of microspheres from Example 5. The X axis denotes the size of the microsphere and the Y axis the percentage of microspheres in a given size bin.

[0156] Microspheres from Example 5 were subjected to granulometry. As shown, the sieved microspheres formed in Example 5 fall within a particular size distribution of between about 100 μm and about 300 μm. The results of the granulometry experiments are shown in Table 2.

[0157] Table 2. Characteristics of MRI Detectable Microspheres from Example 5

	Number	Minimum	Maximum	Average
Length [μm]	1254	114.91	320.73	207.61
Width [μm]		106.11	319.72	203.66

[0158] Microspheres from Example 5 were further subjected to microscopy using a microscope linked to a computer for analysis of the images. The microscopy results for Example 5 are shown in Figures 8A, 8B, 8C and 8D. As shown in the images, the microspheres formed in Example 5 are substantially spherical.

[0159] Example 6 – Preparation of MRI-Detectable Microspheres using AMPS Monomers

[0160] In a beaker containing 300 ml of demineralized water, 58 g of sodium chloride and 27 g of sodium acetate were dissolved. Next 400 ml of glycerol was added. Then, 90 g of N-[tris-(hydroxymethyl)methyl] acrylamide, 42.7 g of AMPS and 10 g of N,N-methylene-bis-acrylamide were added. The volume was adjusted to 1 liter by addition of water and the monomer solution was then heated to 50°C.

[0161] Separately, a suspension of 25 ml of iron oxide (ferucarbotran – equivalent to 0.5 mol Fe/L) was filtered. After all monomers were dissolved, the pH of the solution was adjusted to between 5.9 and 6.1 with sodium hydroxide. The monomer solution was filtered, and the filtered solution of iron oxide was added along with 20 ml of a 70 mg/ml ammonium persulfate solution. This resulting solution was rapidly poured into 4 liters of paraffin oil at 60°C containing 3 ml of Arlacel 83 (sorbitan sesquioleate) and 4 ml of TEMED (N,N,N',N' – tetramethylethylenediamine) under stirring.

[0162] The suspension was left for 45 minutes at 60°C and the microspheres were then recovered by decanting, and washed with 60°C water, and saline solution to remove the excess oil.

[0163] The microspheres were then sieved into different size ranges. The sieved microspheres were then stored in saline. Figure 9 is a histogram showing the size distribution of microspheres from Example 6. The X axis denotes the size of the microsphere and the Y axis the percentage of microspheres in a given size bin.

[0164] Microspheres from Example 6 were subjected to granulometry. As shown, the sieved microspheres formed in Example 6 fall within a particular size distribution

of between about 100 μm and about 300 μm. The results of the granulometry experiments are shown in Table 3.

[0165] Table 3. Characteristics of MRI Detectable Microspheres from Example 6

	Number	Minimum	Maximum	Average
Length [μm]	320	116.41	276.40	186.62
Width [μm]		107.88	272.51	181.36

[0166] Microspheres from Example 6 were further subjected to microscopy using a microscope linked to a computer for analysis of the images. The microscopy results for Example 6 are shown in Figures 10A and 10B. As shown in the images, the microspheres formed in Example 6 are substantially spherical.

[0167] Example 7 – Preparation of MRI-Detectable Microspheres using CEA Monomers

[0168] In a beaker containing 300 ml of demineralized water, 58 g of sodium chloride and 27 g of sodium acetate were dissolved. Next 400 ml of glycerol was added. Then, 90 g of N-[tris-(hydroxymethyl)methyl] acrylamide, 29.7 g of CEA and 10 g of N,N-methylene-bis-acrylamide were added. The volume was adjusted to 1 liter by addition of water and the monomer solution was then heated to 50°C.

[0169] Separately, a suspension of 25 ml of iron oxide (ferucarbotran – equivalent to 0.5 mol Fe/L) was filtered. After all monomers were dissolved, the pH of the solution was adjusted to between 5.9 and 6.1 with sodium hydroxide and acetic acid. The monomer solution was filtered, and the filtered solution of iron oxide was added along with 20 ml of a 70 mg/ml ammonium persulfate solution. This resulting solution was rapidly poured into 4 liters of paraffin oil at 60°C containing 3 ml of Arlacel 83 (sorbitan sesquioleate) and 4 ml of TEMED (N,N,N',N' – tetramethylethylenediamine) under stirring.

[0170] The suspension was left for 45 minutes at 60°C and the microspheres were then recovered by decanting, and washed with 60°C water and saline solution to remove the excess oil.

[0171] The microspheres were then sieved into different size ranges. The sieved microspheres were then stored in saline. Figure 11 is a histogram showing the size distribution of microspheres from Example 7. The X axis denotes the size of the microsphere and the Y axis the percentage of microspheres in a given size bin.

[0172] Microspheres from Example 7 were subjected to granulometry. As shown, the sieved microspheres formed in Example 7 fall within a particular size distribution of between about 100 μm and about 300 μm. The results of the granulometry experiments are shown in Table 4.

[0173] Table 4. Characteristics of MRI Detectable Microspheres from Example 7

	Number	Minimum	Maximum	Average
Length [μm]	1262	101.19	410.01	183.90
Width [μm]		94.05	320.53	178.70

[0174] Microspheres from Example 7 were further subjected to microscopy using a microscope linked to a computer for analysis of the images. The microscopy results for Example 9 are shown in Figures 12A and 12B. As shown in the images, the microspheres formed in Example 7 are substantially spherical.

[0175] Example 8 – Drug (Doxorubicin) Loading of MRI Detectable Microspheres of Examples 1, 5, 6 and 7

[0176] In vials containing 2 ml of the microspheres synthesized in Examples 1, 5, 6 and 7, the excess supernatant was removed and 8 ml of a doxorubicin (Adriblastin, Pfizer, 50 mg) solution was added to each vial. After addition of doxorubicin, the vials were agitated every minute for the first 10 minutes. Samples of 100 μl of supernatant were drawn from each vial at 15, 30, 45, 60, 90 and 120 minutes.

[0177] The concentration of doxorubicin in the supernatant was analyzed following the procedure described in Example 4. The results of the experiment are shown in Figure 13. The X axis denotes the amount of time the biomaterials were incubated with the doxorubicin solution, and the Y axis denotes the percentage of doxorubicin in the solution that has become associated with the biomaterials.

[0178] Example 9 – Drug (Doxorubicin) Release for MRI Detectable Microspheres of Examples 1, 5, 6 and 7

[0179] The study was performed at room temperature. Two ml of drug loaded MRI detectable microspheres from Example 8 (after 2h of loading) were introduced into 500 ml of saline and 10 mM MES (morpholino ethane sulfonic acid) in a beaker. About 100 μl of the supernatant was sampled periodically and the drug content was analysed by HPLC as described in Example 8.

[0180] The release was calculated using the following equation:

$$\% \text{ release at time t} = \frac{\text{drug mass in the supernatant at time t}}{\text{initial drug mass}} \times 100$$

with the mass at time t = concentration at time t x volume of solution at time t.

[0181] The results of the experiment are depicted in Figure 14. The X axis denotes the amount of time the biomaterials were dialyzed, and the Y axis denotes the percentage of doxorubicin originally associated with the biomaterial that has been released from the biomaterials.

[0182] Example 10 – Drug (Irinotecan) Loading of MRI Detectable Microspheres of Examples 1, 5, 6 and 7

[0183] In vials containing 2 ml of the microspheres synthesized in Examples 1, 5, 6 and 7, the excess supernatant was removed and 5 ml of an irinotecan (Campto, Pfizer, 100 mg) solution was added to each vial. After addition of irinotecan, the vials were agitated every minute for the first 10 minutes. Samples of 100 µl of supernatant were drawn from each vial at 15, 30, 45, 60, 90 and 120 minutes.

[0184] The concentration of irinotecan in the supernatant was analyzed by reverse phase high performance liquid chromatography (Uptisphere CN Interchim column, 250 mm x 4.0 mm). The elution phase consisted in 70% (v/v) water with 0.1% TFA (trifluoro acetic acid), 30% (v/v) acetonitrile. UV detection was at λ_{max} 275 nm.

[0185] The loading efficiency was calculated using the same equation as for Example 8.

[0186] The results of the experiment are shown in Figure 15. The X axis denotes the amount of time the biomaterials were incubated with the irinotecan solution, and the Y axis denotes the percentage of irinotecan in the solution that has become associated with the biomaterials.

[0187] Example 11 – Drug (Irinotecan) Release Dynamics for MRI Detectable Microspheres of Examples 1, 5, 6 and 7

[0188] A dialysis membrane model was used to analyze the release of irinotecan from the microspheres over time, as for Example 4.

[0189] The study was performed at room temperature. Two ml of drug loaded MRI detectable microspheres from Examples 1, 5, 6 and 7 were introduced into a 12 ml dialysis membrane (Slide-A-Lyzer, Thermo Fisher- MWCO 20,000 Da), which was then introduced in a 600 ml graduated beaker filled with 500 ml of saline under

slow stirring. About 100 µl of the saline solution was sampled periodically from the 500 ml reservoir and the drug content was analysed by HPLC as described for Example 10.

[0190] The release was calculated using the same equation as for Example 9.

[0191] The results of the experiment are depicted in Figure 16. The X axis denotes the amount of time the biomaterials were dialyzed, and the Y axis denotes the percentage of irinotecan originally associated with the biomaterial that has been released from the biomaterials.

[0192] It will be obvious to those having skill in the art that many changes may be made to the details of the above-described embodiments without departing from the underlying principles of the invention. The scope of the present invention should, therefore, be determined only by the following claims.

Claims

1. A biomaterial suitable for use as a drug eluting, Magnetic Resonance Imaging ("MRI") detectable implant for vascular occlusion, comprising: a polymer comprising at least one of the following: sodium acrylate, vinyl sulfonate, 2-acrylamido-2-methylpropane sulfonic acid (AMPS), and 2-carboxyethyl acrylate (CEA); an iron oxide particle; and a drug.

2. The biomaterial of claim 1, wherein the biomaterial is in the form of microspheres.

3. The biomaterial of claim 2, wherein the microspheres are substantially spherical.

4. The biomaterial of claim 2, wherein the microspheres have an average major axis of from about 15 μm to about 1000 μm.

5. The biomaterial of claim 2, wherein the microspheres have an average major axis of from about 100 μm to about 300 μm.

6. The biomaterial of any of claims 1-5, wherein the polymer comprises sodium acrylate.

7. The biomaterial of any of claims 1-5, wherein the polymer comprises vinyl sulfonate.

8. The biomaterial of any of claims 1-5, wherein the polymer comprises AMPS.

9. The biomaterial of any of claims 1-5, wherein the polymer comprises CEA.

10. The biomaterial of any of claims 1-9, wherein the polymer is a copolymer.

11. The biomaterial of claim 10, wherein the copolymer comprises: an acrylamide.

12. The biomaterial of claim 11, wherein the copolymer comprises: N-[tris-(hydroxymethyl)methyl] acrylamide.

13. The biomaterial of any of claims 1-12, wherein the polymer comprises a crosslinking agent.

14. The biomaterial of claim 13, wherein the crosslinking agent is N,N-methylene-bis-acrylamide.

15. The biomaterial of any of claims 1-14, wherein the drug is a chemotherapeutic drug.

16. The biomaterial of claim 15, wherein the chemotherapeutic drug is doxorubicin.

17. The biomaterial of claim 15, wherein the chemotherapeutic drug is irinotecan.

18. The biomaterial of any of claims 1-17, wherein the drug is releasably associated with the microsphere.

19. The biomaterial of any of claims 1-18, wherein the microspheres are suspended in a liquid and a drug is added to a suspension of microspheres in an amount of between about 0.5 mg to about 50 mg per milliliter of the suspension.

20. The biomaterial of any of claims 1-19, wherein the iron oxide particle comprises Fe_3O_4.

21. The biomaterial of any of claims 1-20, wherein the iron oxide particle comprises colloidal iron.

22. The biomaterial of any of claims 1-21, wherein the iron oxide particle is a nanoparticle.

23. A method of producing a biomaterial suitable for use as drug eluting, MRI detectable implant for vascular occlusion, comprising: providing a polymer comprising at least one of the following: sodium acrylate, vinyl sulfonate, 2-acrylamido-2-methylpropane sulfonic acid (AMPS), and 2-carboxyethyl acrylate (CEA), wherein the polymer is associated with an iron oxide particle; and associating the polymer with a drug.

24. The method of claim 23, wherein providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition comprises sodium acrylate.

25. The method of claim 23, wherein providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition comprises vinyl sulfonate.

26. The method of claim 23, wherein providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition comprises AMPS.

27. The method of claim 23, wherein providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition comprises CEA.

28. The method of any of claims 23-27, wherein providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition further comprises: one other monomer.

29. The method of claim 28, wherein providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition further comprises: N-[tris-(hydroxymethyl)methyl] acrylamide.

30. The method of any of claims 23-29, wherein providing the polymer comprises polymerizing a monomer composition in the presence of an iron oxide particle, wherein the monomer composition further comprises: a crosslinking agent.

31. The method of claim 30, wherein the crosslinking agent comprises N,N-methylene-bis-acrylamide.

32. The method of any of claims 23-31, wherein the iron oxide particle comprises colloidal iron.

33. The method of any of claims 23-32, wherein the monomer composition and the iron oxide particle are mixed to form a mixture before polymerizing the monomer composition in the presence of the iron oxide particle.

34. The method of claim 33, further comprising: heating the mixture before polymerizing the monomer composition in the presence of the iron oxide particle.

35. The method of claim 34, wherein heating the mixture comprises heating the mixture to a temperature between about 20°C to about 100°C.

36. The method of any of claims 23-35, wherein polymerizing the monomer composition in the presence of the iron oxide particle further comprises forming a polymeric microsphere associated with the iron oxide particle.

37. The method of any of claims 23-36, wherein polymerizing the monomer composition in the presence of the iron oxide particle takes place in oil, such that a polymeric microsphere associated with the iron oxide particle is formed.

38. The method of claim 37, wherein the oil is at a temperature between about 40°C to about 100°C.

39. The method of claim 37, further comprising: sieving the polymeric microspheres to obtain polymeric microspheres with an average major axis of from about 15 micrometers to about 1000 micrometers.

40. The method of claim 37, further comprising: sieving the polymeric microspheres to obtain polymeric microspheres with an average major axis of from about 100 micrometers to about 300 micrometers.

41. The method of any of claims 23-40, wherein the polymer is in the form of a microsphere, and associating the polymer with the drug comprises: suspending the microspheres in a liquid; and adding the drug selected from doxorubicin or irinotecan to the suspension of microspheres in an amount of between about 0.5 mg to about 50 mg per milliliter of the suspension.

42. A method of treating an individual suffering from a solid tumor comprising: administering to the individual a drug eluting, MRI detectable implant for vascular occlusion, comprising: a polymer comprising at least one of the following: sodium acrylate, vinyl sulfonate, 2-acrylamido-2-methylpropane sulfonic acid (AMPS), and 2-carboxyethyl acrylate (CEA); an iron oxide particle; and a drug, wherein administering to the individual the drug eluting, MRI detectable implant for vascular occlusion leads to occlusion of a blood vessel associated with the solid tumor and delivery of the drug to the solid tumor.

43. The method of claim 42, wherein the method further comprises: identifying the location of the drug eluting, MRI detectable implant for vascular occlusion through MRI after administering to the individual the drug eluting, MRI detectable implant for vascular occlusion.

44. The method of claims 42 or 43, wherein the drug eluting, MRI detectable implant for vascular occlusion is in the form of one or more microspheres.

45. The method of claim 44, wherein administering to the individual the drug eluting, MRI detectable implant for vascular occlusion comprises introducing the one or more microspheres into a lumen of a blood vessel associated with the solid tumor through a catheter.

46. The method of any of claims 42-45, wherein the polymer comprises a copolymer.

47. The method of claim 46, wherein the copolymer comprises: sodium acrylate and N-[tris-(hydroxymethyl)methyl] acrylamide.

48. The method of claim 46, wherein the copolymer comprises: vinyl sulfonate and N-[tris-(hydroxymethyl)methyl] acrylamide.

49. The method of claim 46, wherein the copolymer comprises: AMPS and N-[tris-(hydroxymethyl)methyl] acrylamide.

50. The method of claim 46, wherein the copolymer comprises: CEA and N-[tris-(hydroxymethyl)methyl] acrylamide.

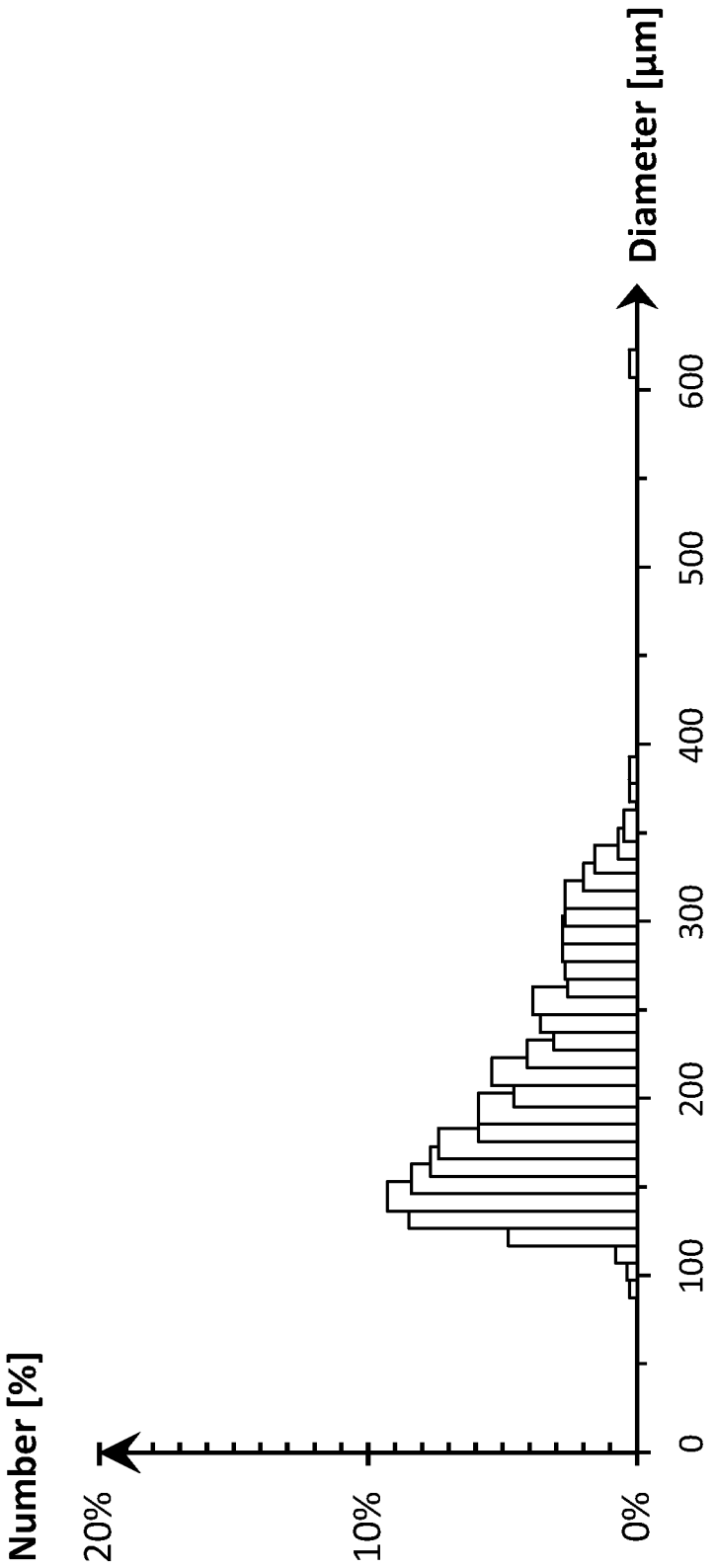

FIG. 1

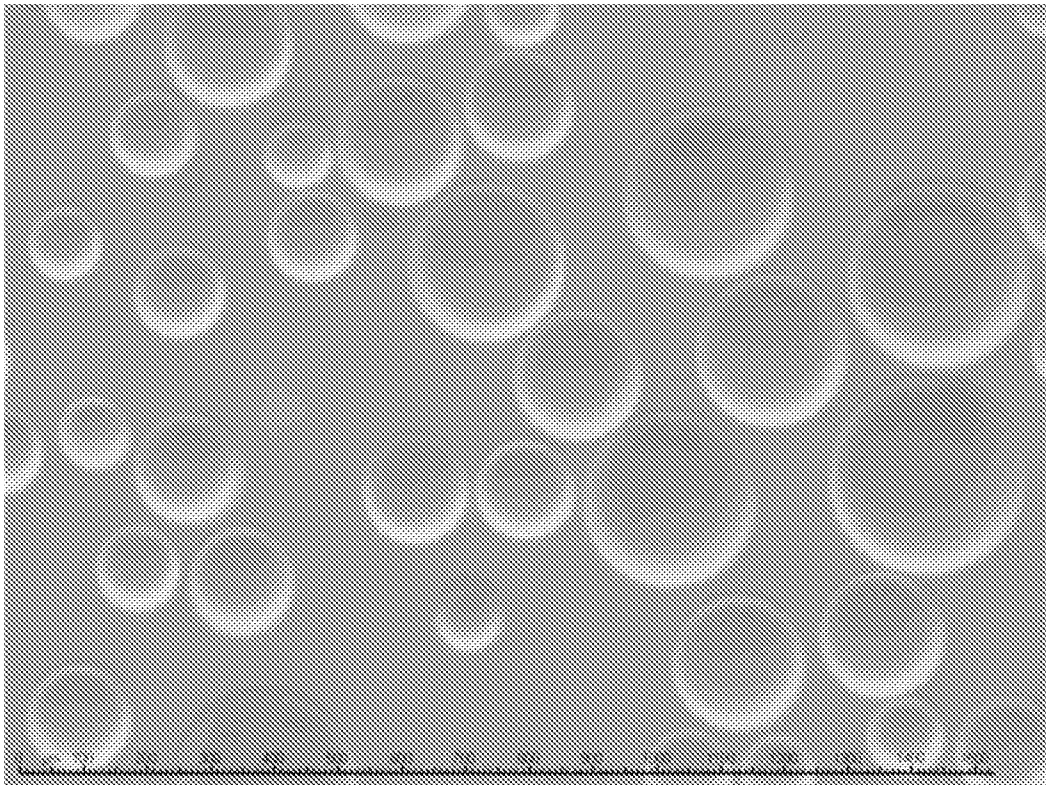

FIG. 2A

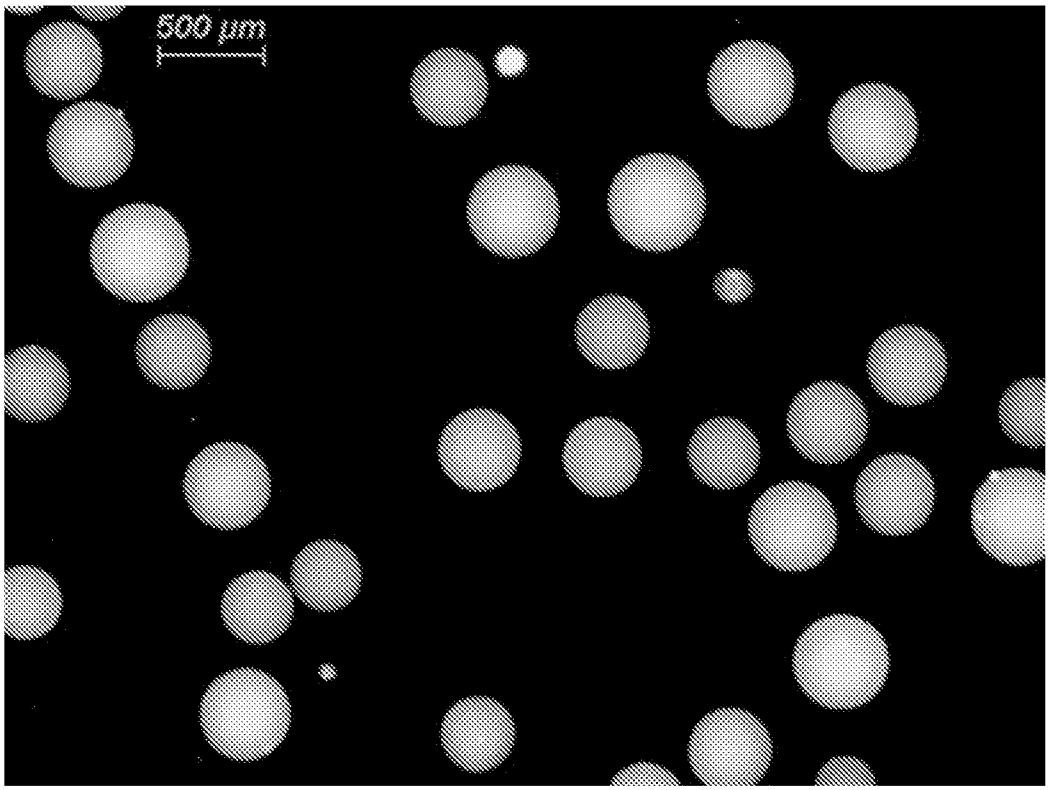

FIG. 2B

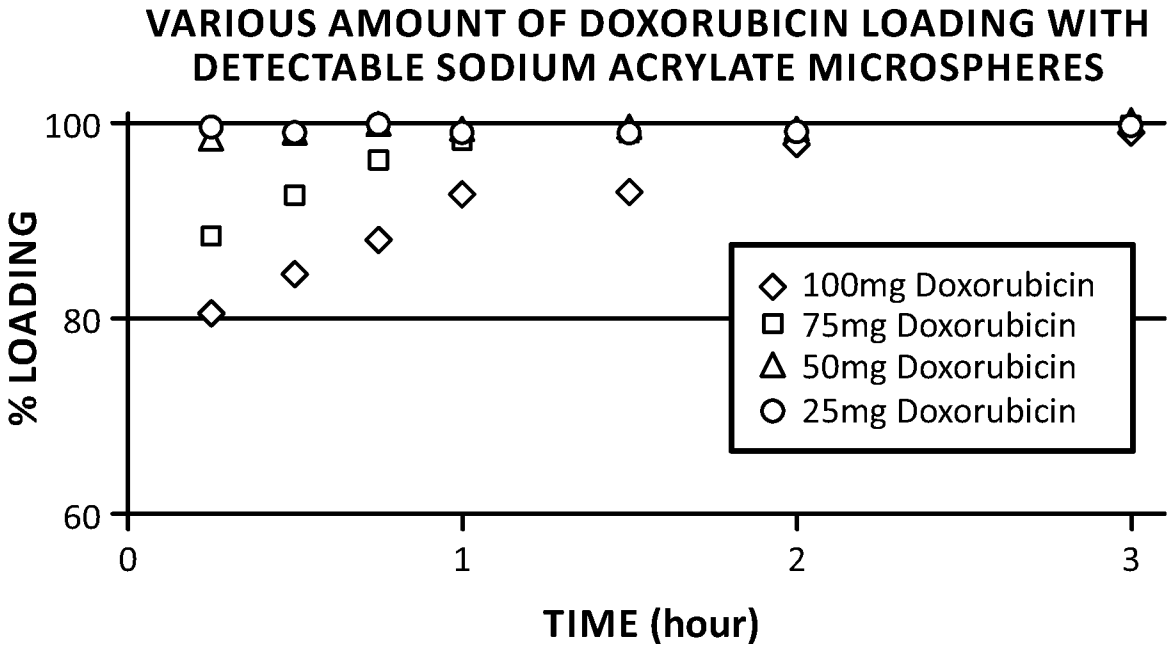
VARIOUS AMOUNT OF DOXORUBICIN LOADING WITH DETECTABLE SODIUM ACRYLATE MICROSPHERES
% LOADING
100
80
60
0
1
2
3
TIME (hour)
100mg Doxorubicin
75mg Doxorubicin
50mg Doxorubicin
25mg Doxorubicin

FIG. 3

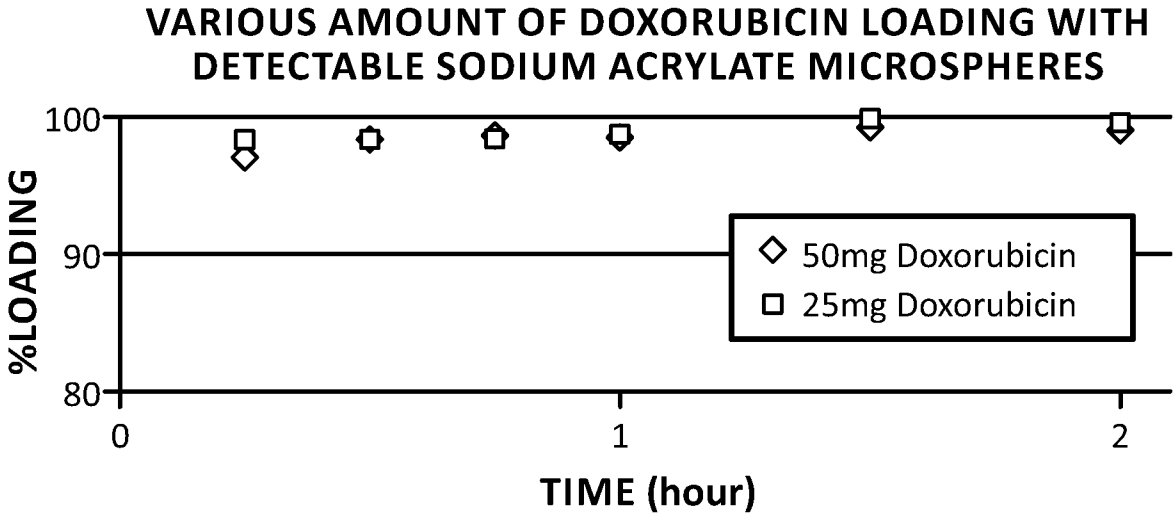
VARIOUS AMOUNT OF DOXORUBICIN LOADING WITH DETECTABLE SODIUM ACRYLATE MICROSPHERES
%LOADING
100
90
80
0
1
2
TIME (hour)
50mg Doxorubicin
25mg Doxorubicin

FIG. 4

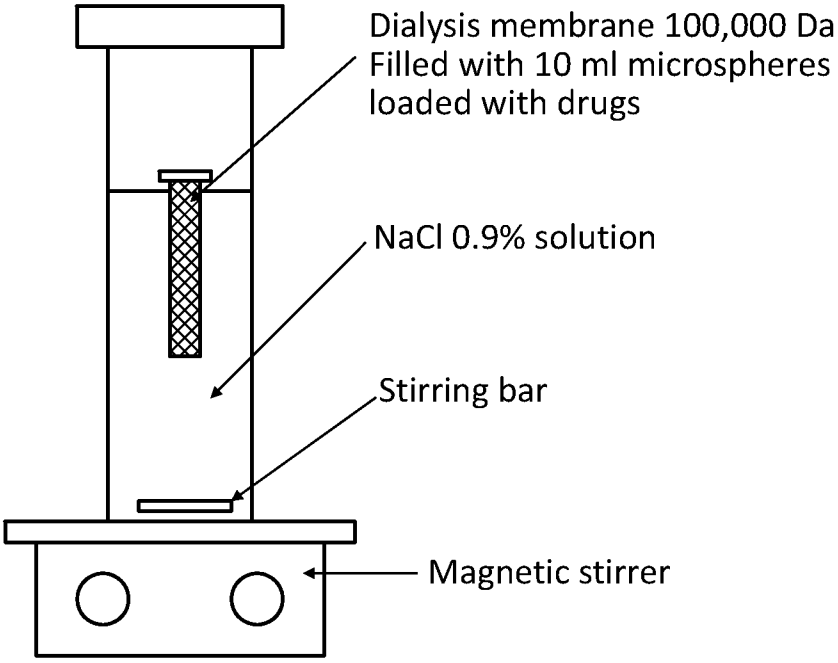
Dialysis membrane 100,000 Da
Filled with 10 ml microspheres
loaded with drugs
NaCl 0.9% solution
Stirring bar
Magnetic stirrer

FIG. 5A

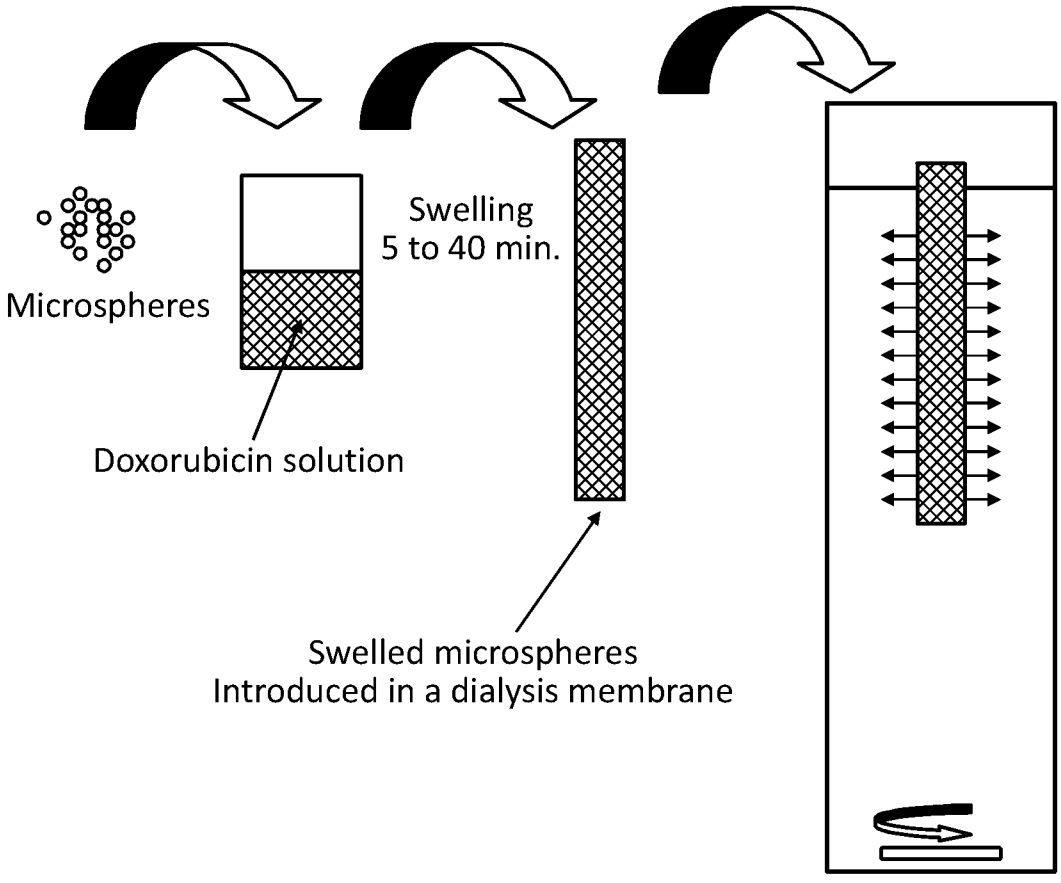
Microspheres
Swelling
5 to 40 min.
Doxorubicin solution
Swelled microspheres
Introduced in a dialysis membrane

FIG. 5B

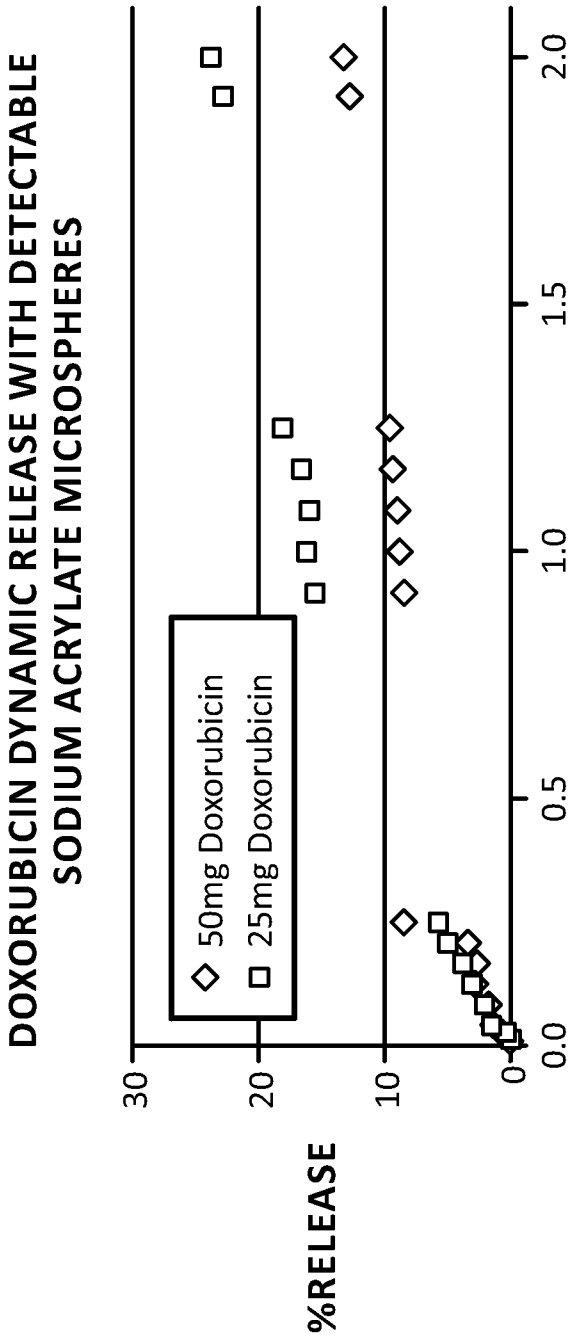
DOXORUBICIN DYNAMIC RELEASE WITH DETECTABLE SODIUM ACRYLATE MICROSPHERES
50mg Doxorubicin
25mg Doxorubicin
%RELEASE
TIME (day)
0
10
20
30
0.0
0.5
1.0
1.5
2.0

FIG. 6

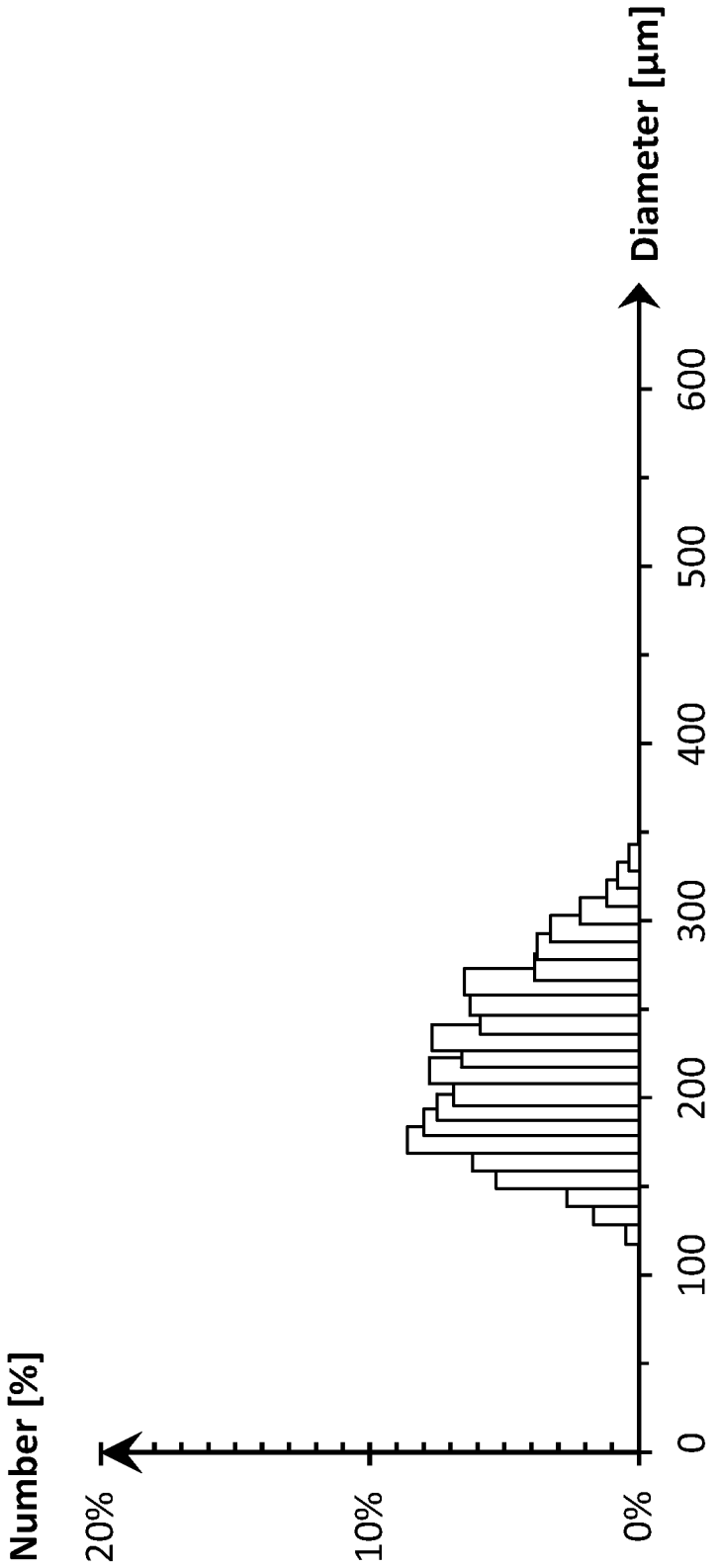

FIG. 7

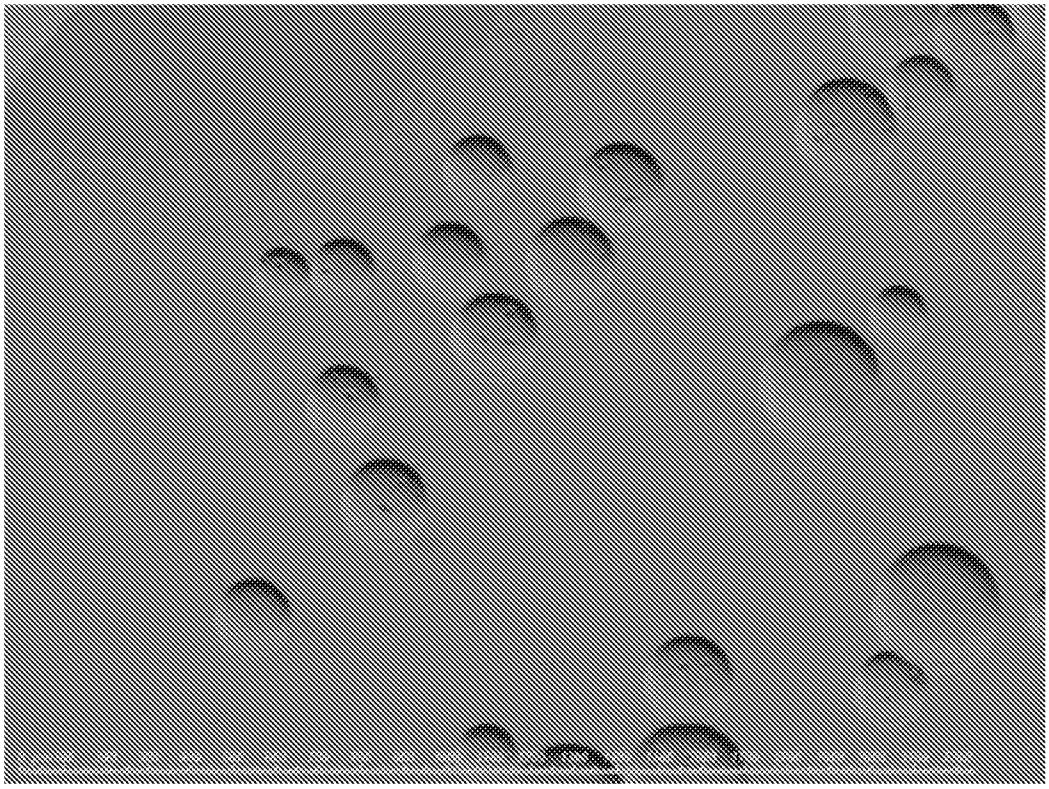

FIG. 8A

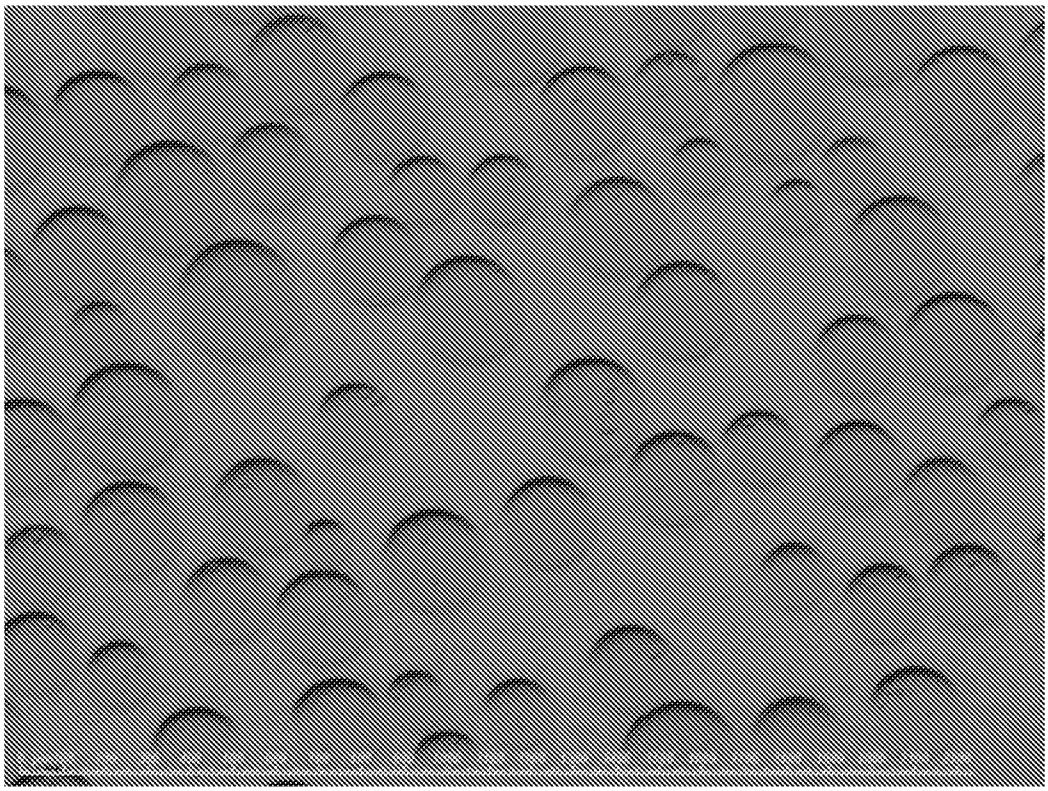

FIG. 8B

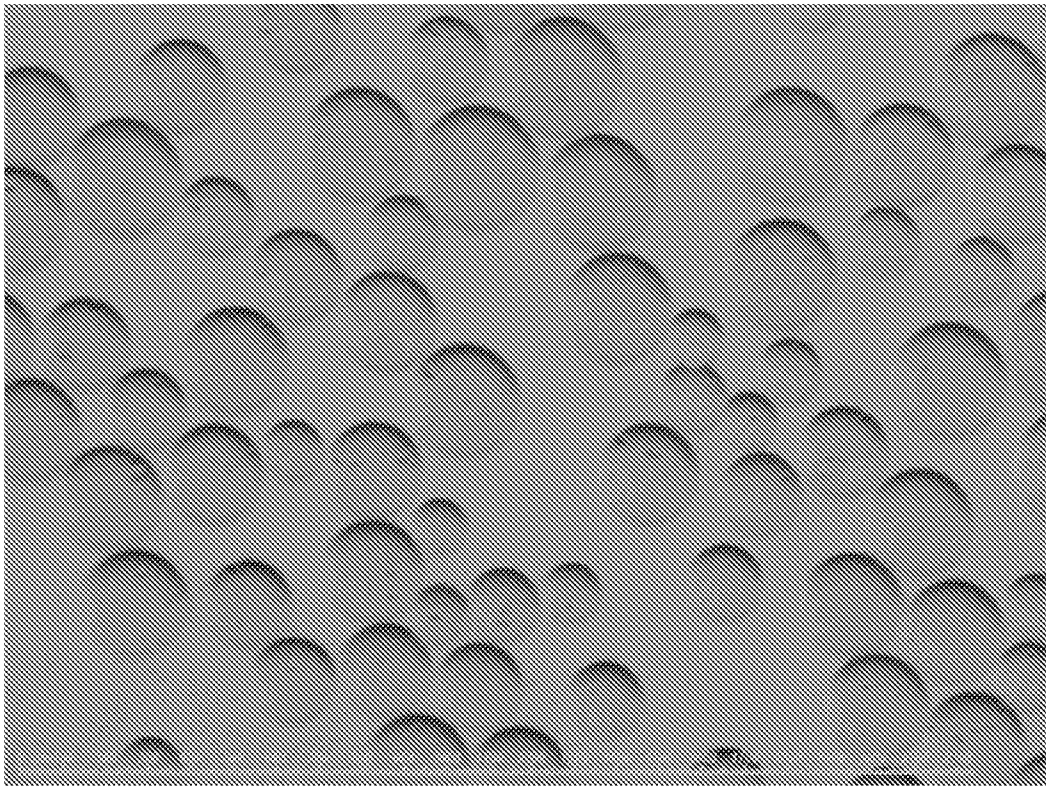

FIG. 8C

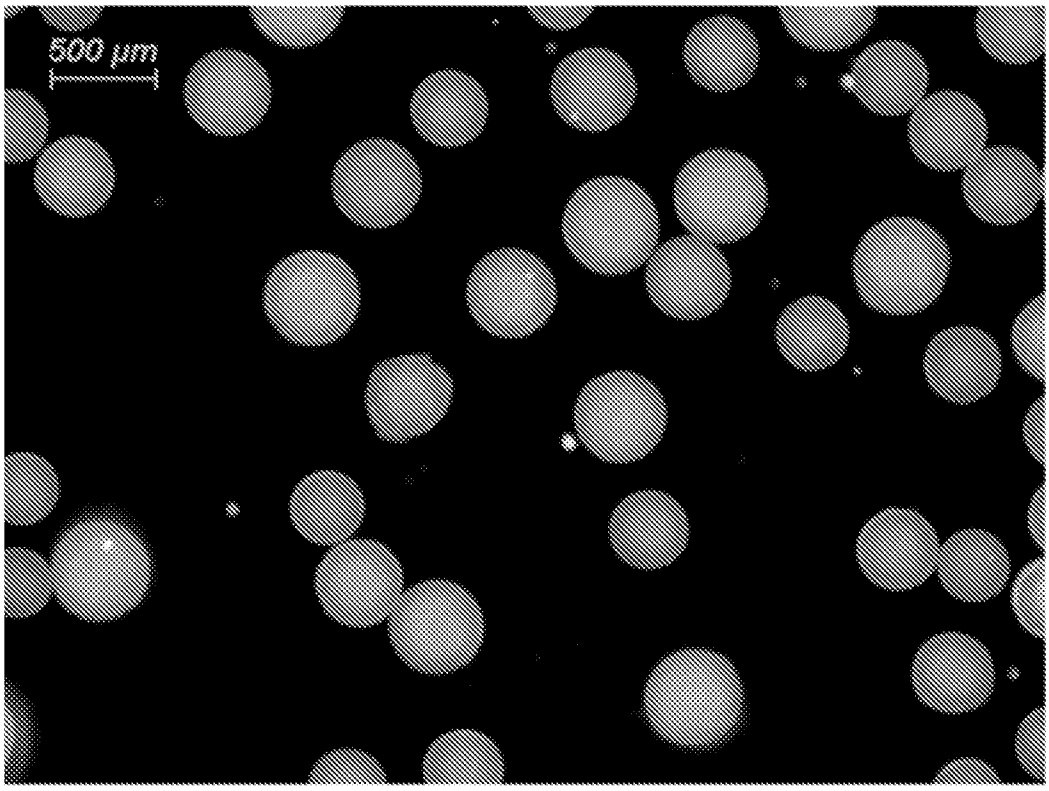

FIG. 8D

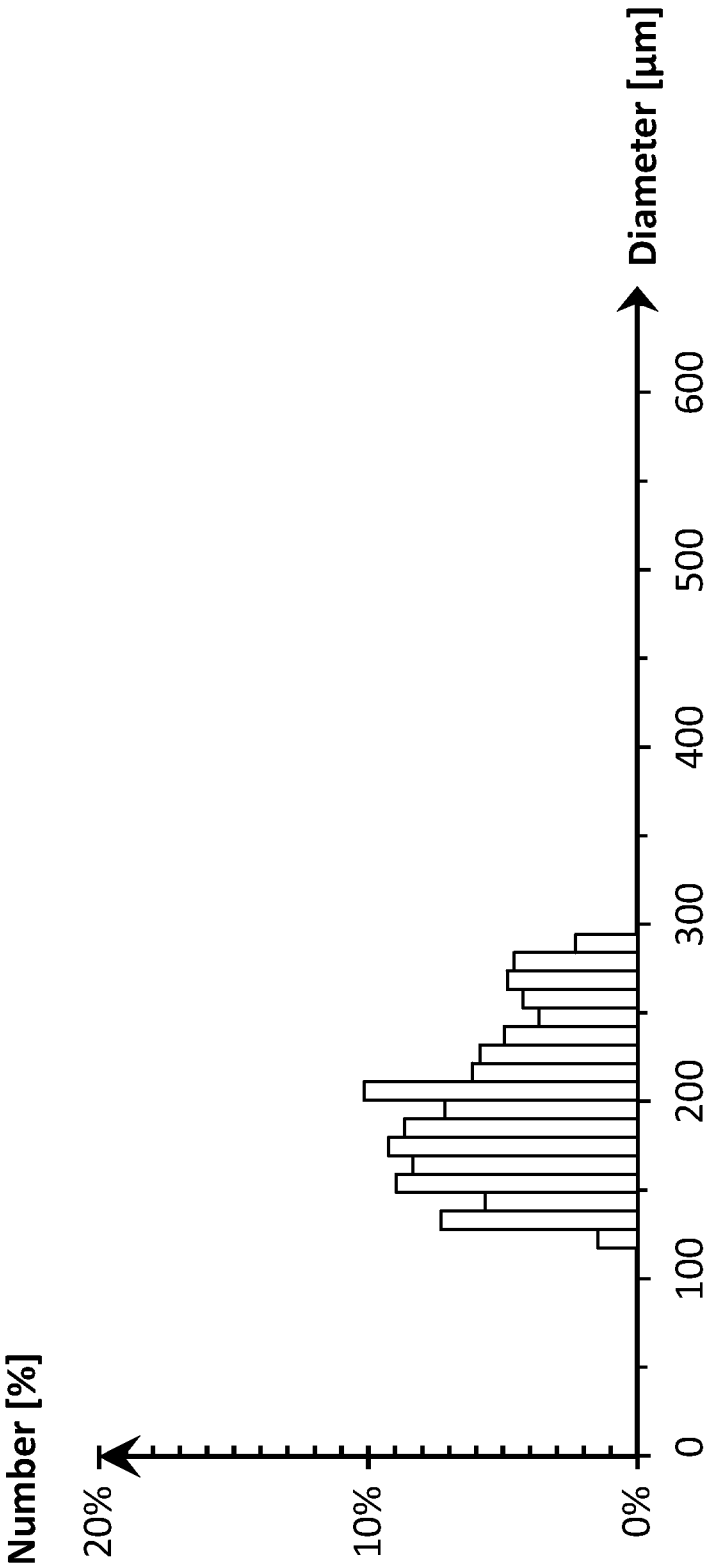

FIG. 9

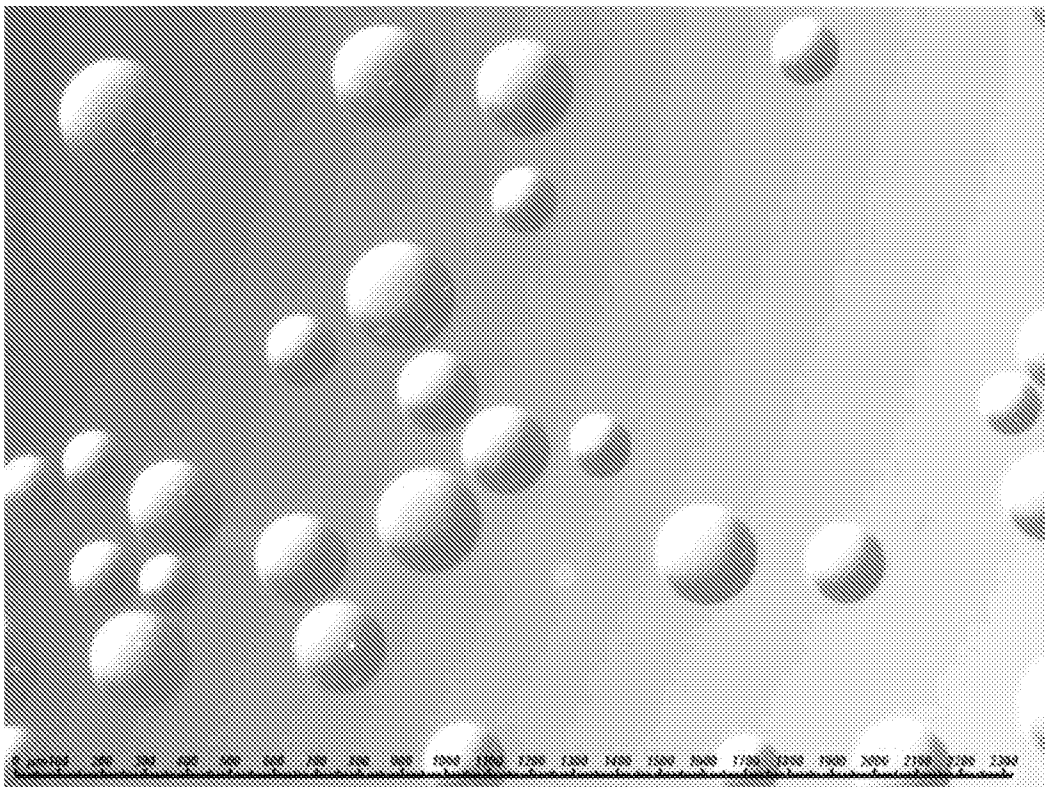

FIG. 10A

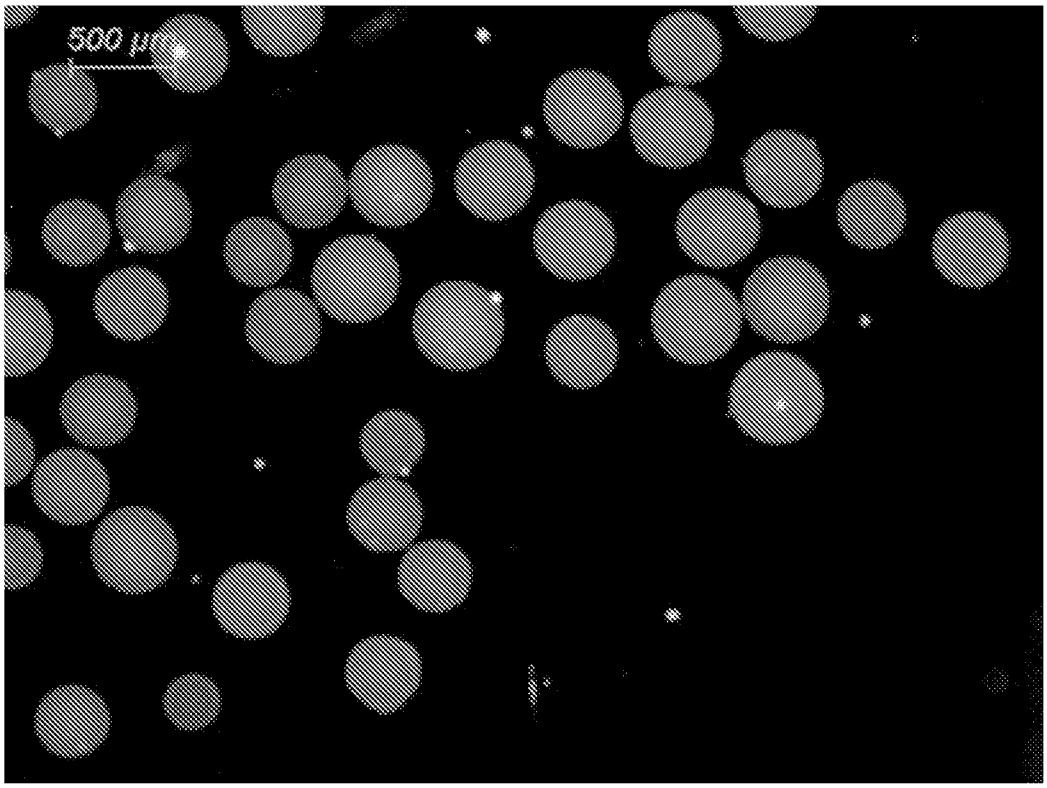

FIG. 10B

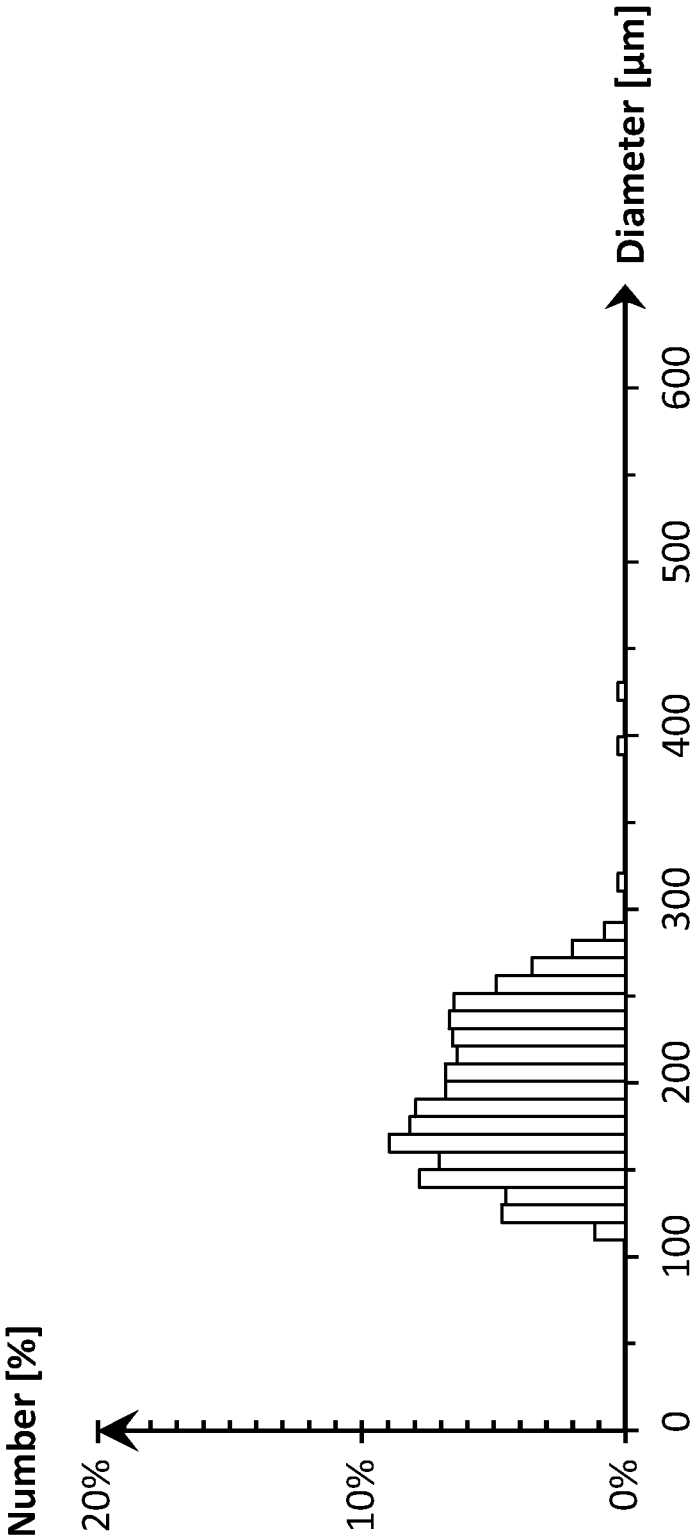

FIG. 11

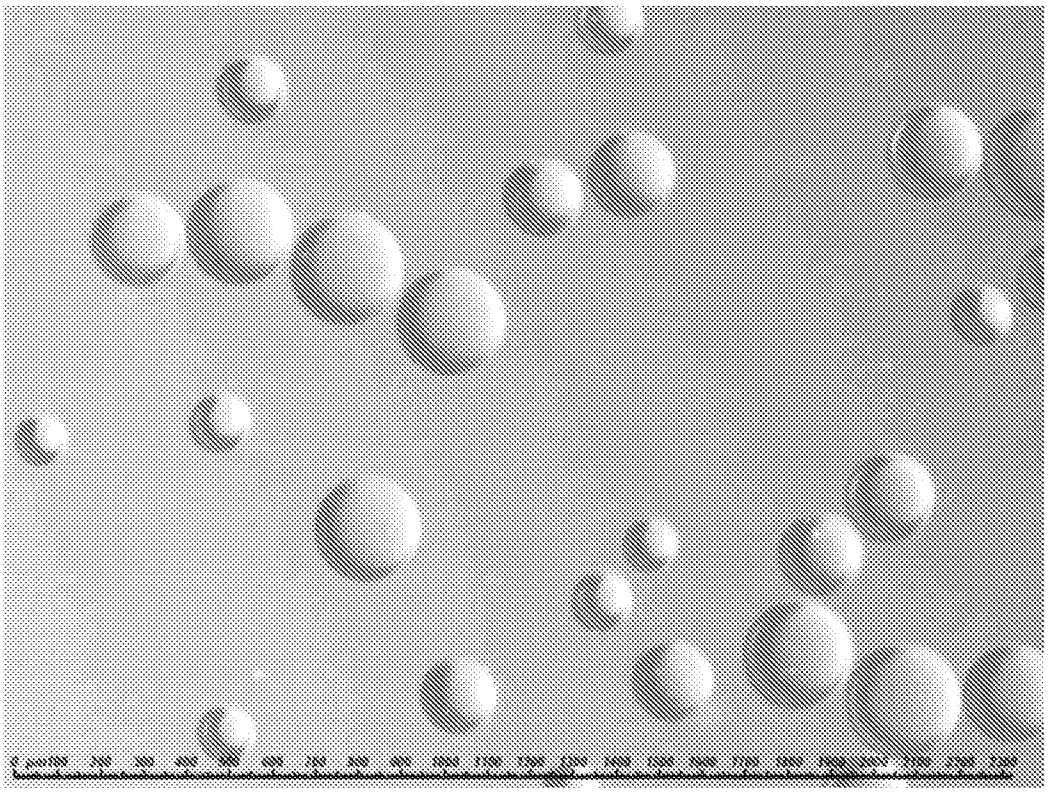

FIG. 12A

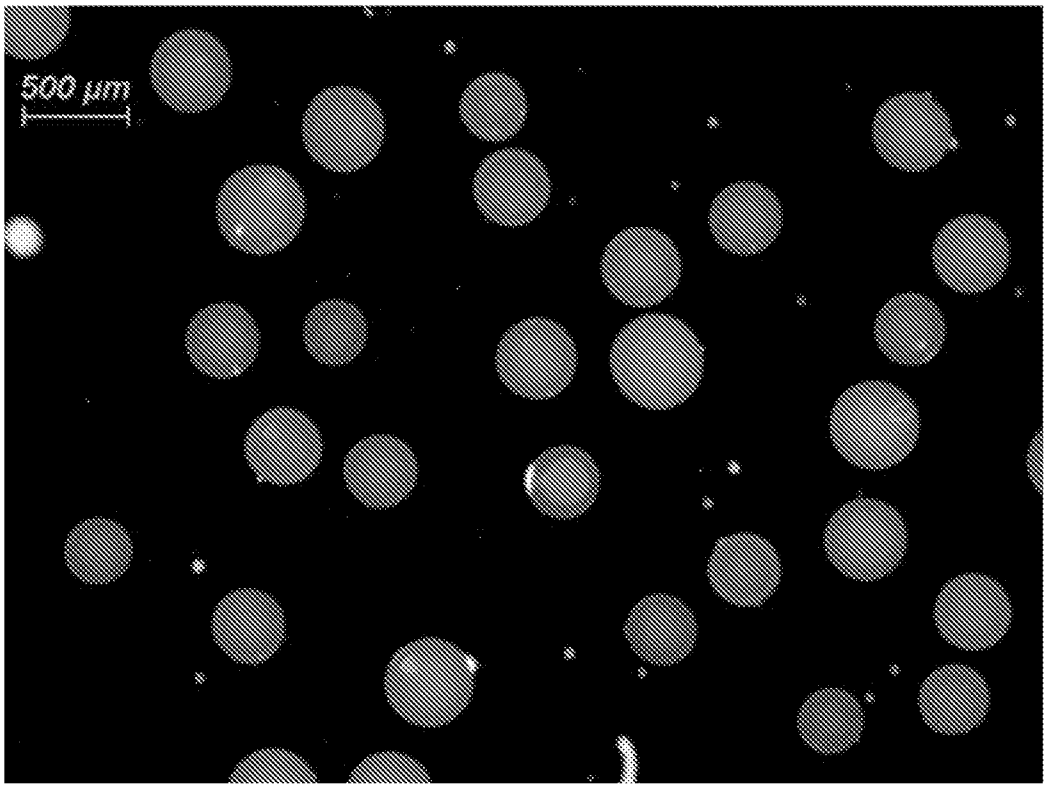

FIG. 12B

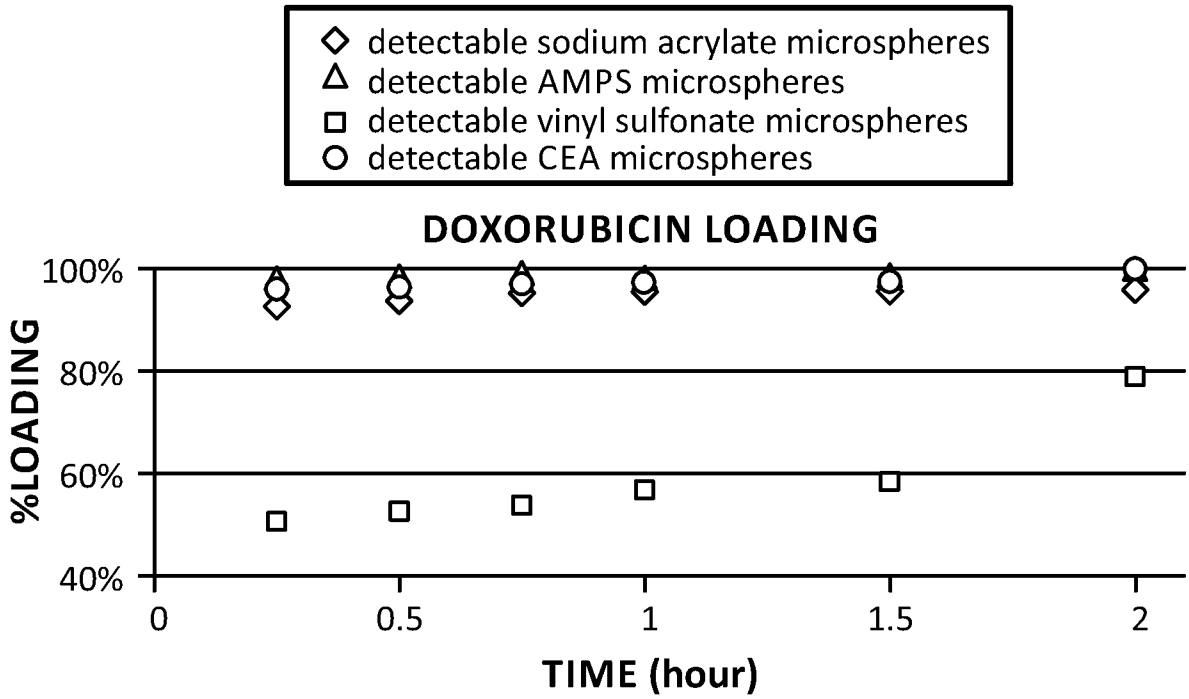
detectable sodium acrylate microspheres
detectable AMPS microspheres
detectable vinyl sulfonate microspheres
detectable CEA microspheres
DOXORUBICIN LOADING
%LOADING
100%
80%
60%
40%
0
0.5
1
1.5
2
TIME (hour)

FIG. 13

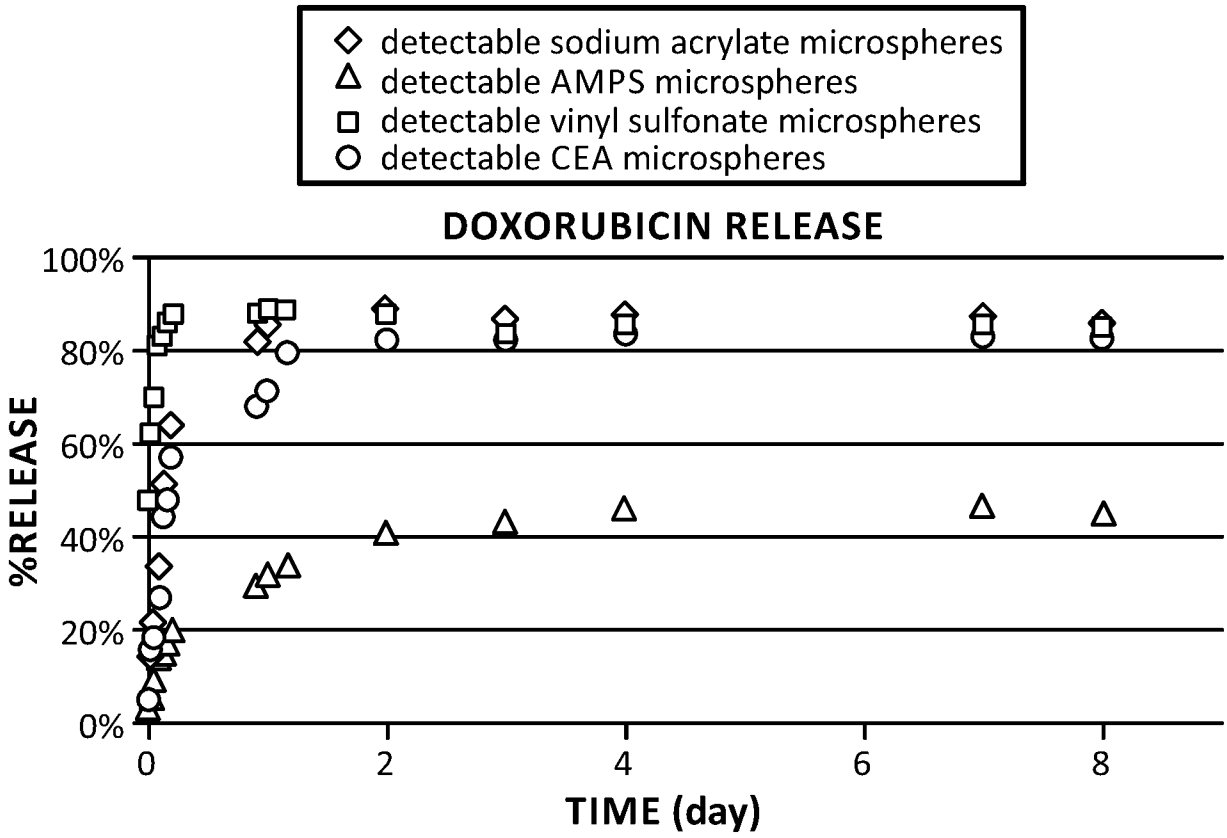
detectable sodium acrylate microspheres
detectable AMPS microspheres
detectable vinyl sulfonate microspheres
detectable CEA microspheres
DOXORUBICIN RELEASE
%RELEASE
100%
80%
60%
40%
20%
0%
0
2
4
6
8
TIME (day)

FIG. 14

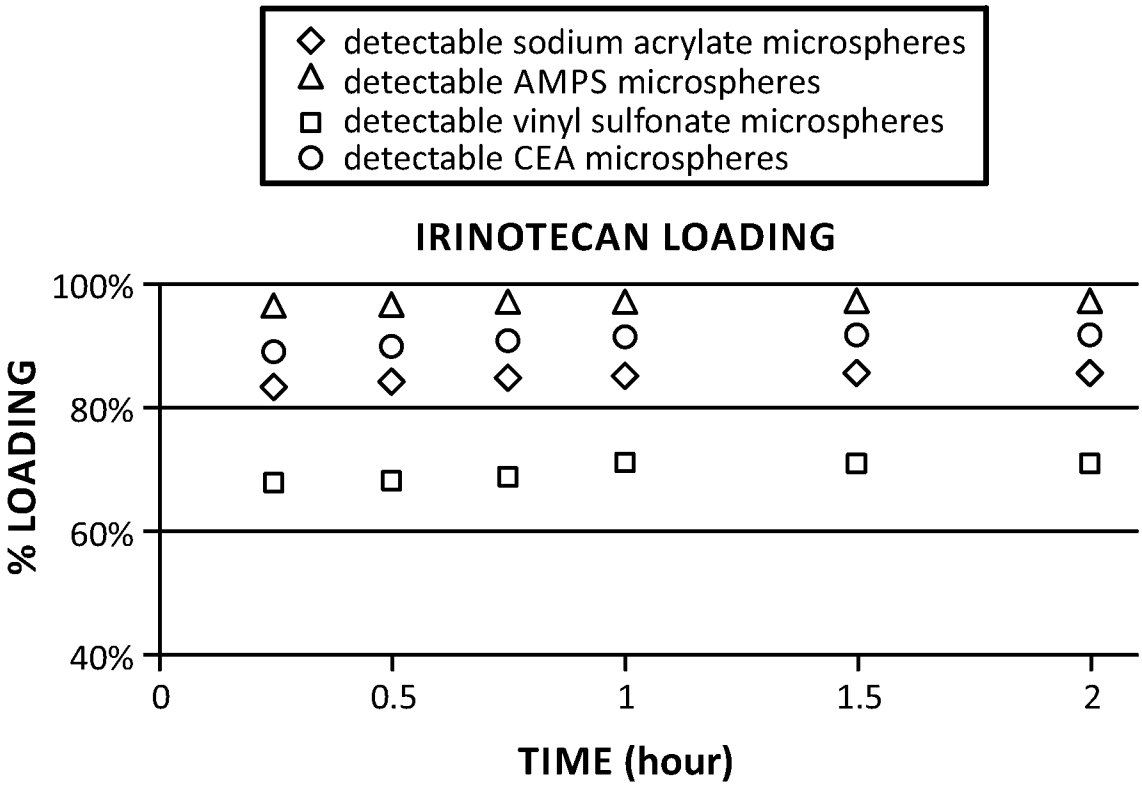
detectable sodium acrylate microspheres
detectable AMPS microspheres
detectable vinyl sulfonate microspheres
detectable CEA microspheres
IRINOTECAN LOADING
% LOADING
100%
80%
60%
40%
0
0.5
1
1.5
2
TIME (hour)

FIG. 15

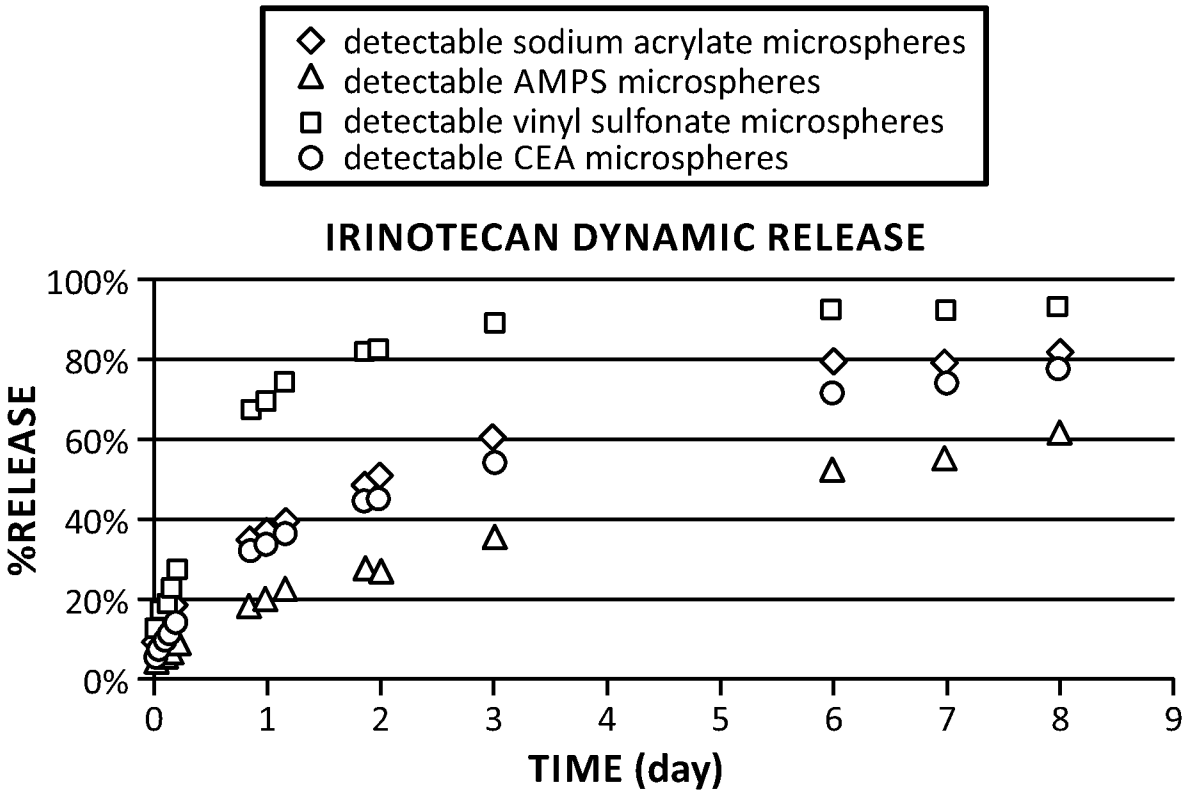
detectable sodium acrylate microspheres
detectable AMPS microspheres
detectable vinyl sulfonate microspheres
detectable CEA microspheres
IRINOTECAN DYNAMIC RELEASE
%RELEASE
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
6
7
8
9
TIME (day)

FIG. 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/042363

A. CLASSIFICATION OF SUBJECT MATTER

A61K 49/06(2006.01)i, A61K 49/12(2006.01)i, A61K 9/16(2006.01)i, A61K 9/14(2006.01)i, A61P 9/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 49/06; A61K 9/14; A61K 49/00; C08K 3/08; A61K 51/00; A61B 5/055; A61K 9/50; A61M 37/00; A61N 2/00; A61K 49/12; A61K 9/16; A61P 9/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: biomaterial, MRI detectable implant, solid tumor, drug eluting, polymer, iron oxide, vascular occlusion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011-0280947 A1 (RIOUX, R. F. et al.) 17 November 2011 See abstract, claims 1, 44-45, 52-53, 56, paragraphs [0004]-[0012], [0023], [0025], [0061], [0063], [0070], [0089], [0096].	1-9,23-29
A	US 2011-0076231 A1 (SCHWARZ, A. et al.) 31 March 2011 See abstract, claims 1, 30-32.	1-9,23-29
A	US 2003-0077225 A1 (LAURENT, A. et al.) 24 April 2003 See abstract, claims 1-5, paragraphs [0011]-[0012].	1-9,23-29
A	US 2005-0058603 A1 (GAO, J. et al.) 17 March 2005 See abstract, claim 1, paragraphs [0011]-[0012].	1-9,23-29
A	LAURENT, A. "Microspheres and Nonspherical Particles for Embolization", Techniques in Vascular and Interventional Radiology, 2007, Vol. 10, pages 248-256 See the whole document.	1-9,23-29
A	US 6315709 B1 (GARIBALDI, J. et al.) 13 November 2001 See abstract, claims 43-44.	1-9,23-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2013 (22.08.2013)	**23 August 2013 (23.08.2013)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/042363

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 42-50
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 42-50 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☒ Claims Nos.: 11, 12, 14, 16, 17, 31, 34, 35, 38-40, 47-50
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 11, 12, 14, 16, 17, 31, 34, 35, 38-40, and 47-50 are unclear, since they refer to one of claims which are not drafted in accordance with PCT Rule 6.4(a) (PCT Article 6).

3. ☒ Claims Nos.: 10, 13, 15, 18-22, 30, 32, 33, 36, 37, 41, 46
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/042363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011-0280947 A1	17/11/2011	EP 1658049 A2	24/05/2006
		US 2004-101564 A1	27/05/2004
		US 8012454 B2	06/09/2011
		US 8273324 B2	25/09/2012
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US 2011-0076231 A1	31/03/2011	AU 2004-224439 A1	07/10/2004
		AU 2004-224439 B2	15/07/2010
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		US 2005-0008610 A1	13/01/2005
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		WO 2004-084703 A3	12/05/2005
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		WO 01-81460 A1	01/11/2001
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		WO 2005-044224 A3	20/03/2008
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		AU 2000-38983 A1	04/10/2000
		EP 1169081 A1	09/01/2002
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		US 6364823 B1	02/04/2002
		US 6375606 B1	23/04/2002
		WO 00-54832 A1	21/09/2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/042363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 00-54835 A1	21/09/2000